How Can We Avoid a Stroke Crisis?

Working Group Report:
Stroke Prevention in Patients with Atrial Fibrillation

Professor Dr Paulus Kirchhof
Department of Cardiology and Angiology, University Hospital Münster, Germany

Dr Adamos Adamou
Former Member of the European Parliament;
Former Co-Chair of the MEP Heart Group, Cyprus

Eve Knight
AntiCoagulation Europe, Bromley, UK

Professor Gregory YH Lip
University of Birmingham Centre for Cardiovascular Sciences, Birmingham, UK

Professor Bo Norrving
Department of Neurology, Lund University, Sweden

Professor Gérard de Pouvourville
ESSEC Business School, Paris, France

Dr med Thomas Ulmer MdEP
Member of the European Parliament, Germany

December 2009

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

Document endorsed by EHRA, a Registered Branch of the ESC

Scientific document endorsed by

How Can We Avoid a Stroke Crisis?

Working Group Report:
Stroke Prevention in Patients with Atrial Fibrillation

ISBN 978-1-903539-09-5

Publication of these recommendations has been made possible with financial support from Bayer Schering Pharma AG.

Printed on elemental chlorine-free paper.

Authors

Writing group

Professor Dr Paulus Kirchhof
Senior Consultant, Department of Cardiology and Angiology, University Hospital Münster; Associate Professor of Medicine, Westfälische Wilhelms-Universität Münster, Germany

Dr Adamos Adamou
Former Member of the European Parliament; Former Co-Chair of the MEP Heart Group, Cyprus

Eve Knight
Chief Executive, AntiCoagulation Europe

Professor Gregory YH Lip
Consultant Cardiologist and Professor of Cardiovascular Medicine, University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, UK

Professor Bo Norrving
Professor in Neurology, Lund University, Sweden; President, World Stroke Organization

Professor Gérard de Pouvourville
Chair, Health Economics, ESSEC Business School, Paris, France

Dr med Thomas Ulmer MdEP
Member of the European Parliament, Germany

Working group

Dr Felicita Andreotti
Certified Professor, Department of Cardiovascular Medicine, Catholic University Medical School, Rome, Italy; Chair, ESC Working Group on Thrombosis

Professor John Camm
Professor of Clinical Cardiology, Chairman of the Discipline of Cardiology and Chairman of the Division of Cardiac and Vascular Sciences, St George's University, London, UK

Professor László Csiba
Professor, Department of Neurology, University of Debrecen, Hungary

Professor Antoni Dávalos
Director, Department of Neurosciences, Hospital Universitari Germans Trias i Pujol, Barcelona; Associated Professor of Neurology, Universitat Autònoma de Barcelona, Spain

Professor Dr Werner Hacke
Professor and Chairman, Department of Neurology, University of Heidelberg, Germany; President, European Stroke Organisation

Professor Dr Karl Heinz-Ladwig
Clinical Psychologist and Professor of Psychosomatic Medicine, Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany

Professor Michael G Hennerici
Professor and Chairman of Neurology, Department of Neurology, University of Heidelberg, Universitätsklinikum Mannheim, Germany; Chairman, European Stroke Conference

Professor Richard Hobbs
Professor and Head of Primary Care Clinical Sciences, University of Birmingham, UK; Chairman, European Primary Care Cardiovascular Society

Dr Torsten Hoppe-Tichy
Chief Pharmacist, Pharmacy Department, University Hospital of Heidelberg, Germany; Member of ADKA (The German Society of Hospital Pharmacists)

Professor Antoine Leenhardt
Professor of Cardiology, Paris 7 University; Head of the Cardiology Department, Lariboisière Hospital, Paris, France

Dr Maddalena Lettino
Staff Physician, CCU-Cardiology Department, S Matteo Hospital, Pavia, Italy; Chairman, Italian Atherosclerosis, Thrombosis and Vascular Biology (ATBV) Working Group

Trudie Lobban MBE
Founder and Trustee, Arrhythmia Alliance; Founder and CEO, Atrial Fibrillation Association

Rod Mitchell
Patient advocate, Board member, European Platform for Patients' Organisations, Science and Industry and European Genetics Alliance Network; past Board member, International Alliance of Patients' Organizations

Dr C Ian Ragan
Executive Director, European Brain Council

Mellanie True Hills
Chief Executive, StopAfib.org

Professor Panos Vardas
Professor, Department of Cardiology, Heraklion University Hospital, Crete; President, European Heart Rhythm Association

Dr Xavier Viñolas
Director, Arrhythmia Unit, Hospital Sant Pau, Barcelona, Spain

Acknowledgements
Support for the writing and editing of this report was provided by Oxford PharmaGenesis™ Ltd.

Publication of these recommendations has been made possible with financial support from Bayer Schering Pharma AG.

Endorsements

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

Organizations

ADKA (The German Society of Hospital Pharmacists)

AntiCoagulation Europe (ACE)

Arrhythmia Alliance (A-A)

Atrial Fibrillation Association (AFA)

ESC Working Group on Thrombosis

European Association of Hospital Pharmacists (EAHP)

European Brain Council (EBC)

European Heart Rhythm Association (EHRA)

European Primary Care Cardiovascular Society (EPCCS)

European Stroke Conference

European Stroke Organisation (ESO)

German Competence Network on Atrial Fibrillation (AFNET)

International Council of Nurses (ICN)

Italian Atherosclerosis, Thrombosis and Vascular Biology (ATBV) Working Group

Sociedad Española de Neurologia (Spanish Neurological Association)

StopAfib.org

World Stroke Organization (WSO)

Individual

Jaime Masjuan
National Coordinator of the Cerebrovascular Diseases Study Group of the Spanish Neurological Association (Sociedad Española de Neurologia)

Table of contents

Foreword	7
Executive summary	9
Call to action	11
Stroke: a significant cause of poor health and death	17
Atrial fibrillation: a major risk factor for stroke	21
Detecting atrial fibrillation and stratifying stroke risk	25
Features of stroke in patients with atrial fibrillation	29
High cost of stroke in atrial fibrillation to individuals and society	31
Stroke prevention in patients with atrial fibrillation	34
Guidelines for stroke prevention in patients with atrial fibrillation	42
Current challenges for stroke prevention in patients with atrial fibrillation	48
New developments for stroke prevention in patients with atrial fibrillation	55
References	60
Appendix 1	70
Appendix 2	72
Glossary	73
Abbreviations	75
Links to endorsing organizations	77

Foreword

Stroke is a disaster that strikes about 2 million Europeans every year. In many cases, the first and only manifestation of stroke is death. Surviving stroke can be worse than death, with victims facing an uncertain future and a life that may be severely damaged by disability. The financial burden of stroke is also staggering, currently costing the European Union (EU) economy about €38 billion per annum. This cost is set to increase dramatically as the number of affected individuals is projected to double by 2050.

Much of this death, damage and cost can be prevented if we take simple actions now. If we do not, we will face a European stroke epidemic. The recommendations in this report spell out those actions for patients with the abnormal heart rhythm known as atrial fibrillation (AF) – a condition that increases the risk of stroke fivefold and is responsible for 15–20% of all strokes caused by blood clots. Importantly, patients with AF are more likely than those without AF to have a severe stroke and, if they do, they have a 50% likelihood of death within 1 year. Furthermore, the presence of AF increases the risk of remaining disabled after a stroke by almost 50%. With AF estimated to affect over 6 million people in Europe alone, the scale of the problem is clear.

As a practising general practitioner throughout my career, I am all too aware that, although very common, AF often goes unrecognized. These recommendations set out to expose our poor understanding of this complex disease, which is often underdiagnosed and undertreated – typically with insufficient attention paid to effective stroke prevention.

The aims of this report are to help patients, policy makers, healthcare professionals and the general public understand that better knowledge and management of AF and better prevention of stroke are possible. Moreover, they are necessary if we are to reduce the damage these conditions cause. But that will not happen unless we take action now.

How will we help? Although the delivery of health remains the responsibility of national governments, cooperation at European level has great potential to bring benefits both to individuals and to health systems overall. We have seen in other areas of medicine that the EU is a very effective vehicle for the spread of best practice, knowledge and education – for example, in cancer, Alzheimer's disease and organ transplantation.

This report is the first step in raising awareness of the need for greater investment in preventing stroke, in particular in patients with AF. Importantly, it contains a clear Call to Action, to which I draw your attention. Implementation of these recommendations at European and national level will be crucial. The task will be to bring together the various strands of policy development, awareness-raising, research and educational activities, and focus them clearly on improving AF management and ensuring effective stroke prevention. The EU will then have a clear strategy to help coordinate national initiatives and benchmark performance.

Our efforts in Brussels will help to ensure that resources are invested wisely so that we can provide better health care for these patients. As a doctor and a policy maker, I firmly believe that only through the coordinated actions of all participants, European and national, will we see the highest number of strokes avoided and the greatest quality of life improvements achieved.

It is a privilege for me as a Member of the European Parliament to participate actively in an initiative that will help to push this important issue up the European agenda. I will seek to set these changes in motion with the support of my parliamentary colleagues, and look forward to your support in driving this important initiative.

Dr med Thomas Ulmer MdEP
Member of the European Parliament, Germany
December 2009

Executive summary

Stroke is the most common cardiovascular disorder after heart disease, afflicting about 9.6 million people in Europe and killing an estimated 5.7 million people annually worldwide.[1]

For many patients, surviving a stroke can be worse than dying from one, with disability and the fear of death never far from mind. The consequences of stroke can devastate not only patients' quality of life,[2] but also that of families and carers.[3] Furthermore, the economic burden of stroke is huge, accounting for 2–3% of total healthcare expenditure in the European Union (EU).[4]

There were an estimated 1.1 million new strokes in the EU in 2000 (about half the number of new cancer cases[5]), and it is predicted that this number will rise to 1.5 million per year by 2025 as the proportion of elderly people in the population increases.[6] This is an epidemic already beginning to happen, and we must act if we are to avoid a crisis.

Atrial fibrillation (AF) is the most common sustained abnormality of heart rhythm, and in Europe an estimated 6 million people have the condition.[7] Individuals with AF have a fivefold increased risk of stroke compared with the general population.[8] AF is a strong independent risk factor for stroke and accounts for approximately 1 in 5 ischaemic strokes (strokes caused by a blood clot blocking a blood vessel in the brain).[9] Moreover, previously undiagnosed AF is a probable cause of many strokes of unknown origin (so-called 'cryptogenic' strokes), and stroke may be the first manifestation of 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).[10]

Furthermore, AF-related strokes are more severe, cause greater disability and have a worse outcome than strokes in patients without AF – and they are associated with a 50% likelihood of death within 1 year.[9] Importantly, the burden of AF-related stroke will become more marked in the years to come because the number of people with AF will increase approximately 2.5-fold by 2050,[11,12] due to ageing of the population and to improved survival following conditions that predispose to AF (such as heart attack).[13]

Patients with AF therefore 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, which has been identified by the Heart Health Charter and EU policy as a key need in Europe.[14]

To prevent AF-related stroke, the ideal would be to prevent or reverse AF itself. Current techniques can only prevent AF in some patients. Hence, there is a clear need to improve detection and therapy of AF in Europe.

Anticlotting therapy reduces stroke risk in patients with AF. When appropriately used and properly monitored, it is highly effective, lowering stroke risk by about two-thirds.[15] Despite the

Stroke is the most common cardiovascular disorder after heart disease, killing about 5.7 million people worldwide every year

About 6 million people in Europe have AF

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

existence of Guidelines for its use and management, however, such therapy is both underused and misused in clinical practice, largely owing to the existence of significant drawbacks[16–18] associated with both vitamin K antagonists, such as warfarin,[19,20] and aspirin.[21–24]

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

Earlier detection and improved treatment of AF can help 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, medical and social care costs, and loss of working hours and tax revenues.

There is therefore an urgent need for coordinated action across the EU to achieve earlier diagnosis and better management of AF and to reduce the risk of stroke in patients with AF. This action will include:

- EU-wide educational and awareness initiatives enacted in each Member State to improve early detection of AF
- more effective use of interventions for the management of AF and the prevention of stroke in patients with AF
- equal and adequate administration of therapy for patients with AF
- greater adherence to Guideline recommendations for AF management
- continuing research into the 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 European Union (EU) action to ensure better detection and management of atrial fibrillation (AF) and more effective measures to prevent AF-related stroke across all Member States. Through this, we will be able to reduce the major social and economic burdens of a largely preventable condition: AF-related stroke.

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

Cardiovascular disorders are the leading cause of death globally.[1] The financial burden for EU healthcare systems from this group of diseases was estimated in 2006 to be just under €110 billion. This represents a cost of €223 per person per year – about 10% of the total healthcare expenditure across the EU.[14]

The most prevalent cardiovascular disorders are coronary heart disease and stroke. AF, the most common sustained kind of abnormal heart rhythm, is a major cause of stroke – in particular, of severe, disabling stroke. The majority of such strokes are preventable. Thus, earlier detection and treatment of AF and more effective prevention of AF-related stroke would help to achieve the aims of the European Heart Health Charter – a joint initiative by the European Health Network and the European Society of Cardiology to reduce substantially the burden of cardiovascular diseases.[14]

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%.[27–29] 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 properly managing such therapy and a widely held belief that the risks of therapy may outweigh the benefits.[16–18] Furthermore, AF is often not diagnosed until the patient suffers a first stroke. This increases the size of the problem, meaning that many potentially preventable strokes occur every year because of delayed diagnosis of AF as well as underuse of anticlotting therapy. The result is a devastating impact on the health and wellbeing of the individual and an increased burden to society in terms of medical and social care resources and loss of working hours and tax revenues.

AF is a major cause of severe, disabling stroke

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

In 2007 the European Commission adopted a new health strategy, 'Together for Health: A Strategic Approach for the EU 2008–2013'.[30] One of the strategic themes of this White Paper is 'Fostering Good Health in an Ageing Europe'. In keeping with

this overarching objective, AF management and stroke prevention in patients with AF will gain increasing prominence over the next decades, as the population ages. As part of the wider initiative for prevention of stroke and cardiovascular disorders in Europe, there is a clear need for:

- coordinated action at the EU level, and potentially beyond
- an EU policy initiative calling for
  - adequate diagnosis of AF prior to the first stroke
  - appropriate and effective management of AF
  - effective stroke prevention in patients who have already developed AF
  - continuing research into the causes of AF.

Such a declaration would be in line with the main priorities of the EU with regard to health: that is, to focus on health determinants (e.g. obesity, high blood pressure) and disease prevention.[14]

We call on the European Parliament and the European Commission to drive policy initiatives to improve early detection and management of AF and to prevent stroke in patients with AF

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 developed AF, their risk of an ischaemic stroke (from a blood clot in the brain) is increased fivefold or more compared with the risk in individuals without the condition.[8,31] Because of the large number of people in the EU living with AF,[7] the human and economic impact of AF and AF-related stroke is huge: the average medical cost alone of stroke per patient with AF has been calculated to be approximately €12 000.[32]

Stroke can be prevented in patients with AF. There is a critical need within the EU 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 causes, and for improvements in strategies for

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 about AF
- Encourage new approaches to the management of AF and the prevention of AF-related stroke
- Improve awareness of physicians about AF management
- Promote equity of access to services and information for patients across the EU
- Advocate adherence to Guidelines for AF management
- Exchange best practice between Member States
- Boost research into the causes, prevention and management of AF

AF detection and management. We call on the European Parliament and the European Commission to drive policy initiatives across Europe to promote understanding, earlier detection and improved management of AF and to prevent stroke in patients with AF.

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

AF is often detected only after a stroke, because many patients are unaware of their heart disorder. However, a simple, inexpensive procedure such as routine pulse-taking 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 are: congestive heart failure, high blood pressure, age over 75 years, diabetes and previous stroke. 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 help to reduce the need for specific stroke prevention treatment.

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, and could play a significant role in improving adherence to therapy. We call on the EU to fund, drive and encourage participation in such educational initiatives to raise awareness of AF.

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

Furthermore, EU-wide collaboration between existing patient organizations as well as the possible creation of a common European platform for patients with AF – to exchange and disseminate information on AF, its diagnosis and management, and on stroke prevention – could serve to collate and compare data from different countries in Europe. Driven by the European Commission, such an initiative would make it possible to identify best practice for the successful management of AF across the EU, leading to benchmarks for management that would stimulate improvements in other countries.

We call on the EU to drive educational initiatives to improve patient understanding of AF

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

Ideally, minimizing risk factors such as high blood pressure, structural heart disease and diabetes will reduce the likelihood of AF developing in the first place. However, some factors that contribute to the emergence of AF, such as genetics and the natural ageing process, are not modifiable, so it will not be possible to eliminate AF entirely.[33]

We call on the Member States to drive more effective use of anticlotting treatment in patients with AF

Thus, other important areas of focus are early diagnosis of AF – prior to the

first stroke – and management of the signs and symptoms of AF. Effective use of anticlotting therapy is essential in most patients who have already developed AF, in order to prevent complications (such as stroke) resulting from a circulating blood clot.

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

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

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

Physicians may be so concerned about the risks of anticlotting therapy that they underestimate its benefits in reducing stroke risk.[34–36] 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. We call for a coordinated EU effort to improve physician education and awareness strategies, supported by adequate resources.

