Updated October 2012

How Can We Avoid a Stroke Crisis in Europe?

Working Group Report:
Prevention of Atrial Fibrillation-Related Stroke

Dr Felicita Andreotti
Catholic University Medical School,
Rome, Italy

Professor John Camm
St George's University,
London, United Kingdom

Professor Antonio Dávalos
Universitat Autònoma de Barcelona,
Barcelona, Spain

Professor Dr Werner Hacke
University of Heidelberg,
Heidelberg, Germany

Professor Richard Hobbs
Oxford University,
Oxford, United Kingdom

Eve Knight
Chief Executive and Co-founder,
AntiCoagulation Europe

Joe Korner
Stroke Association,
London, United Kingdom

Professor Gregory YH Lip
University of Birmingham,
Birmingham, United Kingdom

Trudie Lobban MBE
Arrhythmia Alliance;
AF Association

Professor Bo Norrving
Lund University,
Lund, Sweden

Professor Panos Vardas
Heraklion University Hospital,
Crete, Greece

This report was made possible by Bayer HealthCare Pharmaceuticals.
See reverse of title page and acknowledgements for further information.

Strike Out Stroke
in Atrial Fibrillation
Action for Stroke Prevention

How Can We Avoid a Stroke Crisis in Europe?

Working Group Report:
Prevention of Atrial Fibrillation-Related Stroke

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

ISBN 978-0-9568536-5-3

Action for Stroke Prevention (ASP) has been initiated and funded by Bayer HealthCare as an independent alliance of experts with the aim to increase the awareness of atrial fibrillation and the associated risk of stroke. This booklet has been produced by the ASP with the aid of financial support from Bayer HealthCare. Bayer HealthCare have also been given the opportunity to comment upon the booklet from a regulatory and compliance perspective. However, the content of this booklet has been determined, and full editorial control retained, by the authors independently of Bayer HealthCare in order to ensure the independence of the report and outputs of the group. The views expressed in this publication are not necessarily those of the sponsor.

Authors

Writing group

Dr Felicita Andreotti
Certified Professor, Department of Cardiovascular Sciences, Catholic University, Rome, Italy

Professor John Camm
Professor of Clinical Cardiology, St George's University, London, United Kingdom

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

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

Professor Richard Hobbs
Professor and Head, Department of Primary Care Health Sciences, University of Oxford; National Director, NIHR School for Primary Care Research, United Kingdom; Chairman, European Primary Care Cardiovascular Society

Eve Knight
Chief Executive and Co-founder, AntiCoagulation Europe

Joe Korner
Director of Communications, The UK Stroke Association, London, United Kingdom; Representative for the Stroke Alliance For Europe (SAFE)

Professor Gregory YH Lip
Consultant Cardiologist and Professor of Cardiovascular Medicine, University of Birmingham Center for Cardiovascular Sciences; Director, Haemostasis Thrombosis & Vascular Sciences Biology Unit; City Hospital, Birmingham, United Kingdom

Trudie Lobban MBE
Founder and Trustee, Arrhythmia Alliance; Founder and Chief Executive Officer, AF Association

Professor Bo Norrving
Professor of Neurology, Department of Clinical Neurosciences, Section of Neurology, Lund University, Lund, Sweden; Past-President of the World Stroke Organization (2008–2012)

Professor Panos Vardas
President Elect of the European Society of Cardiology; Professor of Cardiology, University of Crete; Head of Cardiology Department, Heraklion University Hospital, Crete, Greece; President, European Heart Rhythm Association; Founder member of the Hellenic Cardiovascular Research Society and the Society's first President

Working group

Dr Álvaro Avezum
Director, Research Division, Dante Pazzanese Institute of Cardiology, São Paulo, Brazil

Dr Alastair Benbow
Executive Director, European Brain Council, (Brussels Office), Fondation Universitaire, Brussels, Belgium

Dr Carlos Cantú
Chair, Department of Neurology, National Institute of Medical Sciences and Nutrition Salvador Zubirán, Mexico; Professor of Stroke Program, National Autonomous University of Mexico, Mexico; Founding Member of the Mexican Stroke Association

Professor László Csiba
Professor and Head of the Department of Neurology, University of Debrecen, Hungary; President of the European Society of Neurosonology and Cerebral Hemodynamics