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

We call on the EU, via the Member States, to raise awareness of existing Guidelines for the management of AF

All patients within the EU 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 to ensure clear and relevant communication with patients, so that they are partners in determining their care and have a voice in Brussels and throughout the EU.

7. Strongly advocate adherence to Guidelines for the management of patients with AF

Several sets of Guidelines exist for the management of AF. Their recommendations largely overlap, but the degree to which they are properly implemented varies widely between and within countries. This can be demonstrated when the use of anticlotting therapy is analysed in large cohorts of AF patients. For example, according to recent surveys in different parts of Europe, the proportion of patients with AF at high risk of stroke and receiving Guideline-adherent anticoagulation is around 54–61%.[36,37] This figure rises to more than 70% in settings where Guidelines are being more successfully implemented.[38,39] There is therefore a need across much of Europe to improve adherence to Guidelines on the prevention of stroke in patients with AF, because non-adherence is associated with poor outcomes.[37]

The EU can encourage Guideline adherence at a national level by calling for better implementation of the existing European Guidelines (e.g. those developed by the European Society of Cardiology).[25] We call on the EU to raise awareness of the existing

Guidelines, via the Member States. Improved adherence to Guidelines will help to increase the number of eligible patients in Europe who receive adequate anticlotting therapy and ensure that such therapy is optimally delivered. This, in turn, will reduce the number of new cases of AF-related stroke. Improved Guideline adherence, as well as timely updating of Guidelines when appropriate, would also enhance patient safety – in line with a recent communication on patient safety from the European Commission to the European Parliament and the Council.[40,41]

8. Facilitate exchange of best practice between Member States

An EU initiative to harmonize the existing national Guidelines into one set of unified European Guidelines would help to further the goal of stroke prevention. As a second stage, coordination at a European level 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 consistent policy on stroke prevention in patients with AF across all Member States. It would also help to ensure that the principle of healthcare equality across the EU is implemented and individual patients receive similar (and the best possible) care in all EU Member States. The EU can call for better alignment between Member States, to identify key areas where the guidance is being overlooked or where agreement is required on divergent advice.

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

The ideal would be to prevent AF-related strokes by preventing AF itself, an abnormality of heart rhythm that affects mainly older people. The first objective of the European Commission's 2007 White Paper, which is to foster 'good health in an ageing Europe', highlights that by 2050 the number of people in the EU aged over 65 years will grow by 70%.[30] This underscores the importance of increasing our understanding of the causes of AF and of developing strategies for the prevention and treatment of AF through scientific and medical research.

We advocate an EU initiative to develop a unified European Guideline for the management of AF, and to share and promote best practice among all Member States

The EU can provide funding to boost research into these areas, via a coordinated research strategy. It may be possible to utilize the resources of the Seventh and Eighth Framework Programme, which provides EU funding for research and technological development, and/or to benefit from the Innovative Medicines Initiative Joint Undertaking – the unique partnership between the European Commission and the European Federation of Pharmaceutical Industries and Associations. Research topics that the EU 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 Europe-wide patient experience 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
- Europe-wide studies monitoring the effect of interventions to manage AF and prevent AF-related stroke.

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

The EU already acknowledges the importance of stimulating cardiovascular disease research activities at the European level by

providing direct financial support for research projects through the Seventh Framework Programme. In 2008, over €21 million was committed over the following 5 years to supporting the European Stroke Network (ESN) in their efforts to coordinate the largest ever multidisciplinary European stroke research programme. To augment and complement the efforts of the ESN, an EU-wide 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

- Stroke accounts for nearly 10% of all deaths worldwide, and each year 5 million stroke sufferers are left permanently disabled.
- Approximately 9.6 million people in Europe have suffered at least one stroke in their lifetime.
- Latest data show that about 2 million Europeans suffer a stroke each year, and the number of strokes per year is predicted to rise dramatically as the population ages.
- The overall economic cost of stroke to the European Union (EU) was over €38 billion in 2006.

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 a bleed from a blood vessel in the brain. An ischaemic stroke is the more common type, accounting for approximately 85% of all strokes,[42] and is caused by a blood clot in the brain. This blood clot may have developed in the brain, or it may have formed somewhere else in the body and 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%.[43,44] Studies have shown that in the 90 days following a TIA, the risk of stroke exceeds 10%.[43]

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

Incidence and prevalence of stroke in Europe and the EU

Stroke is the most common cardio-vascular disorder after heart disease, accounting for 5.7 million deaths annually worldwide (9.7% of all deaths).[1] The prevalence (i.e. total number of cases) of stroke in Europe has been estimated to be 9.6 million.[1] A World Health Organization (WHO) study reported the incidence (i.e. number of new cases) in the whole of Europe to be 2 million in 2004.[1] This compares with an estimated incidence of 2.9 million cancer cases in the same year in Europe.[5] For countries within the EU, a study based on data from the WHO estimated the number of first and recurrent strokes to be 1.1 million in 2000;[6] by comparison, the incidence of cancer cases in the EU

9.6 million people in Europe have suffered a stroke, and about 2 million new or repeat strokes occur each year

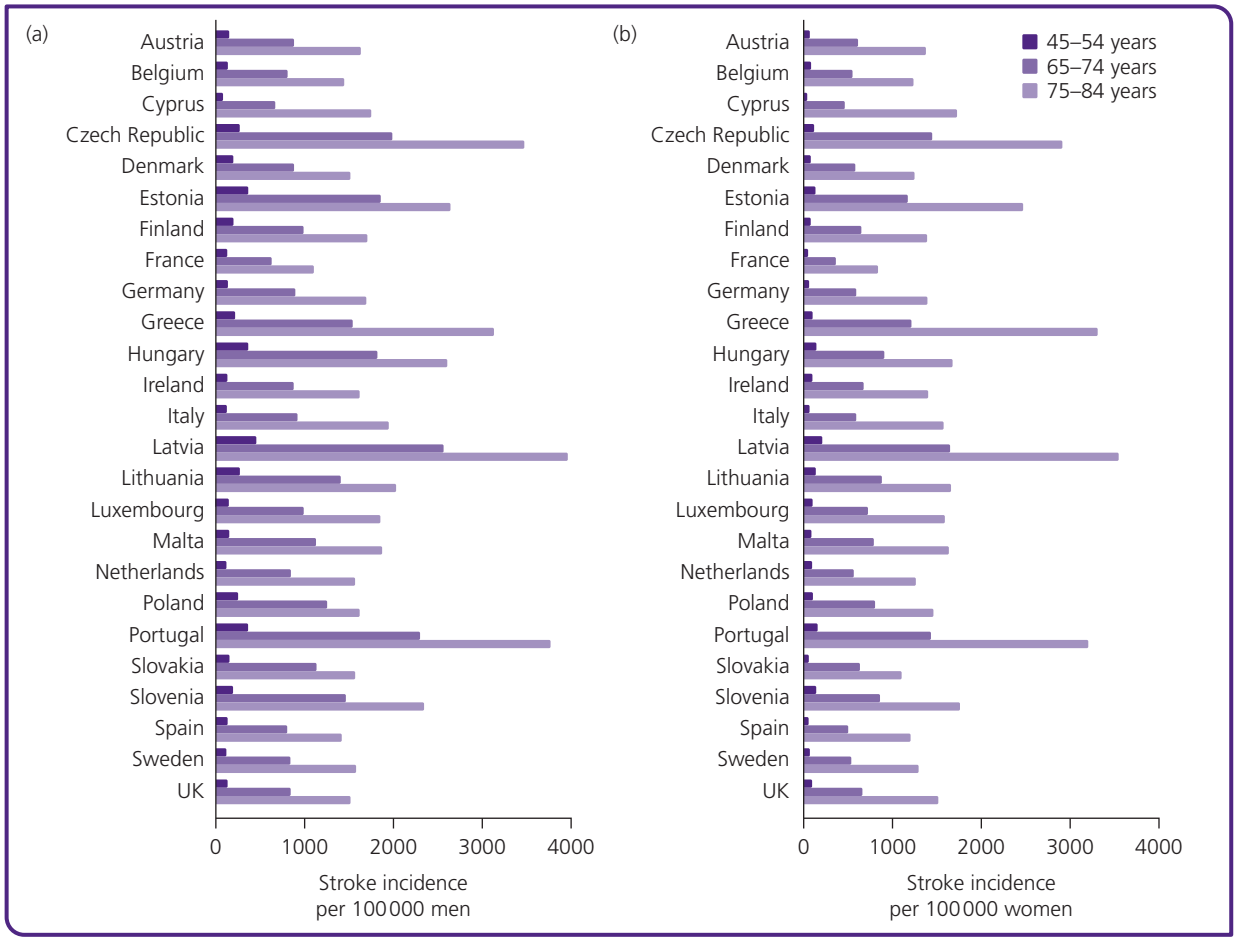
was around 2 million in 2004.[5] Furthermore, it has been predicted that stroke incidence will increase to 1.5 million per year by 2025, largely owing to the increasing proportion of elderly individuals in the EU.[6]

The incidence of stroke in individual countries in the EU has also been estimated by the WHO (Figure 1).[6] This shows that, for both men and women, the number of individuals experiencing stroke increases substantially with age. For example, in Belgium the incidence of stroke in men aged 75–84 years is 10 times that in men aged 45–54 years; in women aged 75–84 years, it is nearly 15 times that in women aged 45–54 years. Furthermore, these data show that stroke incidence is higher in men than in women, across most countries and age ranges.

Although strokes in young adults are relatively uncommon, approximately 25% of strokes occur in people aged below 65 years,[45] and a national survey of stroke in the USA estimated that 3.7% of strokes occurred in patients aged 15–45 years.[46]

Some ethnic differences in stroke epidemiology may exist, reflecting differences in the predisposition to some of the risk factors associated with stroke. For example, there is a high prevalence of high blood pressure and, as a consequence, stroke, among

Figure 1. Estimates of stroke incidence (a) per 100000 men and (b) per 100000 women at selected ages in the European Union (from the World Health Organization). The number of individuals experiencing stroke increases substantially with age. Data taken from Truelsen *et al.* 2006.[6]



Afro-Caribbean populations. In the UK, death rate from stroke has been found to be higher among individuals of South Asian origin than among the Caucasian population.[47] As ethnic diversity increases in the EU, appreciation of the risk factors in different ethnic populations should be high on the agenda.

Death and poor health in patients with stroke

Stroke accounts for nearly 10% of all deaths worldwide.[1,42] Stroke is generally thought of as a problem of the elderly; however, the death rate from stroke in individuals aged up to 64 years in the EU was estimated to be 15 per 100000 of the population in 2005.[4] This figure rises substantially in individuals over the age of 64 years. For example, the death rate from stroke in England in patients aged 65–74 years was about 124 per 100000 of the population in 2005.[48]

Additionally, stroke is a major cause of long-term disability worldwide – each year, 5 million stroke sufferers are left permanently disabled.[42] 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 or had not undergone major vascular surgery; a majority of survivors reported emotional, social or physical effects that lessened their quality of life.[49]

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,[42] stroke can also adversely affect mental health.[50]

Because its onset is sudden, the affected individual and their family are often poorly prepared to deal with the consequences of stroke.[50] The development of chronic disability can severely affect quality of life of both the patient and his or her relatives. Thus, the impact of stroke on society, in terms of morbidity (ill health) and health burden, is substantial.

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

Case study: the impact of stroke

"As an Air Force Colonel, it was very hard when they told me I couldn't go back to work. During the rehabilitation period, I got very depressed … one day I was making progress and the next day I wasn't. It was more difficult when I got back to Norway, having been an active person, taking initiatives – now I was just sitting there. That is a tremendous challenge because you move into a completely new life."

Financial cost of stroke in Europe

The total cost of stroke in the EU was calculated to be over €38 billion in 2006. This figure included healthcare costs (about 49% of the total cost), productivity loss due to disability and death (23% of the total cost) and informal care costs (29% of the total cost).[4]

Stroke costs in the EU were over €38 billion in 2006

The total healthcare costs attributable to stroke in 2006 are shown in Figure 2a for each country in the EU.[4] Healthcare costs attributable to stroke were approximately €18.5 billion, and costs unrelated to health care were approximately €20 billion (where 1 billion is defined as 1000 million). These figures demonstrate the

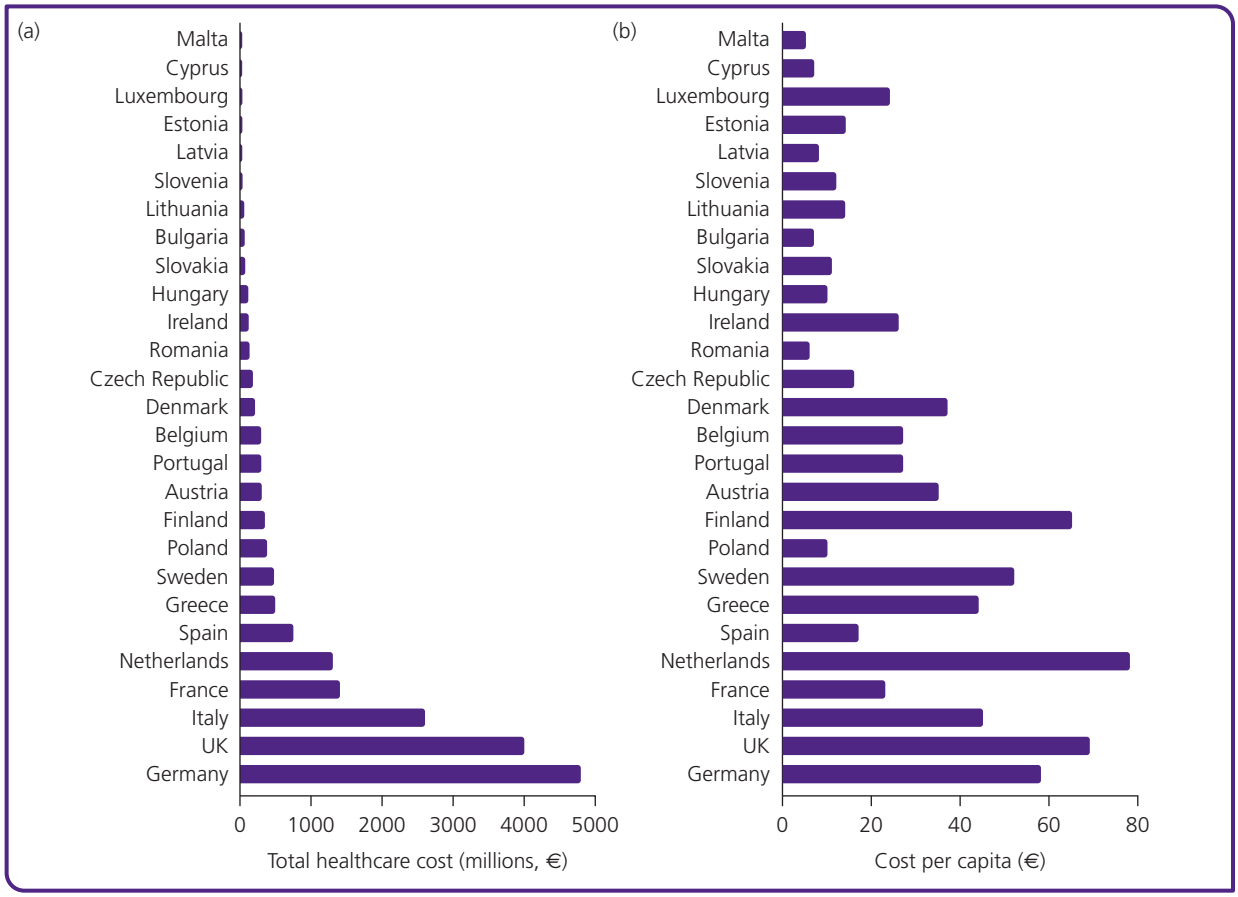
Stroke places a massive burden on patients, their families, carers, friends and society

tremendous financial burden to society posed by stroke in Europe.

The per capita costs associated with stroke in 2006 for each EU country are shown in Figure 2b. These data show that the amount spent on stroke per year varies greatly within the EU, from €5 per person (Malta) to €78 per person (the Netherlands).

It is therefore clear that stroke is a costly health problem in Europe, and a massive 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 atrial fibrillation (AF) would help to reduce the burden of stroke in the EU. Furthermore, the prevention of stroke with pharmacological or non-pharmacological therapies in patients at high risk has the potential to reduce this huge economic burden significantly.[51] For example, in patients with AF, who are known to have a high risk of stroke, the cost of treating a stroke has been calculated to be almost fourfold greater than the estimated costs of prevention with anticoagulant (anticlotting) therapy over a 10-year period.[52] The cost-effectiveness of anticoagulant therapy in patients with AF is discussed further in the section 'Cost of vitamin K antagonist therapy in stroke prevention in atrial fibrillation' (page 39).

Figure 2. Healthcare costs attributable to stroke in the European Union in 2006. (a) Total healthcare cost; (b) cost per capita. Data taken from Allender *et al*.[4] Healthcare cost is estimated to be 49% of the total cost of stroke, but varies greatly between countries.[4]



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% of all strokes.
- AF is estimated to affect over 6 million people in Europe.
- 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 and diabetes. Dietary and lifestyle factors also contribute to the risk of developing AF.
- The likelihood of developing AF increases with advancing age. People over the age of 40 years have a 1 in 4 risk of developing AF over their remaining lifetime.