Dr Jorge González-Zuelgaray
Director of the Center of Cardiac Arrhythmias and of the Career of Specialists in Arrhythmias and Clinical Electrophysiology, University of Buenos Aires; Chief of Service of Arrhythmias and Electrophysiology (Sanatorio de la Trinidad San Isidro, Buenos Aires, Argentina); President of Arrhythmia Alliance and AF Association, Argentina

Professor Shinya Goto
Professor of Medicine, Department of Medicine (Cardiology) and the Metabolic Disease Center, and the Department of Metabolic Systems Medicine, Institute of Medical Science, Tokai University, Kanagawa, Japan

Professor Graeme J Hankey
Head of Stroke Unit, Royal Perth Hospital, Perth, Western Australia; Clinical Professor, School of Medicine and Pharmacology, University of Western Australia, Nedlands, Australia

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

Mellanie True Hills
Founder and Chief Executive Officer, StopAfib.org and the American Foundation for Women's Health

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

Professor Dayi Hu
Chief of the Cardiology Division of Peking University's People's Hospital, Dean of the Medical College of Shanghai at Tongji University; Dean of the Cardiology Department of Capital University of Medical Science, Beijing, China; President of Chinese Society of Cardiology; President of the Chinese College of Cardiovascular Physicians

Professor Han-Hwa Hu
Professor of Neurology, National Yang-Ming University, Taipei, Taiwan; Emeritus Chief of the Neurovascular Section, Neurological Institute, Taipei Veterans General Hospital, Taipei, Taiwan; President of the Taiwan Stroke Association

Professor Dr Paulus Kirchhof
Chair in Cardiovascular Medicine, School of Clinical and Experimental Medicine, University of Birmingham, Birmingham, United Kingdom; Senior Consultant, Department of Cardiology and Angiology, University Hospital Münster; Germany

Professor Dr Karl-Heinz Ladwig
Professor of Psychosomatic Medicine and Psychological Medicine, Technical University of Munich; Deputy Director of the Chronic Disease Epidemiology Department of the Institute of Epidemiology at the Helmholtz Zentrum München, German Research Centre for Environmental Health, Neuherberg, Germany

Professor Antoine Leenhardt
Professor of Cardiology, Paris 7 University; Head of the Arrhythmia Department, Bichat Hospital, Paris, France; Past-President of the French Working Group of Cardiac Arrhythmias and Pacing

Dr Maddalena Lettino
Chief of the Clinical Cardiology Unit, Istituto Clinico Humanitas, Rozzano (Milano), Italy; Past-Chair, Italian Atherosclerosis, Thrombosis and Vascular Biology (ATBV) Working Group; Chair of the Italian Working Group on Acute Cardiac Care; Board member of the ESC Acute Cardiovascular Care Association

Professor Lorenzo Mantovani
Professor, Faculty of Pharmacy, Federico II University of Naples, Naples, Italy

Dr Ayrton Massaro
Past-President of Ibero-American Stroke Society; Co-chair of the 2012 World Stroke Conference, Brazil

Rod Mitchell
Patient Advocate, Board Member, European Platform for Patients' Organisations, Science and Industry (Epposi) and the European Genetics Alliance Network (EGAN); Past Board member, International Alliance of Patients' Organizations

Dr David KL Quek
Consultant Cardiologist, Pantai Hospital Kuala Lumpur, Kuala Lumpur, Malaysia; President of the Malaysia Medical Association and Elected Member of the Malaysian Medical Council

Dr Walter Reyes-Caorsi
Chief, Electrophysiology Service, Casa de Galicia Hospital, Montevideo, Uruguay; Member, Continuing Medical Committee, Uruguayan Society of Cardiology; Member, Editorial Committee, Uruguayan Journal of Cardiology; Board Member, Honorary Commission for Cardiovascular Health; Director, Arrhythmia Council, South American Society of Cardiology

Professor Dr Kui-Hian Sim
Head of the Department of Cardiology and Head of Clinical Research Centre (CRC), Sarawak General Hospital, Sarawak, Malaysia; President of the National Heart Association of Malaysia

Professor Norio Tanahashi
Professor of Neurology, Saitama International Medical Center, Saitama Medical University, Hidaka City, Japan

Professor Hung-Fat Tse
Professor of Medicine, Cardiology Division, Department of Medicine, The University of Hong Kong, Hong Kong, China

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

Professor Byung-Woo Yoon
Department of Neurology, Seoul National University Hospital; Director of Clinical Research Center for Stroke, Korea; Current President of the Korean Society of Stroke