AF is the most common sustained heart rhythm abnormality[53] and is a major risk factor for ischaemic stroke and death in the general population.[9,53] 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.[54] The five major modifiable risk factors – the 'big five' – that merit targeting in the prevention of stroke have been identified as:[55]

- 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,[56] accounting for approximately 40% of all strokes.[42,56,57] AF, by comparison, is estimated to be responsible for approximately 15% of all strokes[58] (20% of all ischaemic strokes[9]) and patients with AF have a 3–4% risk per year of developing stroke.[59] High blood pressure is therefore responsible for a greater proportion of the global burden of stroke than AF. However, 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 3).[8,31] 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 40).

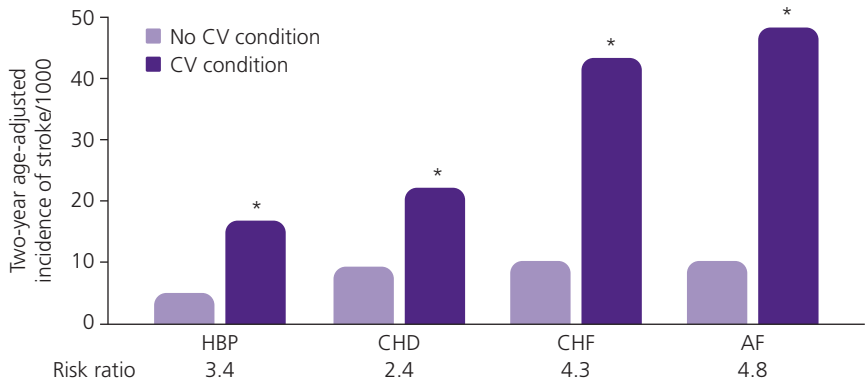
AF is responsible for about 15% of all strokes

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 3. Two-year age-adjusted incidence of stroke in the presence and absence of cardiovascular (CV) conditions. Atrial fibrillation confers a fivefold increase in the risk of stroke; in patients with high blood pressure, stroke risk is increased threefold. *$p < 0.001$. Adapted with permission from Wolf *et al.* 1991.[8]



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

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

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.[60]

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 and diabetes.[61,62] 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 sections involve patients with non-valvular, rather than valvular, AF. This reflects the improved management of rheumatic valve disease in Europe in recent decades, resulting in a decrease in the proportion of patients with AF in whom the abnormal heart rhythm is attributable to valvular disease. Dietary, lifestyle and other factors that contribute to the risk of AF include emotional and physical stress and excessive caffeine, alcohol or illicit drug intake.[63]

Emotional and physical stress increase the risk of AF – as do excessive intake of caffeine, alcohol or illicit drugs

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.[33,64] In addition, there are limited data to suggest that the incidence of AF is higher than normal in athletes.[65,66] Furthermore, an increasing 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.[65] 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.[67] However, many people with AF have no symptoms, or vague, non-specific symptoms. 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 goes to see 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.[63] 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.[68] This indicates that many patients with AF are not being managed effectively and are at risk of serious long-term consequences, such as stroke.

The National Institute for Health and Clinical Excellence (NICE) in the UK recommends further assessment for the presence of AF in individuals with breathlessness, palpitations, fainting/dizziness, chest discomfort, stroke or TIAs.[69] 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.[67] Management of AF is discussed in more detail in the chapter 'Stroke prevention in patients with atrial fibrillation', page 34.

AF may occur in isolation, or in association with other disturbances of normal heart rhythm, most commonly atrial flutter. Atrial flutter can precede or co-exist with AF, but there are differences in the mechanisms of the two rhythm disturbances.[25] Atrial flutter will not be discussed in further detail in this document.

Prevalence and incidence of atrial fibrillation

Increase with age

The prevalence of AF has been shown to increase with each advancing decade beyond the age of 50 years, from around 0.5% at the age of 50–59 years to almost 9% at the age of 80–89 years.[53] The incidence of AF has also been found to increase with each decade of age.[53] In a population-based cohort study in Rotterdam, the incidence of AF was investigated during a mean follow-up period of almost 7 years in 6432 individuals. This revealed an incidence of 1.1 per 1000 person-years in those aged 55–59 years, rising to 20.7 per 1000 person-years in those aged 80–84 years.[70] The incidence was higher in men than in women.

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

Increase over time

The prevalence of AF also appears to be increasing over time. In one cross-sectional study of almost 18000 adults with AF diagnosed between July 1996 and December 1997 in California, USA, it was estimated that approximately 2.1 million people in the USA had AF.[11] By 2001, this number was thought to have risen to 2.3 million, and it is projected to increase approximately 2.5-fold – to more than 5.6 million – by 2050 (Figure 4).[11] 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.[71] In Europe, AF is estimated currently to affect over 6 million patients.[7]

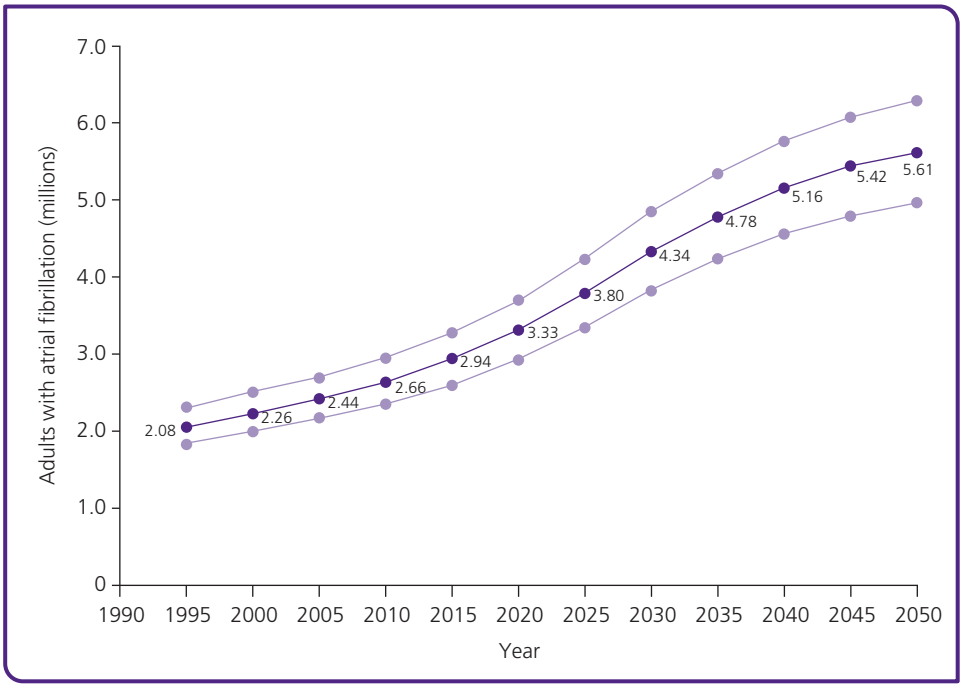
The prevalence and incidence of AF are rising as population age increases

AF affects over 6 million people in Europe

Lifetime risk of atrial fibrillation

A report of 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

Figure 4. 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 with permission from Go *et al.* 2001.[11]



condition at first examination. The study sample involved 3999 men and 4726 women who were followed from 1968 to 1999.[72] For men and women aged 40 years and older, the remaining lifetime risk of AF developing was found to be 1 in 4. Similar data are available from a European population.[70]

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

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, the remaining lifetime risk of dementia in middle-aged individuals is approximately 1 in 6;[73] for breast cancer, the remaining lifetime risk is 1 in 8 for women aged 40 years.[72]

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. The following chapters will discuss AF as a risk factor for stroke.

Detecting atrial fibrillation and stratifying stroke risk

Key points

- AF is often not detected until a serious complication such as stroke or heart failure develops.
- Routine pulse-taking plays an important role in the detection of AF in at-risk patients.
- A history of stroke in patients with AF increases the likelihood of another stroke threefold.
- Female gender, advanced age, high blood pressure, heart disease and diabetes also increase the risk of stroke in patients with AF.
- Patients in the EU may currently be receiving inconsistent advice and therapy, due to 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 electrocardiogram (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.[63]

Detection and diagnosis of atrial fibrillation

Increased detection and diagnosis of silent AF are therefore imperative, in order to initiate timely and effective treatment and thus prevent many of the complications related to AF, including AF-related stroke. Indeed, the NICE Guidelines in the UK recommend that an ECG should be performed in all patients, whether symptomatic or not, in whom AF is suspected following detection of an irregular pulse.[63] Opportunistic assessment for AF may therefore be prudent, and also realistic, given that 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. Different strategies have been evaluated for detection of AF in people aged 65 years and over, including targeted versus whole population screening.[63]

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

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

population aged 65 years and over, based on a variety of screening strategies.[74] The SAFE study involved 50 primary care practices and almost 15000 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 10000 to systematic or opportunistic screening for 12 months. 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 screening clinic, where pulse rate and a 12-lead ECG were recorded. All patients in the systematic screening arm were invited by letter to attend a screening clinic.

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

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 [$p = 0.027$ for opportunistic vs control arm]). The cost per case detected by systematic screening was £1787 compared with £363 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.[74]

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.[74] Several recommendations are made for future research that could help define further the optimum patient pathway (Table 1).

Table 1. Some of the recommendations for further research, based on the findings of the Screening for AF in the Elderly (SAFE) study.[74]

- How the implementation of a screening programme for atrial fibrillation (AF) influences the uptake and maintenance of anticoagulation therapy in patients aged 65 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 increase further the risk of stroke in patients with AF include:[25,71]

- female gender
- advanced age
- prior stroke or TIA
- high blood pressure
- heart disease, for example, heart failure and valvular heart disease
- diabetes.

Although stroke and AF are both more prevalent in men than in women,[6,75,76] the literature shows that death rate from stroke is increased fourfold in women with AF compared with twofold in men with AF.[77] However, it should be noted that not all studies have demonstrated such a significant difference between the genders.[77,78]

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 is approximately sevenfold higher in patients in their 80s compared with those in their 40s.[79] High blood pressure increases the risk of stroke approximately threefold in patients with AF.[8]

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

In order 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 co-existing 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.[15,80] Some risk stratification systems that are currently widely used are summarized in Table 2. The schemes vary somewhat in the

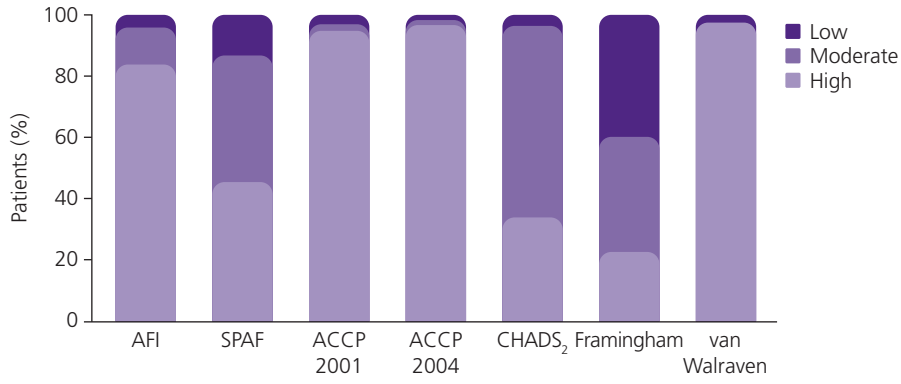
Several models have graded the likelihood of stroke according to widely accepted risk factors

Table 2. Summary of the main systems for stratifying the risk of stroke in patients with atrial fibrillation. Adapted from Lip and Tse 2007[80] and Lip and Lim 2007,[15] with permission from Elsevier.

Reference	Stroke risk strata		
	High	Intermediate	Low
$CHADS_2$[10]*	Score 3–6	Score 1–2	Score 0
ACCP[81]	Prior stroke, TIA or systemic embolic event; age > 75 years; moderate or severely impaired LV function with or without congestive cardiac failure; hypertension or diabetes	Age 65–75 years with no other risk factors	Age < 65 years with no risk factors
NICE/ Birmingham[63]	Previous ischaemic stroke or TIA or thromboembolic event; age ≥ 75 years with hypertension, diabetes or vascular disease; clinical evidence of valve disease or heart failure; impaired LV function on echocardiography	Age ≥ 65 years with no high-risk factors; age < 75 years with hypertension, diabetes or vascular disease	Age < 65 years, with no history of embolism, hypertension, diabetes or other clinical risk factors
ACC/AHA/ESC Guidelines[25]	Prior thromboembolism (stroke, TIA, systemic embolism); valve disease; more than one of: age ≥ 75 years, hypertension, heart failure, impaired LV systolic function; or diabetes mellitus	Age ≥ 75 years; hypertension; heart failure; impaired LV systolic function; or diabetes mellitus	AF (no other 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).
ACC, American College of Cardiology; AF, atrial fibrillation; AHA, American Heart Association; ESC, European Society of Cardiology; ACCP, American College of Chest Physicians; LV, left ventricular; NICE, National Institute for Health and Clinical Excellence; TIA, transient ischaemic attack.

Figure 5. Percentage of patients with atrial fibrillation (enrolled in the SPORTIF III and V trials) classified as being at low, moderate and high risk of stroke, based on the individual risk stratification schemes. The results show that different models predict stroke risk differently. Adapted with permission from Baruch *et al.* 2007.[84]



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

Predictions from risk stratification models are inconsistent, resulting in inequality of advice and therapy across the EU

specific risk factors they incorporate and the methods of scoring and evaluation.

Among patients not receiving anticoagulation therapy, the $CHADS_2$[a] scheme has been found to be a more accurate stroke predictor than two pre-existing schemes (AFI[82,b] and SPAF[83,c]).[10] In patients receiving anticoagulation therapy, three schemes have predicted stroke significantly better than chance: Framingham, $CHADS_2$ and SPAF.[84] 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.[84,85] Few models have addressed the cumulative nature of risk factors, whereby a combination of factors would confer a greater risk than any factor alone.[77]

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 EU may receive inconsistent advice and therapy, depending on local choices.

[a]Scheme produced by the National Registry of Atrial Fibrillation (see Table 2).
[b]Scheme produced by the Atrial Fibrillation Investigators.
[c]Scheme produced by the Stroke Prevention and Atrial Fibrillation III study.

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 following stroke by almost 50%.

Increased severity of stroke

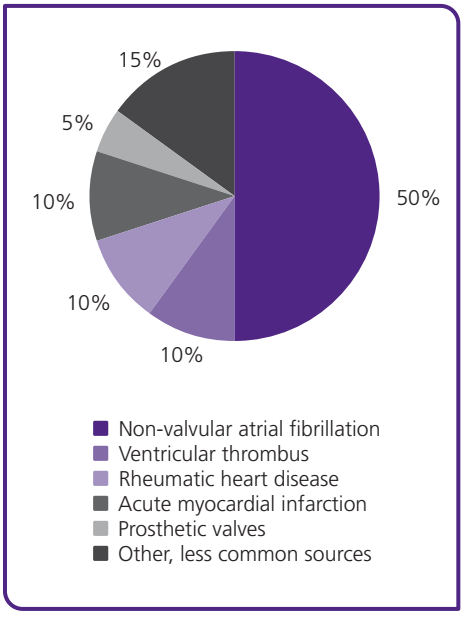
In addition to a high risk of stroke, patients with AF suffer from more severe strokes and have a poorer prognosis after the event than patients without AF.[78] The increased severity of strokes in patients with AF is thought to be because such strokes are predominantly cardioembolic.[78] A cardioembolic stroke is caused by a blood clot in the heart, part of which breaks away and becomes trapped in large arteries in the brain.[78] 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.

A study of more than 500 patients in Germany showed that those who had suffered cardioembolic stroke had more severe clinical deficits on admission, worse recovery on discharge, and increased length of hospital stay than those with non-cardioembolic stroke. Moreover, the mean costs of acute care were higher for cardioembolic stroke (€4890 per patient) than for non-cardioembolic stroke (€3550).[86] In addition to being more severe, cardioembolic strokes are associated with a higher risk of recurrence than other types of stroke.[87] AF is the cause of 50% of cardioembolic strokes (Figure 6).[88]

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

The increased severity of strokes in patients with AF compared with other strokes suggests that these patients will experience a greater impairment in quality of life than patients without AF.

Figure 6. The main cause of cardioembolic stroke is non-valvular atrial fibrillation. Image reprinted with permission from e.Medicine.com.[88]



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

Patients with AF are therefore a key target population for reducing the overall burden of stroke on society.

Increased death rate

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

The death rate from stroke is significantly higher in patients with AF than in those without AF. The Copenhagen Stroke Study was the first study to analyse in detail the characteristics and consequences of stroke in patients with AF compared with those without AF, reporting a 70% increase in death rate in the presence of AF.[78] In a more recent large-scale Italian study of patients who had suffered a first stroke, AF was found to increase the 5-year death rate from stroke almost twofold (Table 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.[9] The Austrian stroke registry also demonstrated an almost doubling of death rate from stroke in the presence, compared with the absence, of AF (25% versus 14%).[89]

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

Table 3. Annual death rates from first stroke (rounded to nearest decimal place) in patients with and without atrial fibrillation (AF). Modified with permission from Marini *et al.* 2005.[9]

	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 last 20 years has been reported,[90] which may reflect the increasing age of the population. With both its prevalence[11] 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.

Increased disability and poor health

AF-related stroke is more severe and is associated with more ill health than stroke unrelated to AF.[9,18,62,78] In the European Stroke Community Project, the presence of AF increased the risk of remaining disabled 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 compared with those without AF, both immediately after the stroke and after rehabilitation.[78] 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.

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

Significant impact on quality of life

The impact of a stroke on an individual's health can be expressed as a utility score. These scores are used to express the impact of a state of health on health-related quality of life on a scale of 0 to 10, where 10 represents perfect health and 0 represents death. Murphy *et al.*[91] found that mild stroke yielded a higher utility score (9/10) than severe stroke (4/10). As AF-related strokes are more severe than strokes in patients without AF, this indicates that AF-related strokes 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.[92]

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.

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

AF also increases the risk of medical complications following stroke. Compared with those without AF, patients with AF suffer more frequently from pneumonia, pulmonary oedema (accumulation of fluid in the lungs) and bleeding in the brain after stroke.[89]

AF increases the risk of medical complications following stroke

Heavy burden on carers, families and society

More than one-third of patients who experience a stroke return to their home with some level of permanent disability.[42] 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

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

Table 4. Outcome of stroke in patients with and without atrial fibrillation (AF). Adapted with permission from Jorgensen *et al.* 1996.[78]

	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)	33 (72)	17 (171)
Discharged to nursing home, % (n)	19 (41)	14 (135)
Discharged to own home, % (n)	48 (104)	69 (662)

Data are presented as mean, rounded to nearest decimal place.
*Scandinavian Stroke Scale.[93]
†Barthel Index.[94]

include mood swings, personality changes, irritability, anxiety, memory loss and depression.[42,95] 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.[42,95]

Case study: a carer's perspective

"For the past 9 months my sister and I have been acting as full-time carers to our mother, who is bedridden following a stroke. She is unable to do anything for herself and needs 24-hour care in her own home, where she feels comfortable and safe. We have had to leave our husbands and our own homes to give mother our full support.

Full-time carers can lose their sense of identity and independence as their social life is curtailed. I am also concerned for my husband's welfare."

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

Case study: a child's perspective

"The first time I saw Daddy again, he was sitting in a wheelchair tied on with a sheet so that he would not fall. His mouth was drooping and he was making funny noises which we could not understand. I was scared of him, I didn't want to see him any more. I was ashamed of him… he does not remember much about it. He doesn't look like Daddy any more."

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.[42,96] 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

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.[97] The total economic cost of stroke is probably even greater than this, as these calculations largely omit costs incurred by the patient and carers, because they may be difficult to capture. In 2006, the total cost of stroke in the whole of Europe, including healthcare costs, productivity costs and informal costs, was calculated to be over €38 billion.[4]

As stroke in patients with AF is more severe than stroke in patients without AF,[78] it is likely to incur greater costs. In a French study, the mean cost of a severe stroke was €34 809 per patient, more than three times higher than the mean cost for a mild stroke (€10 530 per patient).[98] Similarly, in Sweden, the estimated costs for the first year of care after a severe stroke (€8642–58 897) were considerably higher than those for a mild stroke (€6268–19 723).[99]

There is also direct evidence for the increased cost of stroke in patients with AF. In the Berlin Acute Stroke Study, the average direct costs of stroke per patient were significantly higher in patients with AF (€11 799) than in patients without AF (€8817).[32] The effect of AF on stroke-related inpatient costs was also recently analysed over a 3-year period in Sweden.[100] Among stroke survivors, the inpatient costs over this period were on average €818 higher in patients with AF compared with patients without AF (€10 192 versus €9374) after controlling for additional risk factors and death rates. As AF is estimated to be responsible for approximately 15% of all strokes,[58] the increased cost of AF-related strokes compared with other strokes represents a significant economic burden for the EU.

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

Strong rationale for stroke prevention in patients with atrial fibrillation

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

Stroke prevention in patients with atrial fibrillation

Key points

- Direct treatment of AF can help to prevent strokes. Drugs and non-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.
- Currently available anticlotting therapies, such as warfarin and aspirin, are effective in the prevention of AF-related stroke but have significant drawbacks.
- High blood pressure and diabetes, which commonly affect patients with AF, also require management to reduce the risk of stroke.

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

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

Strategies for stabilizing heart rhythm

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

Effective management of AF will in itself prevent stroke. AF is most commonly managed using 'rhythm control' or 'rate control' strategies.[62] 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.[62] 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) and radiofrequency catheter ablation (an invasive procedure used to remove a faulty electrical pathway from the heart).

Anticlotting therapies for preventing stroke

Patients receiving treatment for AF should also receive anticlotting therapy

AF predisposes to the formation of a blood clot, or thrombus, in the heart. Part of the blood clot can break away, forming what is known as an embolus, which can then become trapped in blood vessels in the brain, causing a stroke. Thus, strategies for the prevention of stroke in patients with AF involve the use of anticlotting drug therapy. It is recommended that patients receiving treatment for AF as described above also receive some form of anticlotting therapy (see 'Guidelines for stroke prevention in patients with atrial fibrillation', page 42).[48]

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

- anticoagulants, which interrupt the pathway of chemical reactions that result in the formation of a blood clot (the coagulation pathway; Figure 7)
- antiplatelet drugs, which limit the aggregation 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.

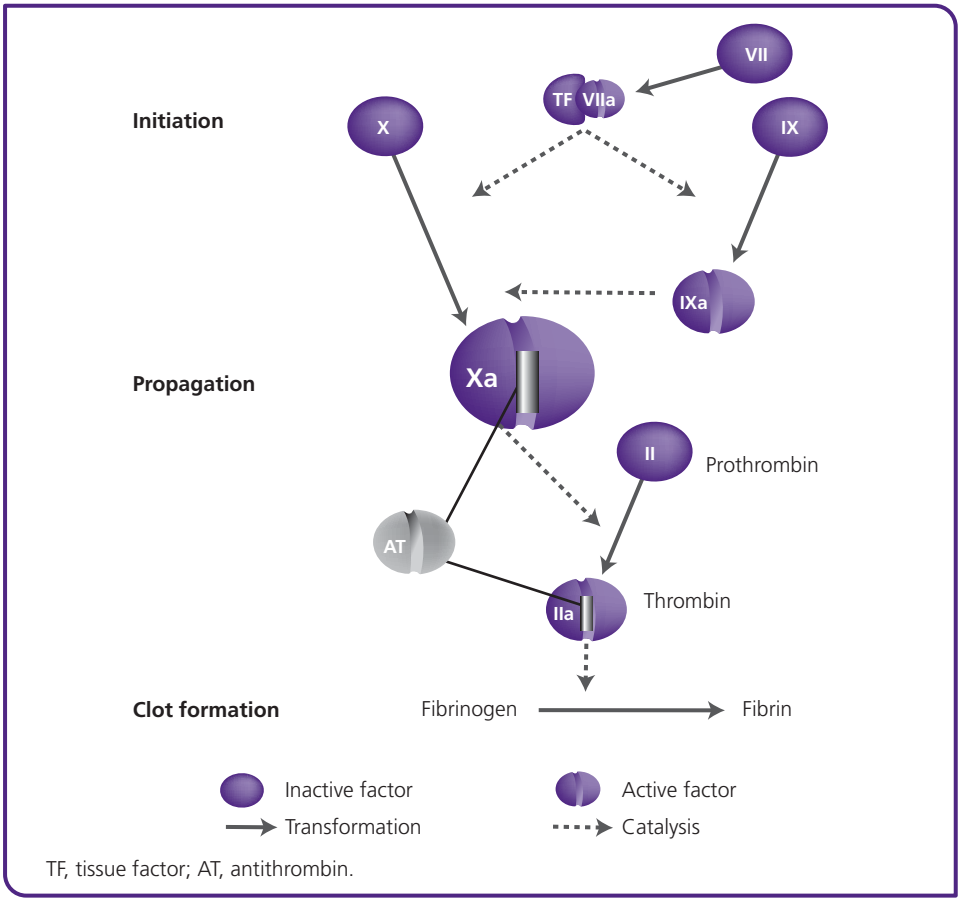
Vitamin K antagonists (VKAs), which are oral anticoagulants, and acetylsalicylic acid (or aspirin), an antiplatelet agent, are currently the most widely used drugs in the prevention of stroke in patients with AF.

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 (Figure 7).[9,19] This pathway is a series of enzyme reactions that 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[101] and interactions with other drugs and food.[20] Furthermore, there is a narrow window between the doses

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

Figure 7. 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.

of VKAs that achieve therapeutic efficacy and the doses that confer 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. 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 international normalized ratio (INR). The use of INR standardizes results by removing differences between laboratories. A target INR range of 2.0–3.0 is typically recommended for patients receiving VKA therapy.[25,54] 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 (Figure 8). If a patient's INR is found to be outside the target range, the dose of the VKA should be adjusted accordingly.

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

VKAs interact with food and other drugs – including amiodarone, an anti-arrhythmic drug used in the treatment of AF.[102] It can therefore be very challenging to maintain the INR within the target range. The resulting need for frequent monitoring and dose adjustment is a significant barrier to effective anticoagulation in everyday practice.

Patient populations in clinical trials may not reflect normal clinical practice

Efficacy of vitamin K antagonists in clinical trials

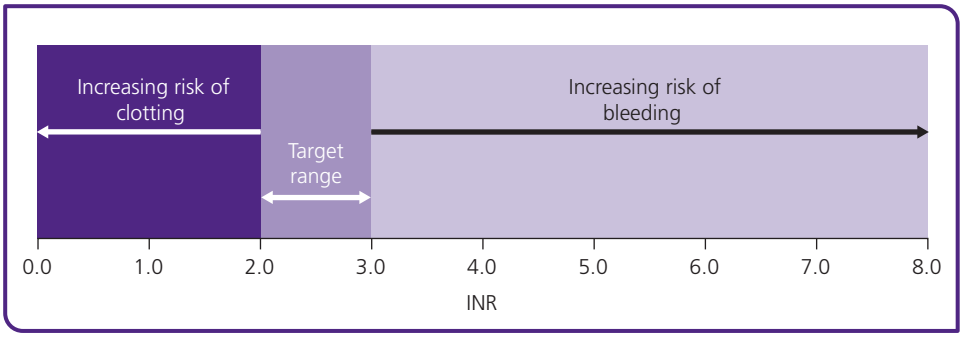
Systematic reviews of clinical trials in patients with AF have shown that, compared with no therapy, warfarin (with close monitoring and dose adjustment if necessary) provides a 62–68% reduction in the risk of stroke (Figure 9) and a 26–33% reduction in death rate[27–29,108] without significantly increasing the risk of major bleeding. The implication is that for every 1000 patients treated with warfarin, 31 ischaemic strokes will be prevented each year.[27]

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.[109,110]

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 risk of bleeding observed with VKAs in the controlled clinical trial setting are not reflective of, and cannot be achieved in, clinical practice.[111] In addition to monitoring highly motivated patients closely, clinical trials often recruit relatively few elderly patients and

Figure 8. The international normalized ratio (INR) should be maintained in the range 2.0–3.0 for patients receiving warfarin. If values fall outside this range, the patient is at increased risk of a blood clot (INR < 2.0) or bleeding (INR > 3.0).



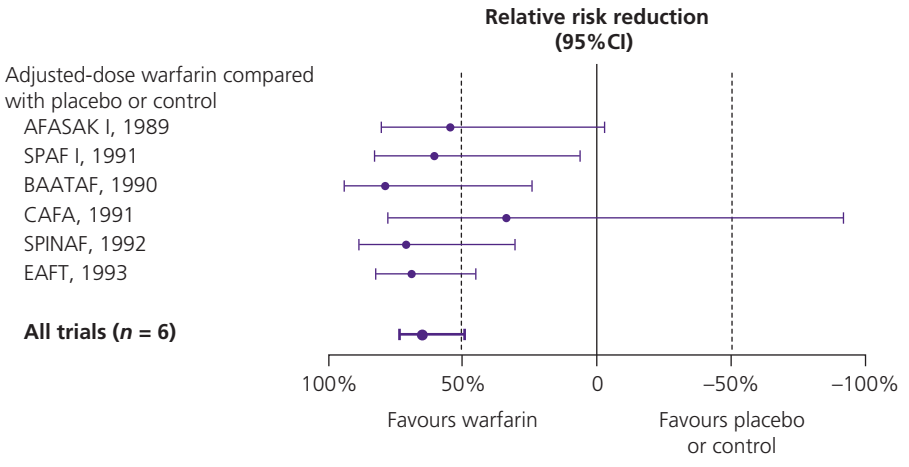
frequently exclude those with a high risk of bleeding.[27,111]

Retrospective studies and cohort studies with an observational design have shed further light on this matter. In a large-scale cohort of more than 11 500 patients with non-valvular AF treated in a clinical practice setting, warfarin provided a 51% reduction in the risk of thromboembolism (formation of a blood clot and then circulation of part of the blood clot in the bloodstream) and a 31% reduction in the risk of death compared with either no therapy or aspirin, after adjusting for potentially confounding factors.[112] Overall, there were 148 cases of ischaemic stroke or other thrombo-embolic events 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.

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

Further investigations in the clinical practice setting in Italy and the UK have demonstrated reductions in the risk of stroke of approximately 26–66% in patients with AF receiving VKAs – including elderly patients – compared with those not receiving VKAs.[113–115] Despite an increased risk of bleeding, the overall rates of ill health and death were significantly lower in patients receiving VKAs than in those not receiving VKAs.[114,115] However, the risk reduction observed in the UK study (26%) was substantially lower than in clinical trials.[114] Furthermore, an analysis of the process and quality of oral anticoagulation use in clinical practice has highlighted major management differences between anticoagulation clinic care and routine medical care, with less time within the therapeutic INR range being achieved in

Figure 9. 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 with permission from Hart *et al.* 2007.[28]



AF, atrial fibrillation; AFASAK I, AF, Aspirin, and Anticoagulation Study;[103] SPAF I, Stroke Prevention in AF study;[83] BAATAF, Boston Area Anticoagulation Trial for AF;[104] CAFA, Canadian AF Anticoagulation Study;[105] SPINAF, Stroke Prevention in Non-rheumatic AF;[106] EAFT, European AF Trial.[107]

Case study: an elderly woman receiving warfarin

Mrs W, a 75-year-old woman, was admitted to hospital with pneumonia. She had AF, and had recently been started on warfarin. On admission, staff should have completed two different drug charts – a separate one being required for warfarin because it needs to be monitored and given as a variable dose. However, the warfarin chart was not completed, resulting in warfarin being omitted for 2 days. Antibiotics which interact with warfarin were subsequently started, causing her INR to rise to 6.0. Mrs W was then found to have an empyema (pus within the lining surrounding the lung), which required her to have a drain inserted into her chest. The high INR put her at risk of bleeding, so this procedure was delayed for 2 days while vitamin K was given to lower the INR. Two weeks later, the drain was taken out, but the medical team did not remember until just before discharge that she needed to be restarted on warfarin. Mrs W was not keen on this, because it would mean frequent trips to the hospital to have her blood taken. The difficulties with monitoring warfarin have unfortunately made Mrs W unwilling to continue taking it, thus putting her at risk of stroke.

Fortunately, the issues with maintaining Mrs W's INR within the correct range did not cause any immediate life-threatening problems in this instance. It would be ideal, however, if an oral anticoagulant existed that required infrequent monitoring, could be given at a fixed daily dose, and was unaffected by changes in diet or other medications.

Efficacy and safety of VKAs may be less favourable in routine medical practice than in clinical trials

routine medical care.[114,116] Thus, the efficacy and safety profiles of VKAs do appear to be somewhat less favourable in routine medical practice than in clinical trials. Overall, however, the benefits still outweigh the risks in the majority of patients.

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

VKAs are therefore currently recommended as first-line therapy in patients with AF and a moderate or high risk of developing stroke.[25,54] This is despite the major drawbacks associated with VKA therapy, which include: 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 give up taking VKAs, Guidelines are not always followed, despite the fact that Guideline-adherent management is associated with improved outcomes.[86] Thus, many patients with AF and a moderate-to-high risk of stroke do not receive anticoagulant therapy and therefore remain unprotected.[37,117] 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 42).

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.[118] 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%).[28] 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.[119,120] 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]

Aspirin is therefore recommended only in patients with a low or moderate risk of stroke and in those with contra-indications to VKA therapy.[25,54] It should be noted, however, that there is some doubt as to the real benefit of aspirin in patients at low risk of stroke.[121,122]

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

In a UK study, the cost of preventing one AF-related stroke per year using VKA therapy was estimated to be £5260, with regular INR monitoring and hospital admissions for bleeding complications being the major cost drivers.[123] The cost of prevention thus appears to be favourable when compared with an average direct per capita cost of €11 799 for treating stroke in the EU (see section on 'High economic cost', page 33).[32] 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 of a stroke over a 10-year period was estimated to be almost fourfold greater than the estimated 10-year direct costs of anticoagulation,[52] 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 a moderate or high risk of stroke when compared with no therapy or aspirin.[77,124] Management of complications following suboptimal anticoagulation is the major driver of cost.[124]

Cost-effectiveness of therapies is often expressed as cost per quality-adjusted life-year (QALY). A QALY is a single measure that represents numerous outcomes affecting quality of life; one year in perfect health is considered to be equal to 1.0 QALY, while one year at anything less than perfect health would be equal to less than 1.0. The expression of cost per QALY saved offers the advantage of allowing comparisons of different interventions in different disease areas. A review of such studies in patients with AF reported that, in the majority of cases, VKA therapy was associated with a low cost per QALY, particularly in patients considered to be at moderate-to-high risk of stroke.[124] In one study, the cost of VKA therapy for patients with non-valvular AF and one additional risk factor for stroke was reported to be $8000 per QALY saved[125] – well below the range of acceptable cost-effectiveness of £20 000–30 000 per QALY established by NICE in the UK.[126] For comparison, the cost of screening adults for high blood pressure is estimated at approximately $8000–45 000 per QALY saved.[127]

Clinical trials have shown VKAs to be significantly superior to aspirin in the prevention of stroke in AF

The cost of preventing stroke in AF compares favourably with the direct cost of treating stroke

It should be noted that the cost-effectiveness of VKA therapy is dependent on achieving a significant reduction in the risk of thrombo-embolism. 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. INR monitoring in clinical

practice may also incur additional costs, to the patient, carer and society, not captured in the cost-effectiveness studies. A study of the cost to society associated with attending anti-coagulation clinics has shown that carers who accompany patients to clinic visits experience a cost of €17 per visit in Portugal and €10 per visit in the UK.[128] Although not all patients in Europe who receive anticoagulation therapy regularly attend anticoag-ulation clinics, in the UK – where the frequency of clinic visits is typically 8–12 per year – this figure would equate to an annual cost to the carer of up to €120.

VKA therapy may be less cost-effective in clinical practice than in clinical trials, because of difficulties in regulating the dose

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

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

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

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

Blood pressure control is particularly important in the management of AF, and uncontrolled blood pressure increases the risk of stroke 2–3-fold.[8,129] 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.[130]

It is therefore clear that conditions that increase the risk of stroke and that co-exist 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 cost-effective in patients with AF and a moderate-to-high risk of stroke. 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 strokes 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 improve further 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 55).

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 recommended in Guidelines only for patients at a low or moderate risk of stroke.
- Although several sets of Guidelines exist for preventing stroke in patients with AF, the recommendations are not universally applied.
- In many parts of Europe, fewer than 60% of at-risk patients receive adequate, Guideline-adherent therapy to prevent blood clots.
- 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

Guidelines endorsed by major societies exist for the prevention of stroke in patients with AF

Several sets of Guidelines exist for the prevention of stroke in patients with AF. Those developed jointly by the American College of Cardiology, the American Heart Association and the European Society of Cardiology (ACC/AHA/ESC)[25] represent American–European consensus Guidelines. The American College of Chest Physicians (ACCP) produces international Guidelines that are regularly updated; the current version (8th edition) was published in 2008.[81] Both the ACC/AHA/ESC and 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.

European guidelines for the prevention of stroke in patients with AF, published by the European Stroke Organisation in 2008,[54] are summarized in Table 6. These have now replaced earlier Guidelines developed by the European Stroke Initiative.[131]

Country-specific Guidelines for stroke prevention in patients with AF exist for several countries in Europe, including the UK,[69] Italy,[132] France[133] and Spain (a Spanish summary[134] is available of the Guidelines by Fuster *et al.* 2006[25]); see Appendix 1 (page 70) for summaries of these Guidelines. The UK Guidelines from NICE deserve special mention, because they are based on systematic reviews and cost-effectiveness analysis, in contrast to the methodology of expert consensus that is used to produce the ACC/AHA/ESC and ACCP Guidelines.[135] No specific Guidelines exist in Germany, but the Germany Cardiology Association recommends treatment as defined by the ACC/AHA/ESC 2006 Guidelines.[25,136]

The Guidelines differ in the specific recommendations that they make regarding stroke prevention in patients

Table 5. Summary of the American College of Chest Physicians (ACCP) 2008 Guidelines (8th edition) and 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.

Guideline	Risk category	Recommendation (robustness)*	Definition of risk factors
ACCP 2008[81]	No risk factor (low risk)	Long-term aspirin, 75–325 mg/day (Grade 1B)	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) (Grade 1A), or aspirin, 75–325 mg/day (Grade 1B) Suggest VKA rather than aspirin (Grade 2A)	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) (Grade 1A)	
	High risk	Long-term oral VKA (e.g. warfarin) (INR 2.0–3.0, target 2.5) (Grade 1A)	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 (Class 1A)	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) (Class 1A)	Moderate-risk factors • Age ≥ 75 years • Hypertension • Heart failure
	Any high-risk factor or ≥ 1 moderate-risk factor	Warfarin (Class 1A)	High-risk factors • Previous stroke, TIA or embolism • Mitral stenosis • Prosthetic heart valve

***Robustness**

Grade 1A: strong recommendation; high-quality consistent evidence from randomized controlled trials, or exceptionally strong evidence from observational studies.
Grade 1B: strong recommendation; moderate-quality evidence from randomized controlled trials with important limitations, or very strong evidence from observational studies.
Grade 2A: weak recommendation; high-quality consistent evidence from randomized controlled trials, or exceptionally strong evidence from observational studies.
Class 1 recommendation : evidence and/or general agreement that procedure/therapy is beneficial, useful and effective.
Level of evidence A: based on multiple randomized trials or meta-analyses.

INR, international normalized ratio; TIA, transient ischaemic attack; VKAs, vitamin K antagonists.

with AF; however, generally there is Guideline agreement that patients at low risk of stroke should receive aspirin therapy, those at moderate risk should receive aspirin or oral anticoagulant therapy (i.e. VKAs) and those at high risk should receive therapy with oral anticoagulants.

Guidelines: theory versus practice

Despite the existence of several sets of international, European and country-specific Guidelines for the prevention of stroke in patients with AF, their application varies greatly, and VKA therapy is often underused.[137] In some

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

Table 6. Summary of Europe-wide Guideline for the prevention of stroke in patients with atrial fibrillation.

Guideline	Risk category	Recommendation	Robustness
European Stroke Organisation[54]	Patients unable to receive anticoagulants	Aspirin (Class IA)	Class I evidence: adequately powered, prospective, blinded, randomized controlled trials or systematic review of randomized controlled trials Class II evidence: prospective, matched group, cohort study or randomized controlled trial with one design flaw Level of recommendation A: requires ≥ one class I study or ≥ two class II studies
	Patients < 65 years of age and free of vascular risk factors	Aspirin (Class IA)	
	Patients aged 65–75 years and free of vascular risk factors, unless contraindicated	Aspirin or an oral anti-coagulant (INR 2.0–3.0) (Class IA)	
	Patients aged > 75 years or who are younger with risk factors such as high blood pressure, left ventricular dysfunction or diabetes mellitus	Oral anticoagulant (INR 2.0–3.0) (Class IA)	

INR, international normalized ratio.

There is discrepancy between Guideline recommendations and clinical practice

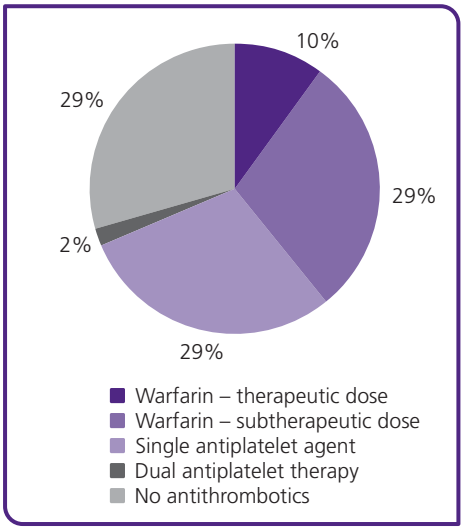
cases, patients eligible for VKA therapy may receive aspirin therapy instead, or the dose of VKA may be outside the recommended range (Figure 10).[16] For example, a questionnaire was used to examine the 'theoretical' adherence of Swedish physicians to European and Swedish Guidelines for the prevention of stroke in patients with AF.[117] Of 498 physicians who responded to the questionnaire, more than 94% stated that patients at risk of blood clots and chronic AF should receive long-term VKA therapy. In the same study, the records of 200 consecutive patients hospitalized for acute AF were evaluated to determine 'actual' adherence to Guidelines. In total, 108 patients had chronic AF with one or more risk factor for stroke, and no contraindications to warfarin; however, only 40% of these patients received VKA therapy.[117] This study highlights the discrepancy that is often found between Guidelines (i.e. the theory of stroke prevention in patients with AF) and what happens in clinical practice.

Similarly, in a study conducted in seven European countries, only 8.4% of patients with AF who had a stroke were receiving anticoagulants at the time of their stroke, and the proportion decreased by 4% per year with increasing age.[18]

It is worth noting that not all studies into the use of VKAs in patients with AF indicate that they are under-used.[138–141] 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.[17] According to recent surveys in different parts of Europe, the proportion of patients with AF at high risk of stroke who are receiving adequate anticoagulation is around 54–61%,[36,37] but can rise to 71% or as high as 88% in settings where Guidelines are being more successfully applied in the real world.[38,39]

Data from the Euro Heart Survey were analysed to assess the consequences of deviating from current Guidelines on VKA use in patients with AF. Underuse of anticoagulant therapy in patients

Figure 10. 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 with permission from Gladstone *et al.* 2009.[16]



with AF and a high risk of stroke was associated with a significantly greater risk of thromboembolism during the 1-year study period, while overtreatment was not associated with a significantly higher risk of bleeding.[37]

Reasons for poor adherence to Guidelines

Adherence to Guidelines for the prevention of stroke in patients with AF may be low for several reasons. These include difficulties in maintaining INR within the therapeutic range (see section on 'Anticlotting therapies for preventing stroke', page 34)[20] and physicians' concerns about bleeding risk, particularly in the elderly.[35]

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

A multicentre, observational study in Germany showed that patients with AF who were receiving VKAs were within the target INR range (defined in Guidelines as 2.0–3.0) 56% of the time, above it 30% of the time (leading to an increased risk of bleeding) and below it 14% of the time (leading to an increased risk of a blood clot).[141]

Many patients find the frequent monitoring and necessary dose adjustments associated with VKAs inconvenient and time consuming, and may miss appointments. 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.[142] The greater the length of time that a patient's INR is within the target range, the lower their risk of a blood clot or of uncontrolled bleeding.

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

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 thrombo-embolism and stroke; conversely, they may underestimate the bleeding risk of aspirin therapy and overestimate its benefits.[34,35,143] As a result, some eligible patients are not receiving optimum therapy that could prevent strokes.[16] 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 per day. Furthermore, since elderly patients are particularly prone to falls, there is a fear among physicians that elderly patients who fall may suffer a severe haemorrhage if they are taking VKA therapy.[144–146] However, evidence has shown that, in patients with AF who are receiving anticoagulant agents, the risk of a cerebral bleed from falling is so

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

small that the benefits of treatment outweigh the risk.[147] Furthermore, the incidence of stroke among patients aged 75 years or more with AF is lower in those who are receiving VKA therapy than in those taking aspirin, without increasing the risk of haemorrhage.[120]

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

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.[148] In contrast, having a patient who experienced an ischaemic stroke while not receiving VKA therapy did not influence a physician's prescribing behaviour towards subsequent patients.[148] 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.

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

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.[149] Major bleeding events related to anticoagulation are dramatic and therefore easily remembered and may lead to reductions in VKA prescribing. Secondly, Feinstein's 'chagrin factor' postulates that, when choosing between alternatives, physicians avoid those actions that cause them the most regret.[150] 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'.[148]

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.[151] In order for VKA therapy to be justified, physicians considered that it needed to prevent a significantly higher number of strokes than patients felt acceptable (Table 7). The number of strokes that needed to be prevented to justify aspirin therapy did not differ significantly between patients and physicians.

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 7). Moreover, the results suggest that physicians perceive the risk of bleeding to be higher with VKAs than with aspirin. This perception is at variance with the findings by Mant *et al.* that warfarin decreases stroke risk without increasing the risk of bleeding.[120]

These results indicate that patients place more value than physicians do on the avoidance of stroke, and less

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

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 ± 10.3	10.3 ± 6.1	$p < 0.001$
Aspirin	14.7 ± 6.7	6.7 ± 6.2	$p < 0.001$

NS, not significant. SD, standard deviation.

value on the avoidance of bleeding.[151] It is important that the views of the individual patient are taken into account when assessing whether to use anticoagulant therapy, even if the physician is risk averse.

To summarize, adherence to Guidelines for the prevention of stroke in patients with AF is often suboptimal, largely because of the drawbacks associated with VKA therapy and a lack of physician and patient education regarding the benefit-to-risk ratio of therapy. There is a clear need for improvements in adherence to Guidelines across Europe.

Current challenges for stroke prevention in patients with atrial fibrillation

Key points

An EU-wide commitment to reducing AF-related stroke is needed to:

- coordinate strategies for early and adequate diagnosis of AF, and promote the development of relevant research programmes
- raise awareness and understanding of AF and AF-related stroke among patients and carers
- 'empower' patients and carers to take more active roles in determining and evaluating their care
- encourage the uptake and use of new therapies and procedures
- improve knowledge and awareness among physicians involved in AF management
- optimize the continuum of care for all patients with AF
- provide equity of access to AF therapy, and information for all patients across the EU
- promote 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 below.

Improved detection and diagnosis of atrial fibrillation

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

Awareness of the early signs of AF and common co-existing 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. There may be scope for introducing more widespread AF screening programmes, following the positive results of the SAFE study.[74] 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.[74] These need to be followed up and acted upon.

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. The patient organization, AntiCoagulation Europe, has conducted a survey as part of the *It's about time* campaign,[152] which aims to provide insights into patients' experiences of their treatment with VKAs. The survey reveals a lack of awareness among patients about the potential interactions of VKAs with both over-the-counter medication and herbal remedies. Furthermore, one-quarter of patients did not remember receiving any information on AF at their diagnosis, and over one-third felt that their doctor could have told them more regarding their medication and how it would affect their lifestyle.[152]

Similarly, a study of 119 patients with AF in the UK showed that 37% were unaware of their specific heart condition and 48% did not know the reasons for commencing VKA therapy.[153] Approximately two-thirds of the 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 cross-sectional questionnaire in a wider, multi-ethnic population receiving anticoagulation therapy has also revealed gaps in the knowledge of patients from ethnic minorities and deficiencies in the provision of patient information.[154]

Better adherence to therapy

According to AntiCoagulation Europe, adherence to therapy is reliant on patients' 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.[152]

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

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.[155] Indeed, patient education and involvement in the management of VKA therapy has been shown to reduce the risk of major bleeding.[156] Thus, patient information should help to empower patients by being consistent and available in formats appropriate for all affected, including people with different native languages and different levels of literacy.

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

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

Patient 'empowerment' is associated with improved clinical outcomes

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

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 found that 68% of patients with chronic AF would be interested in new anticoagulation drugs for which routine monitoring was not needed.[157] Progress in this area is discussed in more detail in the chapter 'New developments for stroke prevention in patients with atrial fibrillation' (page 55).

Improved knowledge and awareness among healthcare professionals

Benefits of current treatments to prevent stroke

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

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

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

Healthcare professionals should be convinced of the importance of communicating the benefits and risks of potential therapy to patients. There is a significant amount of information for patients to absorb in one consultation with the physician. Therefore, written information needs to be provided, critical facts and advice repeated and the patients' full understanding confirmed during future consultations. In addition, communication between different healthcare professionals interacting with the patient needs to be improved to ensure that consistent information and advice is provided. If the patient is overwhelmed by too much information and/or contradictory opinions, they are unlikely to agree to, and subsequently adhere to, therapy.

Management of patients receiving VKAs

There is a clear need for a proper infrastructure for the delivery and monitoring of VKAs across all the countries of Europe 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.[158] 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.[159] 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.[159]

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,[158] 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.[116,160] However, access to anticoagulation clinics varies across Europe and delivery of VKA therapy differs from country to country.

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.[158] Therefore, healthcare providers may need education and support in ensuring a seamless transition between the different strands in the patient pathway. As management of patients receiving anticoagulants evolves, anticoagulation clinics will change and adapt.[158] The staff who run them may have an increasing role as educators and coordinators of anticoagulation therapy, providing support for other healthcare providers.

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.[161,162] A study in Germany has also shown self-management to be cost-effective.[163] However, this approach may not be appropriate for all patients; therefore, adequately trained physicians will be needed for support in order for self-management to be successful.[164]

Computer programs that analyse several variables and recommend the level of adjustment of the VKA dose, if required, have been developed to assist in management. Such computer programs have been shown to perform as well as staff in anticoagulation clinics, and may therefore be a useful tool for optimizing care.[165,166] 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.

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.

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.[167] Although a patient-centred approach is widely advocated, it is not always implemented.[167] Instead, health care is typically centred on treating the disorder, rather than considering patients' individual needs.[167,168] There is evidence that anticlotting therapy tailored to patients' preferences is more cost-effective in terms of QALYs than giving the same therapy to every patient.[169] There is therefore a need to provide physicians with further education on the benefits of patient-centred care and with support in implementing this approach locally.

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

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

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. As the provision of health care often involves several different service providers, continuity of care is defined as 'coherent health care with a seamless transition over time between various providers in different settings'.[170]

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

Biem *et al.* have described seven characteristics (the seven Cs) of optimal continuity of care.[170]

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.[171,172] Comprehensive, timely and appropriate discharge information is essential – possibly in some portable format[173] – so that the primary care practice has all it needs for appropriate follow-up care. Insufficient discharge information can contribute to hospital readmission.[174] 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 study opposite.

Equity of access to health care and information

European Patients' Forum – a reference point for decision makers

The European Patients' Forum (EPF) is the umbrella organization of pan-European patient organizations active in the field of public health and health advocacy. The EPF has been set up to coordinate the views of patients, as external stakeholders in the European healthcare debate, via a broad, truly representative and independent patient group resource. The aim is to become the natural first point of reference for the European Commission and other European institutions when seeking the opinions of patients and/or when consulting patient groups.[175]

According to the EPF, current healthcare systems can be unfair and divisive and fail to put the patients' perspective first.[176] There are significant differences across EU Member States on how health literacy is perceived and prioritized.[177]

Exchange of information – a benchmark for management

An example from another area of medicine illustrates how best practice can be exchanged between Member

Case study: the importance of continuity of care

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

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

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

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

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

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

Case study adapted from Biem *et al.* 2003[170]

States. 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.[178] The way in which MS is managed varies across Europe; hence, the EMSP has set up an 'MS barometer' to record the experiences of patients with MS with regard to health care and quality of life and to allow comparisons of these experiences across Europe. The aim is to identify which aspects of the disease are well managed and in which countries, as well as in what areas healthcare providers need to improve their policies and practices.

In addition to providing patients with information, an equivalent organization for AF could serve to collate and compare data from different countries in Europe, potentially identifying successes and benchmarks for management and helping to drive improvements where necessary.

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

Equal access for all

In addition to variations in care among countries in the EU, people of different ethnic backgrounds may have different

The EPF calls for equal and timely access to quality health care and better information for all patients

access to health care, or their perceptions of the health care they receive may differ. It has been demonstrated that cultural beliefs can influence individuals' ideas about illness.[179]

The EPF believes that all patients within the EU have a basic right to equal access to quality medical treatment, regardless of where they live, their status or their income. The EPF manifesto calls for equal and timely access to safe, effective diagnosis, treatments and support, better information and resources for patients to be partners in determining their care, and for patients' voices to be heard in Brussels and throughout the EU.[176]

Collaborative approach to Guideline development

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

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 and may thereby increase adherence.[35,180] Furthermore, there is a rationale for providing standardized Guidelines for the whole of Europe, as 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%.[181] Guidelines also need to be easy to follow and readily available to all relevant healthcare professionals.

Summary of current challenges

In summary, numerous challenges remain in the prevention of stroke in patients with AF. 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 are in the final stages of development for 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 34). These limitations have led to an ongoing search for alternative effective and convenient therapies. In addition, there have been developments in anti-arrhythmic drugs used to treat AF. These developments are discussed in more detail below.

Anticoagulant agents

The characteristics of an ideal anticoagulant for long-term use in a chronic condition such as AF include:[182]

- effectiveness
- a wide therapeutic window (i.e. a wide separation between doses that reduce the risk of a blood clot and those that substantially increase 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.

The search for new anticoagulants has therefore focused on compounds that meet more of the criteria for an ideal anticoagulant. Several new oral anticoagulants are in development: relevant phase III trials (large, late-stage

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

New oral anticoagulants are in advanced stages of clinical development

studies) of these drugs that are listed on the global clinical trials registry, www.clinicaltrials.gov, are shown in Appendix 2 (page 72). In the coagulation pathway (Figure 7, page 35) there are many potential targets for new anticoagulant agents. The agents that are currently most advanced in their development target single proteins in the coagulation pathway (factor Xa and thrombin).[182] Those agents in phase III development or recently licensed are discussed below.

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.[183] Inhibition of factor Xa should achieve effective anticoagulation by inhibiting thrombin generation, while allowing existing thrombin to continue its vital role in blood clotting.[183] Oral direct inhibitors of factor Xa include rivaroxaban, apixaban and edoxaban. The only direct factor Xa inhibitor currently approved by the European Medicines Agency (EMEA) is rivaroxaban,[184] which is licensed for short-term use for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery. It is taken orally once daily at a fixed dose. Unlike VKAs, rivaroxaban has a wide therapeutic window and does not require routine monitoring. Studies of oral direct factor Xa inhibitors are under way in stroke prevention in patients with AF and a range of additional indications.

Rivaroxaban

Phase II studies of rivaroxaban for the treatment and secondary prevention of VTE have been completed. These studies of VTE treatment also served as dose-finding for phase III studies into stroke prevention in patients with AF. ROCKET-AF is a randomized, double-blind study to compare the efficacy and safety of rivaroxaban 20 mg once daily with warfarin for the prevention of stroke in approximately 14000 patients with AF.[182,185] In this study, patients with moderate renal impairment (creatinine clearance 30–49 mL/min) will receive a fixed oral dose of rivaroxaban of 15 mg once daily.[182,185] Results are expected in 2010.

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.[182,185] Another phase III study (AVERROES) is investigating whether apixaban is more effective than aspirin in preventing stroke in patients with AF (Appendix 2, page 72).[185]

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.[186] 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.[185]

Indirect factor Xa inhibitors

Biotinylated idraparinux is an indirect inhibitor of factor Xa that acts via antithrombin (Figure 7, page 35). Unlike the direct factor Xa inhibitors in development, biotinylated idraparinux must be administered by subcutaneous injection.[182] A phase III study (BOREALIS-AF) is ongoing to evaluate whether biotinylated idraparinux,

administered subcutaneously once a week, is at least as effective as warfarin for the prevention of stroke and systemic thromboembolic events in patients with AF.[185]

Oral direct thrombin inhibitors

Dabigatran etexilate is an oral direct thrombin inhibitor. This class of drug blocks the conversion of fibrinogen to fibrin in the coagulation pathway. Dabigatran has been approved by the EMEA for short-term use for the prevention of VTE in adult patients undergoing elective hip or knee replacement surgery.[187] A phase III randomized, non-inferiority study, RE-LY, 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 18000 patients with AF and at risk of stroke were enrolled in this study and followed up for a median of 2 years. At a dose of 110 mg twice daily, dabigatran was associated with a similar rate of stroke and systemic embolism to dose-adjusted warfarin and a significantly lower rate of major bleeding than warfarin.[188] 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. Further studies of dabigatran and other direct thrombin inhibitors are ongoing.

Other anticoagulants

There are several other anticoagulants in earlier stages of development.[185] Agents currently 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.[185,189] An inhibitor of vitamin K epoxide reductase known as ATI-5923 (tecarfarin) is also being studied in phase II trials.[185]

Indirect factor Xa inhibitors act via antithrombin and are administered subcutaneously

Antiplatelet agents

Clopidogrel is an inhibitor of platelet aggregation. Reduced platelet aggregation reduces the risk of a blood clot forming and helps to prevent another heart attack or stroke. Clopidogrel is currently indicated for the prevention of atherothrombotic events in patients suffering from heart attack, ischaemic stroke or established peripheral arterial disease and in patients suffering from acute coronary syndrome.[190] Studies are under way to assess the efficacy and safety of clopidogrel for stroke prevention in patients with AF.[185]
A recent clinical study (the ACTIVE-A trial) has 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 with AF ($p < 0.001$) but was also associated with a significantly greater rate of major bleeding ($p < 0.001$).[191]

Several other anticoagulants are in development

Other antiplatelet agents are in phase III clinical trials (ticagrelor) or have recently been approved for clinical use (prasugrel).[192] However, there are no data on the use of these drugs for the prevention of stroke in patients with AF.[185]

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

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.[192]

Alternative strategies in development

Current strategies are focused on reducing thromboembolic risk with drugs that target the process of clot formation. However, other strategies are emerging for stroke prevention in patients with AF. These include: management of AF itself through the use of drugs to control heart rhythm and/or rate; non-pharmacological methods that control rhythm and/or rate or prevent blood clots reaching the brain; and surgical interventions to reduce thromboembolic risk.[62]

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

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 being developed for the treatment of patients with AF. 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.[193] 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.[194]

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.[62] 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)
- radiofrequency 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).

The existing data suggest that catheter ablation is more effective than anti-arrhythmic drug therapy in maintaining normal heart rhythm.[195] Whether this intervention results in fewer AF-related strokes requires testing in clinical trials.

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

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).[62] 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 stroke.[196,197] One of these devices has recently received approval for use in Europe.[197] The results of a recently published trial assessing the efficacy and safety of another such

device suggest that it has limitations, and may not provide an adequate alternative to warfarin in patients with non-valvular AF.[198,199]

Next steps

To summarize, there are several pharmacological agents in development 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 from real-life registries. A number of registries of AF patients are in existence, most of which are country specific or focused on North America. Existing registries vary in size, the German Competence Network on Atrial Fibrillation being one of the larger groups, with over 9600 patients.[200]

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) will prospectively follow 50 000 patients newly diagnosed with AF and 5000 patients with previously diagnosed AF – all eligible for long-term anticoagulant therapy – over 6 years.[201] Patients will be included and followed, regardless of whether or not they receive appropriate therapy. The GARFIELD registry will document 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.[202]

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.

References

1. World Health Organization. The global burden of disease: 2004 update. http://www.who.int/healthinfo/global_burden_disease/2004_report_update/en/index.html. Accessed March 2009
2. Wolfe CD. The impact of stroke. *Br Med Bull* 2000;56:275–86
3. White CL, Poissant L, Cote-LeBlanc G *et al*. Long-term caregiving after stroke: the impact on caregivers' quality of life. *J Neurosci Nurs* 2006;38:354–60
4. Allender S, Scarborough P, Peto V *et al*. European Cardiovascular Disease Statistics 2008 Edition. http://www.heartstats.org/uploads/documents%5Cproof30NOV2007.pdf. Accessed March 2009
5. Boyle P, Ferlay J. Cancer incidence and mortality in Europe, 2004. *Ann Oncol* 2005;16:481–8
6. Truelsen T, Piechowski-Jozwiak B, Bonita R *et al*. Stroke incidence and prevalence in Europe: a review of available data. *Eur J Neurol* 2006;13:581–98
7. Kannel WB, Benjamin EJ. Status of the epidemiology of atrial fibrillation. *Med Clin North Am* 2008;92:17–40
8. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991;22:983–8
9. Marini C, De Santis F, Sacco S *et al*. Contribution of atrial fibrillation to incidence and outcome of ischemic stroke: results from a population-based study. *Stroke* 2005;36:1115–19
10. Gage BF, Waterman AD, Shannon W *et al*. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001;285:2864–70
11. Go AS, Hylek EM, Phillips KA *et al*. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA* 2001;285:2370–5
12. Miyasaka Y, Barnes ME, Gersh BJ *et al*. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation* 2006;114:119–25
13. Briffa T, Hickling S, Knuiman M *et al*. Long term survival after evidence based treatment of acute myocardial infarction and revascularisation: follow-up of population based Perth MONICA cohort, 1984–2005. *BMJ* 2009;338:b36
14. Health-EU: Cardiovascular diseases. http://ec.europa.eu/health-eu/health_problems/cardiovascular_diseases/index_en.htm. Accessed April 2009
15. Lip GY, Lim HS. Atrial fibrillation and stroke prevention. *Lancet Neurol* 2007;6:981–93
16. Gladstone DJ, Bui E, Fang J *et al*. Potentially preventable strokes in high-risk patients with atrial fibrillation who are not adequately anticoagulated. *Stroke* 2009;40:235–40
17. Bungard TJ, Ghali WA, Teo KK *et al*. Why do patients with atrial fibrillation not receive warfarin? *Arch Intern Med* 2000;160:41–6
18. Lamassa M, Di Carlo A, Pracucci G *et al*. Characteristics, outcome, and care of stroke associated with atrial fibrillation in Europe: data from a multicenter multinational hospital-based registry (The European Community Stroke Project). *Stroke* 2001;32:392–8
19. Hirsh J, Dalen J, Anderson DR *et al*. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. *Chest* 2001;119:8S–21S
20. Turpie AG. Warfarin replacements: Mechanisms underlying emerging agents. *Can J Cardiol* 2008;24 Suppl C:56–60C

21. Aspirin for the prevention of cardiovascular disease: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2009;150:396–404

22. Dorsch MP, Lee JS, Lynch DR *et al*. Aspirin resistance in patients with stable coronary artery disease with and without a history of myocardial infarction. *Ann Pharmacother* 2007;41:737–41

23. Patel D, Moonis M. Clinical implications of aspirin resistance. *Expert Rev Cardiovasc Ther* 2007; 5:969–75

24. Palikhe NS, Kim SH, Park HS. What do we know about the genetics of aspirin intolerance? *J Clin Pharm Ther* 2008; 33:465–72

25. Fuster V, Ryden LE, Cannom DS *et al*. ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation* 2006;114:e257–354

26. Kirchhof P, Auricchio A, Bax J *et al*. Outcome parameters for trials in atrial fibrillation: recommendations from a consensus conference organized by the German Atrial Fibrillation Competence NETwork and the European Heart Rhythm Association. *Europace* 2007;9:1006–23

27. Singer DE, Albers GW, Dalen JE *et al*. Antithrombotic therapy in atrial fibrillation: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;126:429S–56S

28. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;146:857–67

29. Hart RG, Benavente O, McBride R *et al*. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med* 1999;131:492–501

30. Commission of the European Communities. White paper: Together for Health: A Strategic Approach for the EU 2008–2013. http://ec.europa.eu/health/ph_overview/Documents/strategy_wp_en.pdf. Accessed April 2009

31. Du X, McNamee R, Cruickshank K. Stroke risk from multiple risk factors combined with hypertension: a primary care based case-control study in a defined population of northwest England. *Ann Epidemiol* 2000;10: 380–8

32. Bruggenjurgen B, Rossnagel K, Roll S *et al*. The impact of atrial fibrillation on the cost of stroke: the Berlin acute stroke study. *Value Health* 2007;10: 137–43

33. Kirchhof P, Bax J, Blomstrom-Lundquist C *et al*. Early and comprehensive management of atrial fibrillation: executive summary of the proceedings from the 2nd AFNET-EHRA consensus conference 'research perspectives in AF'. *Eur Heart J* 2009;doi:10.1093/eurheartj/ehp235

34. Man-Son-Hing M, Laupacis A. Anticoagulant-related bleeding in older persons with atrial fibrillation: physicians' fears often unfounded. *Arch Intern Med* 2003;163:1580–6

35. Bungard TJ, Ghali WA, McAlister FA *et al*. Physicians' perceptions of the benefits and risks of warfarin for patients with nonvalvular atrial fibrillation. *CMAJ* 2001;165:301–2

36. Friberg L, Hammar N, Ringh M *et al*. Stroke prophylaxis in atrial fibrillation: who gets it and who does not? Report from the Stockholm Cohort-study on Atrial Fibrillation (SCAF-study). *Eur Heart J* 2006;27: 1954–64

37. Nieuwlaat R, Olsson SB, Lip GY *et al*. Guideline-adherent antithrombotic treatment is associated with improved outcomes compared with under-treatment in high-risk patients with atrial fibrillation. The Euro Heart Survey on Atrial Fibrillation. *Am Heart J* 2007; 153:1006–12

38. Nabauer M, Gerth A, Limbourg T *et al*. The Registry of the German Competence NETwork on Atrial

Fibrillation: patient characteristics and initial management. *Europace* 2009;11:423–34

39. Meiltz A, Zimmermann M, Urban P *et al*. Atrial fibrillation management by practice cardiologists: a prospective survey on the adherence to guidelines in the real world. *Europace* 2008; 10:674–80

40. Commission of the European Communities. Proposal for a council recommendation on patient safety, including the prevention and control of healthcare associated infections. http://ec.europa.eu/health/ph_systems/docs/patient_rec2008_en.pdf. Accessed May 2009

41. Commission of the European Communities. Communication from the commission to the European Parliament and the Council on patient safety, including the prevention and control of healthcare-associated infections. http://ec.europa.eu/health/ph_systems/docs/patient_com2008_en.pdf. Accessed May 2009

42. Wolfe CD, Rudd AG. The Burden of Stroke White Paper: Raising awareness of the global toll of stroke-related disability and death. http://www.safestroke.org/Portals/10/FINAL%20Burden%20of%20Stroke.pdf. Accessed March 2009

43. Easton JD, Saver JL, Albers GW *et al*. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. *Stroke* 2009;40:2276–93

44. Chandratheva A, Mehta Z, Geraghty OC *et al*. Population-based study of risk and predictors of stroke in the first few hours after a TIA. *Neurology* 2009;72:1941–7

45. Daniel K, Wolfe CD, Busch MA *et al*. What are the social consequences of stroke for working-aged adults? A systematic review. *Stroke* 2009;40: e431–40

46. Bevan H, Sharma K, Bradley W. Stroke in young adults. *Stroke* 1990;21: 382–6

47. Gunarathne A, Patel JV, Gammon B *et al*. Ischemic stroke in South Asians. A review of the epidemiology, pathophysiology, and ethnicity-related clinical features. *Stroke* 2009;40;e415–23

48. Death rates from stroke, adults aged 65 to 74, 1969 to 2006, England. http://www.heartstats.org/temp/Figsp1.1fspweb08.xls. Accessed March 2009

49. Kappelle LJ, Adams HP Jr, Heffner ML *et al*. Prognosis of young adults with ischemic stroke. A long-term follow-up study assessing recurrent vascular events and functional outcome in the Iowa Registry of Stroke in Young Adults. *Stroke* 1994;25:1360–5

50. Mayo NE, Wood-Dauphinee S, Ahmed S *et al*. Disablement following stroke. *Disabil Rehabil* 1999;21: 258–68

51. Asplund K, Marké L-A, Terént A *et al*. Costs and gains in stroke prevention: European perspective. *Cerebrovasc Dis* 1993;3 (Suppl 1):34–42

52. Lightowlers S, McGuire A. Cost-effectiveness of anticoagulation in nonrheumatic atrial fibrillation in the primary prevention of ischemic stroke. *Stroke* 1998;29:1827–32

53. Kannel WB, Wolf PA, Benjamin EJ *et al*. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. *Am J Cardiol* 1998; 82:2N–9N

54. Ringleb PA, Bousser MG, Ford GA *et al*. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis* 2008;25:457–507

55. Kjellstrom T, Norrving B, Shatchkute A. Helsingborg Declaration 2006 on European stroke strategies. *Cerebrovasc Dis* 2007; 23:231–41

56. World Health Organization. The atlas of heart disease and stroke. http://www.who.int/cardiovascular_diseases/resources/atlas/en/. Accessed March 2009

57. Marmot MG, Poulter NR. Primary prevention of stroke. *Lancet* 1992; 339:344–7

58. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham Study. *Arch Intern Med* 1987;147:1561–4

59. Hart RG, Pearce LA. Current status of stroke risk stratification in patients with atrial fibrillation. *Stroke* 2009; 40:2607–10

60. NHS choices. Atrial fibrillation: introduction. http://www.nhs.uk/conditions/Atrial-fibrillation. Accessed March 2009

61. Lip GY, Beevers DG, Singh SP *et al*. ABC of atrial fibrillation. Aetiology, pathophysiology, and clinical features. *BMJ* 1995;311:1425–8

62. Iqbal MB, Taneja AK, Lip GY *et al*. Recent developments in atrial fibrillation. *BMJ* 2005;330:238–43

63. Royal College of Physicians. Atrial fibrillation. National clinical guideline for management in primary and secondary care. National Collaborating Centre for Chronic Conditions. http://www.nice.org.uk/nicemedia/pdf/cg036fullguideline.pdf. Accessed March 2009

64. Gudbjartsson DF, Arnar DO, Helgadottir A *et al*. Variants conferring risk of atrial fibrillation on chromosome 4q25. *Nature* 2007;448:353–7

65. Aizer A, Gaziano JM, Cook NR *et al*. Relation of vigorous exercise to risk of atrial fibrillation. *Am J Cardiol* 2009; 103:1572–7

66. Farrar MW, Bogart DB, Chapman SS *et al*. Atrial fibrillation in athletes. *Mo Med* 2006;103:297–301

67. National Institute for Health and Clinical Excellence. Understanding NICE guidance: Atrial fibrillation. http://www.nice.org.uk/nicemedia/pdf/CG036publicinfo.pdf. Accessed May 2009

68. AF AWARE. AF AWARE cardiology groups call for greater awareness and better education on atrial fibrillation. Press release 2009. http://www.world-heart-federation.org/press/press-releases/news-details/article/af-aware-cardiology-groups-call-for-greater-awareness-and-better-education-on-atrial-fibrillation/. Accessed 16 June 2009

69. National Institute for Health and Clinical Excellence. Guideline 36 – Atrial fibrillation: the management of atrial fibrillation. http://www.nice.org.uk/nicemedia/pdf/CG036niceguideline.pdf. Accessed March 2009

70. Heeringa J, van der Kuip DA, Hofman A *et al*. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart J* 2006;27:949–53

71. Murphy NF, Simpson CR, Jhund PS *et al*. A national survey of the prevalence, incidence, primary care burden and treatment of atrial fibrillation in Scotland. *Heart* 2007;93:606–12

72. Lloyd-Jones DM, Wang TJ, Leip EP *et al*. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation* 2004;110: 1042–6

73. Seshadri S, Wolf PA. Lifetime risk of stroke and dementia: current concepts, and estimates from the Framingham Study. *Lancet Neurol* 2007;6:1106–14

74. Hobbs FD, Fitzmaurice DA, Mant J *et al*. A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study. *Health Technol Assess* 2005;9:1–74

75. Cabin HS, Clubb KS, Hall C *et al*. Risk for systemic embolization of atrial fibrillation without mitral stenosis. *Am J Cardiol* 1990;65:1112–16

76. Stewart S, Hart CL, Hole DJ *et al*. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med* 2002;113:359–64

77. Hughes M, Lip GY. Stroke and thromboembolism in atrial fibrillation: a systematic review of stroke risk factors, risk stratification schema and cost effectiveness data. *Thromb Haemost* 2008;99:295–304

78. Jorgensen HS, Nakayama H, Reith J *et al*. Acute stroke with atrial

fibrillation. The Copenhagen Stroke Study. *Stroke* 1996;27:1765–9

79. Frost L, Vukelic Andersen L, Godtfredsen J *et al*. Age and risk of stroke in atrial fibrillation: evidence for guidelines? *Neuroepidemiology* 2007;28:109–15

80. Lip GY, Tse HF. Management of atrial fibrillation. *Lancet* 2007;370:604–18

81. Singer DE, Albers GW, Dalen JE *et al*. Antithrombotic therapy in atrial fibrillation: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). *Chest* 2008;133:546S–92S

82. Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med* 1994;154:1449–57

83. Stroke Prevention in Atrial Fibrillation Investigators. Stroke Prevention in Atrial Fibrillation Study. Final results. *Circulation* 1991;84:527–39

84. Baruch L, Gage BF, Horrow J *et al*. Can patients at elevated risk of stroke treated with anticoagulants be further risk stratified? *Stroke* 2007;38: 2459–63

85. Stroke Risk in Atrial Fibrillation Working Group. Comparison of 12 risk stratification schemes to predict stroke in patients with nonvalvular atrial fibrillation. *Stroke* 2008;39:1901–10

86. Winter Y, Wolfram C, Schaeg M *et al*. Evaluation of costs and outcome in cardioembolic stroke or TIA. *J Neurol* 2009;256:954–63

87. Ferro JM. Cardioembolic stroke: an update. *Lancet Neurol* 2003;2:177–88

88. Schneck M, Lei X. Cardioembolic stroke. eMedicine Neurology 2008. http://emedicine.medscape.com/article/1160370-overview. Accessed March 2009

89. Steger C, Pratter A, Martinek-Bregel M *et al*. Stroke patients with atrial fibrillation have a worse prognosis than patients without: data from the Austrian Stroke registry. *Eur Heart J* 2004;25:1734–40

90. Wattigney WA, Mensah GA, Croft JB. Increased atrial fibrillation mortality: United States, 1980–1998. *Am J Epidemiol* 2002;155:819–26

91. Murphy R, Sackley CM, Miller P *et al*. Effect of experience of severe stroke on subjective valuations of quality of life after stroke. *J Neurol Neurosurg Psychiatry* 2001;70:679–81

92. Gage BF, Cardinalli AB, Owens DK. The effect of stroke and stroke prophylaxis with aspirin or warfarin on quality of life. *Arch Intern Med* 1996;156:1829–36

93. Scandinavian Stroke Study Group. Multicenter trial of hemodilution in ischemic stroke–background and study protocol. *Stroke* 1985; 16:885–90

94. Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. *Md State Med J* 1965;14:61–5

95. Grant JS, Glandon GL, Elliott TR *et al*. Caregiving problems and feelings experienced by family caregivers of stroke survivors the first month after discharge. *Int J Rehabil Res* 2004; 27:105–11

96. Young AJ, Rogers A, Addington-Hall JM. The quality and adequacy of care received at home in the last 3 months of life by people who died following a stroke: a retrospective survey of surviving family and friends using the Views of Informal Carers Evaluation of Services questionnaire. *Health Soc Care Community* 2008;16:419–28

97. Evers SM, Struijs JN, Ament AJ *et al*. International comparison of stroke cost studies. *Stroke* 2004;35:1209–15

98. Spieler JF, Lanoe JL, Amarenco P. Socioeconomic aspects of postacute care for patients with brain infarction in France. *Cerebrovasc Dis* 2002;13: 132–41

99. Claesson L, Gosman-Hedstrom G, Johannesson M *et al*. Resource utilization and costs of stroke unit care integrated in a care continuum: A 1-year controlled, prospective, randomized study in elderly patients: the Goteborg 70+ Stroke Study. *Stroke* 2000;31:2569–77

100. Ghatnekar O, Glader EL. The effect of atrial fibrillation on stroke-related inpatient costs in Sweden: a 3-year analysis of registry incidence data from 2001. *Value Health* 2008; 11:862–8

101. Schwarz UI, Ritchie MD, Bradford Y *et al*. Genetic determinants of response to warfarin during initial anticoagulation. *N Engl J Med* 2008;358:999–1008

102. Lu Y, Won KA, Nelson BJ *et al*. Characteristics of the amiodarone-warfarin interaction during long-term follow-up. *Am J Health Syst Pharm* 2008;65:947–52

103. Petersen P, Boysen G, Godtfredsen J *et al*. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study. *Lancet* 1989;1:175–9

104. BAATAF Investigators. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. *N Engl J Med* 1990;323:1505–11

105. Connolly SJ, Laupacis A, Gent M *et al*. Canadian Atrial Fibrillation Anticoagulation (CAFA) Study. *J Am Coll Cardiol* 1991;18:349–55

106. Ezekowitz MD, Bridgers SL, James KE *et al*. Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators. *N Engl J Med* 1992;327:1406–12

107. EAFT Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. EAFT (European Atrial Fibrillation Trial) Study Group. *Lancet* 1993;342: 1255–62

108. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med* 1994;154:1449–57

109. Hart RG, Pearce LA, Miller VT *et al*. Cardioembolic vs. noncardioembolic strokes in atrial fibrillation: frequency and effect of antithrombotic agents in the stroke prevention in atrial fibrillation studies. *Cerebrovasc Dis* 2000;10:39–43

110. Miller VT, Pearce LA, Feinberg WM *et al*. Differential effect of aspirin versus warfarin on clinical stroke types in patients with atrial fibrillation. Stroke Prevention in Atrial Fibrillation Investigators. *Neurology* 1996;46: 238–40

111. Hylek EM. Contra: 'Warfarin should be the drug of choice for thrombo-prophylaxis in elderly patients with atrial fibrillation'. Caveats regarding use of oral anticoagulant therapy among elderly patients with atrial fibrillation. *Thromb Haemost* 2008; 100:16–17

112. Go AS, Hylek EM, Chang Y *et al*. Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? *JAMA* 2003;290:2685–92

113. Burton C, Isles C, Norrie J *et al*. The safety and adequacy of antithrombotic therapy for atrial fibrillation: a regional cohort study. *Br J Gen Pract* 2006;56:697–702

114. Currie CJ, Jones M, Goodfellow J *et al*. Evaluation of survival and ischaemic and thromboembolic event rates in patients with non-valvar atrial fibrillation in the general population when treated and untreated with warfarin. *Heart* 2006;92:196–200

115. Monte S, Macchia A, Pellegrini F *et al*. Antithrombotic treatment is strongly underused despite reducing overall mortality among high-risk elderly patients hospitalized with atrial fibrillation. *Eur Heart J* 2006;27: 2217–23

116. Ansell J, Hollowell J, Pengo V *et al*. Descriptive analysis of the process and quality of oral anticoagulation management in real-life practice in patients with chronic non-valvular atrial fibrillation: the international study of anticoagulation management (ISAM). *J Thromb Thrombolysis* 2007;23:83–91

117. Frykman V, Beerman B, Ryden L *et al*. Management of atrial fibrillation: discrepancy between guideline recommendations and actual practice exposes patients to risk for complications. *Eur Heart J* 2001;22:1954–9

118. Catella-Lawson F. Vascular biology of thrombosis: platelet-vessel wall interactions and aspirin effects. *Neurology* 2001;57:S5–7

119. van Walraven C, Hart RG, Singer DE *et al*. Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation: an individual patient meta-analysis. *JAMA* 2002;288:2441–8

120. Mant J, Hobbs FD, Fletcher K *et al*. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet* 2007;370:493–503

121. Sato H, Ishikawa K, Kitabatake A *et al*. Low-dose aspirin for prevention of stroke in low-risk patients with atrial fibrillation: Japan Atrial Fibrillation Stroke Trial. *Stroke* 2006;37:447–51

122. Baigent C, Blackwell L, Collins R *et al*. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009; 373:1849–60

123. Abdelhafiz AH, Wheeldon NM. Use of resources and cost implications of stroke prophylaxis with warfarin for patients with nonvalvular atrial fibrillation. *Am J Geriatr Pharmacother* 2003;1:53–60

124. Szucs TD, Bramkamp M. Pharmaco-economics of anticoagulation therapy for stroke prevention in atrial fibrillation: a review. *J Thromb Haemost* 2006;4:1180–5

125. Gage BF, Cardinalli AB, Albers GW *et al*. Cost-effectiveness of warfarin and aspirin for prophylaxis of stroke in patients with nonvalvular atrial fibrillation. *JAMA* 1995;274:1839–45

126. Appleby J, Devlin N, Parkin D. NICE's cost effectiveness threshold. *BMJ* 2007;335:358–9

127. Littenberg B, Garber AM, Sox HC Jr. Screening for hypertension. *Ann Intern Med* 1990;112:192–202

128. Jowett S, Bryan S, Mahe I *et al*. A multinational investigation of time and traveling costs in attending anticoagulation clinics. *Value Health* 2008;11:207–12

129. Lip GY, Frison L, Grind M. Effect of hypertension on anticoagulated patients with atrial fibrillation. *Eur Heart J* 2007;28:752–9

130. Du X, Ninomiya T, de Galan B *et al*. Risks of cardiovascular events and effects of routine blood pressure lowering among patients with type 2 diabetes and atrial fibrillation: results of the ADVANCE study. *Eur Heart J* 2009;30:1128–35

131. European Stroke Initiative recommendations for stroke management. European Stroke Council, European Neurological Society and European Federation of Neurological Societies. *Cerebrovasc Dis* 2000;10:335–51

132. Ictus cerebrale: linie guida italiane di preventione e trattamento. Evidenze di riferimento. http://www.spread.it/files/SPREAD_ext.pdf. Accessed May 2009

133. HAS Guide for doctors – long-term conditions atrial fibrillation. http://www.has-sante.fr/portail/upload/docs/application/pdf/guide medecin__af-en_web.pdf. Accessed March 2009

134. Fuster V, Ryden LE, Cannom DS *et al*. [Guidelines for the management of patients with atrial fibrillation. Executive summary]. *Rev Esp Cardiol* 2006;59:1329

135. Lip GY, Rudolf M. The new NICE guideline on atrial fibrillation management. *Heart* 2007;93:23

136. Lewalter T, Tebbenjohanns J, Wichter T *et al*. Kommentar zu "ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation – executive summary". http://www.kompetenznetz-vorhofflimmern.de/intern/download-archiv/Leitlinien/2008-04_kommentar-atrial-fibrillation.pdf. Accessed March 2009

137. Wittkowsky AK. Effective anticoagulation therapy: defining the gap between clinical studies and clinical practice. *Am J Manag Care* 2004;10:S297–306

138. Deplanque D, Leys D, Parnetti L *et al*. Stroke prevention and atrial fibrillation: reasons leading to an inappropriate management. Main results of the SAFE II study. *Br J Clin Pharmacol* 2004;57:798–806

139. Anderson DR, Gardner MJ, Putnam W *et al*. Population-based evaluation of the management of antithrombotic

therapy for atrial fibrillation. *Can J Cardiol* 2005;21:257–66

140. Bravata DM, Rosenbeck K, Kancir S *et al*. The use of warfarin in veterans with atrial fibrillation. *BMC Cardiovasc Disord* 2004;4:18

141. McBride D, Bruggenjurgen B, Roll S *et al*. Anticoagulation treatment for the reduction of stroke in atrial fibrillation: a cohort study to examine the gap between guidelines and routine medical practice. *J Thromb Thrombolysis* 2007;24:65–72

142. Dolan G, Smith LA, Collins S *et al*. Effect of setting, monitoring intensity and patient experience on anticoagulation control: a systematic review and meta-analysis of the literature. *Curr Med Res Opin* 2008;24:1459–72

143. Lip GY, Zarifis J, Watson RD *et al*. Physician variation in the management of patients with atrial fibrillation. *Heart* 1996;75:200–5

144. Maeda K, Sakai T, Hira K *et al*. Physicians' attitudes toward anti-coagulant therapy in patients with chronic atrial fibrillation. *Intern Med* 2004;43:553–60

145. Vasishta S, Toor F, Johansen A *et al*. Stroke prevention in atrial fibrillation: physicians' attitudes to anticoagulation in older people. *Arch Gerontol Geriatr* 2001;33:219–26

146. Hart RG, Aguilar MI. Anticoagulation in atrial fibrillation: selected controversies including optimal anticoagulation intensity, treatment of intracerebral hemorrhage. *J Thromb Thrombolysis* 2008;25:26–32

147. Man-Son-Hing M, Nichol G, Lau A *et al*. Choosing antithrombotic therapy for elderly patients with atrial fibrillation who are at risk for falls. *Arch Intern Med* 1999;159:677–85

148. Choudhry NK, Anderson GM, Laupacis A *et al*. Impact of adverse events on prescribing warfarin in patients with atrial fibrillation: matched pair analysis. *BMJ* 2006;332:141–5

149. Tversky A, Kahneman D. Judgment under uncertainty: heuristics and biases. *Science* 1974;185:1124–31

150. Feinstein AR. The 'chagrin factor' and qualitative decision analysis. *Arch Intern Med* 1985;145:1257–9

151. Devereaux PJ, Anderson DR, Gardner MJ *et al*. Differences between perspectives of physicians and patients on anticoagulation in patients with atrial fibrillation: observational study. *BMJ* 2001;323:1218–22

152. AntiCoagulation Europe. It's about time campaign. http://www.anti coagulationeurope.org/abouttime survey.html. Accessed March 2009

153. Lip GY, Kamath S, Jafri M *et al*. Ethnic differences in patient perceptions of atrial fibrillation and anticoagulation therapy: the West Birmingham Atrial Fibrillation Project. *Stroke* 2002;33: 238–42

154. Nadar S, Begum N, Kaur B *et al*. Patients' understanding of anti-coagulant therapy in a multiethnic population. *J R Soc Med* 2003;96: 175–9

155. Trummer U, Mueller U, Nowak P *et al*. Does physician–patient communication that aims at empowering patients improve clinical outcome? A case study. *Patient Educ Couns* 2006;61:299–306

156. Beyth RJ, Quinn L, Landefeld CS. A multicomponent intervention to prevent major bleeding complications in older patients receiving warfarin. A randomized, controlled trial. *Ann Intern Med* 2000;133:687–95

157. Lip GY, Agnelli G, Thach AA *et al*. Oral anticoagulation in atrial fibrillation: A pan-European patient survey. *Eur J Intern Med* 2007;18:202–8

158. Macik BG. The future of anticoagulation clinics. *J Thromb Thrombolysis* 2003;16:55–9

159. Rodgers H, Sudlow M, Dobson R *et al*. Warfarin anticoagulation in primary care: a regional survey of present practice and clinicians' views. *Br J Gen Pract* 1997;47:309–10

160. Chiquette E, Amato MG, Bussey HI. Comparison of an anticoagulation clinic with usual medical care: anticoagulation control, patient outcomes, and health care costs. *Arch Intern Med* 1998;158:1641–7

161. McCahon D, Murray ET, Jowett S *et al.* Patient self management of oral anticoagulation in routine care in the UK. *J Clin Pathol* 2007;60:1263–7

162. Shojania K, Duncan B, McDonald K *et al*. Making health care safer: A critical analysis of patient safety. AHRG publication. http://www.ahrq.gov/clinic/ptsafety/. Accessed March 2009

163. Taborski U, Wittstamm FJ, Bernardo A. Cost-effectiveness of self-managed anticoagulant therapy in Germany. *Semin Thromb Hemost* 1999;25:103–7

164. Murray E, Fitzmaurice D, McCahon D *et al*. Training for patients in a randomised controlled trial of self management of warfarin treatment. *BMJ* 2004;328:437–8

165. Poller L, Keown M, Ibrahim S *et al*. A multicentre randomised clinical endpoint study of PARMA 5 computer-assisted oral anticoagulant dosage. *Br J Haematol* 2008;143: 274–83

166. Poller L, Keown M, Ibrahim S *et al*. An international multicenter randomized study of computer-assisted oral anti-coagulant dosage vs. medical staff dosage. *J Thromb Haemost* 2008; 6:935–43

167. Groene O, Lombarts M, Klazinga N *et al*. Is patient-centredness in European hospitals related to existing quality improvement strategies? Analysis of a cross-sectional survey (MARQuIS study). *Qual Saf Health Care* 2009;18:i44–i50

168. Ellis S. The patient-centred care model: holistic/multiprofessional/ reflective. *Br J Nurs* 1999;8:296–301

169. Gage BF, Cardinalli AB, Owens DK. Cost-effectiveness of preference-based antithrombotic therapy for patients with nonvalvular atrial fibrillation. *Stroke* 1998;29:1083–91

170. Biem HJ, Hadjistavropoulos H, Morgan D *et al*. Breaks in continuity of care and the rural senior transferred for medical care under regionalisation. *Int J Integr Care* 2003;3:e03

171. Goldfrad C, Rowan K. Consequences of discharges from intensive care at night. *Lancet* 2000;355:1138–42

172. Bell CM, Redelmeier DA. Mortality among patients admitted to hospitals on weekends as compared with weekdays. *N Engl J Med* 2001;345: 663–8

173. van Bemmel JH, van Ginneken AM, Stam B *et al*. Virtual electronic patient records for shared care. *Stud Health Technol Inform* 1998;52 Pt 1: suppl 37–41

174. van Walraven C, Seth R, Austin PC *et al*. Effect of discharge summary availability during post-discharge visits on hospital readmission. *J Gen Intern Med* 2002;17:186–92

175. Declaration of the European Patients' Forum. http://www.eu-patient.eu/core_documents/EPF_declaration.pdf. Accessed March 2009

176. European Patients' Forum. http://www.eu-patient.eu/manifesto/index.php. Accessed March 2009

177. EPF Conference on Health Literacy 8–9 March 2008. http://www.eu-patient.eu/policy/attached_documents/EPF_HealthHiteracyConference_2008_Key_Conclusions.pdf. Accessed March 2009

178. European Multiple Sclerosis Platform. http://www.ms-in-europe.org/emsp/index.php?kategorie=emsp. Accessed March 2009

179. Hillier S. The health and health care of ethnic minority groups. In: Scambler G, editor. Sociology as applied to medicine, 4th ed. Ballière Tindall, 1997:135–47

180. Lip GY. Quality of service provision for anticoagulation in atrial fibrillation. Many patients are ineligible. *BMJ* 1996;312:51

181. Thomson R, McElroy H, Sudlow M. Guidelines on anticoagulant treatment in atrial fibrillation in Great Britain: variation in content and implications for treatment. *BMJ* 1998;316:509–13

182. Turpie AG. New oral anticoagulants in atrial fibrillation. *Eur Heart J* 2007; 29:155–65

183. Turpie AG. Oral, direct factor Xa inhibitors in development for the prevention and treatment of thromboembolic diseases. *Arterioscler Thromb Vasc Biol* 2007;27:1238–47

184. European Medicines Agency Evaluation of Medicines for Human

Use. CHMP Assessment Report for Xarelto. http://www.emea.europa.eu/humandocs/PDFs/EPAR/xarelto/H-944-en6.pdf. Accessed March 2009

185. ClinicalTrials.gov. http://www.clinicaltrials.gov. Accessed May 2009

186. Weitz JI. Randomized, parallel group, multicenter, multinational study evaluating safety of DU-176b compared with warfarin in subjects with non-valvular atrial fibrillation. 50th Annual Meeting of the American Society of Hematology, 5–9 December 2008, San Francisco: Abstract 33

187. European Medicines Agency. Pradaxa Annex 1 Summary of Product Characteristics. http://www.emea.europa.eu/humandocs/PDFs/EPAR/pradaxa/emea-combined-h829en.pdf. Accessed November 2009

188. Connolly SJ, Ezekowitz MD, Yusuf S *et al.* Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:10.1056/nejmoa0905561

189. Khoo CW, Tay KH, Shantsila E *et al*. Novel oral anticoagulants. *Int J Clin Pract* 2009;63:630–41

190. European Medicines Agency. Clopidogrel Annex 1 Summary of Product Characteristics. http://www.emea.europa.eu/humandocs/PDFs/EPAR/clopidogrelbms/H-974-PI-en.pdf. Accessed March 2009

191. The ACTIVE Investigators. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med* 2009;360:2066–78

192. Siddique A, Butt M, Shantsila E *et al*. New antiplatelet drugs: beyond aspirin and clopidogrel. *Int J Clin Pract* 2009;63:776–89

193. Hohnloser SH, Crijns HJ, van Eickels M *et al*. Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med* 2009;360:668–78

194. Connolly SJ, Crijns HJ, Torp-Pedersen C *et al.* Analysis of stroke in ATHENA: a placebo-controlled, double-blind, parallel-arm trial to assess the efficacy of dronedarone 400 mg BID for the prevention of cardiovascular hospitalization or death from any cause in patients with atrial fibrillation/atrial flutter. *Circulation* 2009;120:1174–80

195. Lee R, Kruse J, McCarthy PM. Surgery for atrial fibrillation. *Nat Rev Cardiol* 2009;6:505–13

196. Sick PB, Schuler G, Hauptmann KE *et al*. Initial worldwide experience with the WATCHMAN left atrial appendage system for stroke prevention in atrial fibrillation. *J Am Coll Cardiol* 2007;49:1490–5

197. AtriCure reports first human implant of the Cosgrove–Gillinov left atrial appendage occlusion system. www.bio-medicine.org. Accessed October 2009

198. Holmes DR, Reddy VY, Turi ZG *et al*. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet* 2009;374:534–42

199. McCabe DJ, Kinsella JA, Tobin WO. Left atrial appendage occlusion in non-valvular atrial fibrillation. *Lancet* 2009;374:504–6

200. Nabauer M, Gerth A, Limbourg T *et al*. The Registry of the German Competence NETwork on Atrial Fibrillation: patient characteristics and initial management. *Europace* 2009;11:423–34

201. Kakkar AK, Lip GYH, Breithardt G. The importance of real-world registries in the study of AF-related stroke. http://www.theheart.org/documents/sitestructure/en/content/programs/1003241/transcript.pdf. Accessed October 2009

202. PR Newswire. Largest registry to date to provide the first-ever picture of the real global burden of atrial fibrillation (AF). Barcelona, Spain, 30 August 2009. http://pharmalicensing.com. Accessed October 2009

Appendix 1

Summary of country-specific Guidelines for the prevention of stroke in patients with atrial fibrillation.

Guideline	Risk category	Recommendation
NICE[69] UK	**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
	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
SPREAD[132] Italy	Patients with chronic and paroxysmal AF and valvular heart disease	Oral anticoagulants (INR 2.0–3.0) recommended, independently of the presence of other risk factors (Grade B)*
	Patients with chronic and paroxysmal non-valvular AF	Cardioversion recommended as the first therapeutic approach (Grade D)*
	Patients aged 65–75 years with chronic and paroxysmal non-valvular AF in the absence of haemorrhagic risks	Oral anticoagulant therapy (INR 2.0–3.0) recommended (Grade A)*
	Patients with chronic and paroxysmal non-valvular AF aged > 75 years with additional risk factors for thromboembolism†	Long-term oral anticoagulation therapy (INR 2.0–3.0) recommended
		Each individual case should be evaluated carefully and the increased haemorrhagic risk – especially intracranial – of elderly people should be taken into account (Grade A)*

continued

Guideline	Risk category	Recommendation
SPREAD[132] Italy *(continued)*	Patients with chronic and paroxysmal non-valvular AF • aged > 65 years with contra-indications to oral anticoagulants • aged > 75 years with higher haemorrhagic than thromboembolic risk • with anticipated poor compliance with the anticoagulant therapy or difficult access to reliable therapy-monitoring facilities	Although less effective, aspirin therapy (325 mg/day) is recommended (Grade A)* as an alternative to anticoagulant therapy
	In patients < 65 years of age with isolated chronic and paroxysmal non-valvular AF	No prophylactic treatment recommended because the embolic risk is low. In the presence of additional embolic risks, these must be evaluated in the individual case to decide between aspirin and oral anticoagulant therapy (Grade A)*
HAS[133] France	Patients with ≥ 1 high-risk factor or ≥ 2 moderate-risk factors Most AF patients require long-term oral anticlotting therapy (VKA or aspirin) to reduce the risk of thromboembolism	Long-term anticoagulant treatment with a VKA
	• Low-risk patients	Aspirin (75–325 mg/day)
	• Moderate-risk patients‡	VKA or aspirin depending on the clinical context and patient preferences
	• High-risk patients§	Adjusted doses of VKA (target INR 2.5, range 2.0–3.0)
SEC-SEMES[134] Spain	Patients with valvulopathy	Oral anticoagulant (INR 2.0–3.0)
	Patients with a high or moderate risk of thromboembolic events	Oral anticoagulant (INR 2.0–3.0)
	Patients with a low risk of thromboembolic events	Oral anticoagulant or antiplatelet drugs
	Patients with contraindications to oral anticoagulants	Antiplatelet therapy (aspirin 300 mg/day or clopidogrel 75 mg/day)

*Grading relates to the quality (robustness) of the recommendation; that is, the level of research evidence on which it is based. Grade A is strongest, D is weakest.
†Additional risk factors include diabetes, arterial high blood pressure, heart failure, left atrial dilatation and left ventricular dysfunction.
‡Moderate-risk factors are: age > 75 years, high blood pressure, heart failure, left ventricular ejection fraction below 35% or diabetes.
§High-risk factors for thromboembolism are: history of stroke, TIA or systemic embolism; and valvular heart disease, in particular mitral stenosis or presence of a mechanical prosthetic valve.
AF, atrial fibrillation; HAS, Haute Autorité de Santé; INR, international normalized ratio; NICE, National Institute for Health and Clinical Excellence; SEC, Spanish Society of Cardiology; SEMES, arrhythmia working group of the Spanish Society of Emergency Medicine; SPREAD, Stroke Prevention and Educational Awareness Diffusion; TIA, transient ischaemic attack; VKA, vitamin K antagonist.

Appendix 2

Phase III studies of new pharmaceutical agents for stroke prevention in atrial fibrillation (AF). Data obtained from searching www.clinicaltrials.gov using the term 'stroke prevention AF' (last accessed March 2009). In total, 54 studies were obtained with this search term; 32 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
Oral direct thrombin inhibitor			
Dabigatran etexilate	RE-LY	Randomized evaluation of long-term anticoagulant therapy 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
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	November 2010
	AVERROES	Apixaban versus acetylsalicylic acid to prevent stroke or systemic embolism in atrial fibrillation patients who have failed or are unsuitable for vitamin K antagonist treatment: a randomized double-blind trial	April 2010
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 (Japanese subjects only)	December 2009
	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	June 2010
Edoxaban (DU-176b)	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	March 2011
Indirect factor Xa inhibitor			
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	March 2011
Antiplatelet agent			
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
	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

*ACTIVE I was the factorial evaluation of irbesartan.

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
$CHADS_2$	**C**ongestive heart failure; **H**ypertension; **A**ge > 75 years; **D**iabetes; **S**troke or transient ischaemic attack (a system for scoring risk factors for stroke, assigning 1 point each to C, H, A and D, and 2 points to S)
ECG	Electrocardiogram
EMEA	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
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

Links to endorsing organizations

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

AntiCoagulation Europe (ACE)
www.anticoagulationeurope.org

Arrhythmia Alliance (A-A)
www.heartrhythmcharity.org.uk

Atrial Fibrillation Association (AFA)
www.atrialfibrillation.org.uk

ESC Working Group on Thrombosis
www.escardio.org/thrombosis

European Association of Hospital Pharmacists (EAHP)
www.eahp.eu

European Brain Council (EBC)
www.europeanbraincouncil.org

European Heart Rhythm Association (EHRA)
www.escardio.org/EHRA

European Primary Care Cardiovascular Society (EPCCS)
www.epccs.eu

European Stroke Conference
www.eurostroke.eu

European Stroke Organisation (ESO)
www.eso-stroke.org

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

International Council of Nurses (ICN)
www.icn.ch

Italian Atherosclerosis, Thrombosis and Vascular Biology (ATBV) Working Group
www.atbv.org

Sociedad Española de Neurologia (Spanish Neurological Association)
www.sen.es

StopAfib.org
www.StopAfib.org

World Stroke Organization (WSO)
www.world-stroke.org

About 2 million Europeans suffer a stroke every year, and this number is predicted to increase.

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.

Atrial fibrillation (AF) – the most common sustained abnormality of heart rhythm – affects about 6 million people in Europe. Individuals with AF are at a fivefold increased risk of stroke compared with the general population. Furthermore, strokes related to AF are more severe and have poorer outcomes 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 patients, policy makers, healthcare professionals and the general public 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 across the European Union 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 European and national level, will be crucial.