Professor Shu Zhang
Professor of Medicine, Chief of Department of Cardiology, Director of Arrhythmia Center; National Center for Cardiovascular Disease, Fu Wai Cardiovascular Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; President of Chinese Society of Pacing and Electrophysiology, Beijing, China

Acknowledgments
Support for the writing and editing of this report was provided by Chameleon Communications International Ltd, with funding from Bayer HealthCare. We acknowledge with thanks the contribution of Oxford PharmaGenesis™ Ltd who provided editorial and writing support for a previous report on the European Union: How Can We Avoid a Stroke Crisis? (2009), with funding from Bayer HealthCare.
The content of this report has been determined by the authors independently of Bayer HealthCare in order to ensure the independence of the report and outputs of the group.

Endorsements

Active Citizenship Network	www.activecitizenship.net
ADKA – German Association of Hospital Pharmacists	www.adka.de
"A.L.I.Ce Italia Onlus Associazione per la Lotta all'Ictus Cerebrale"	www.aliceitalia.org
ALT Onlus – Associazione per la Lotta alla Trombosi e alle malattie cardiovascolari	www.trombosi.org
ANA-Aritmie	www.anaaritmie.org
AntiCoagulation Europe	www.anticoagulationeurope.org
Arrhythmia Alliance – International	www.aa-international.org
Arrhythmia Alliance – the Heart Rhythm Charity	www.arrhythmiaalliance.org.uk
Arrhythmia Alliance Czech Republic	www.aa-cz.eu
Arrhythmia Alliance Italy	www.ana-aritmie.org
Arrhythmia Alliance Portugal	www.aa-pt.eu
Arrhythmia Alliance Spain	www.aa-es.eu
Arrhythmia Alliance Sweden	www.aa-se.eu
ATBV – Gruppo di studio Aterosclerosi, Trombosi, Biologia Vascolare	www.atbv.org
AF Association – International	www.afa-international.org
AF Association Bulgaria	www.afa-bg.eu
AF Association Canada	www.afa-ca.org
AF Association Denmark	www.afa-dk.eu
AF Association France	www.afa-fr.eu
AF Association Germany	www.afa-de.eu
AF Association Greece	www.afa-gr.eu
AF Association Hungary	www.afa-hu.eu
AF Association Italy	www.afa-it.eu
AF Association Norway	www.afa-no.eu
AF Association Poland	www.afa-pl.eu
AF Association Portugal	www.afa.pt.eu
AF Association Russia	www.afa-ru.eu
AF Association Spain	www.afa-es.eu
AF Association Sweden	www.afa-se.eu
AF Association Turkey	www.afa-tr.org
AF Association UK	www.atrialfibrillation.org.uk
Bulgaria National Patient Organisation	www.npo.bg
China Committee of Cardio-Cerebral-Vascular Diseases of GSC	

Chinese Society of Cardiology	www.cscnet.org.cn
ECAS – European Cardiac Arrhythmia Society	www.ecas-heartrhythm.org
ESZME – Hungarian Association for Stroke Prevention	www.eszme.hu
European Brain Council	www.europeanbraincouncil.org
European Heart Rhythm Association (EHRA)	www.escardio.org/EHRA
European Primary Care Cardiovascular Society	www.epccs.eu
European Society of Neurosonology and Cerebral Hemodynamics	www.esnch.org
European Stroke Conference	www.eurostroke.eu
European Stroke Organisation	www.eso-stroke.org
Feasan – Federación Española de Asociaciones de Anticoagulados	www.anticoagulados.info
Federación Española de Ictus	www.ictusfederacion.es
Foundation for Development of Electrophysiology	www.sercedlaarytmii.pl
German Competence Network on Atrial Fibrillation	www.kompetenznetzvorhofflimmern.de
Heart Association of Bulgaria	
Hellenic Cardiological Society	www.hcs.gr
Hellenic Cardiovascular Research Society	www.cardioresearch.net
InterAmerican Heart Foundation	www.interamericanheart.org
National Stroke League of Hungary	www.strokeliga.blogspot.de
Norwegian Association for Stroke Survivors	www.slagrammede.org
Open Interaction Association	
Par Sirdi	www.parsirdi.lv
SAFE	www.safestroke.org
Stroke Association	www.stroke.org.uk
Stroke Association Serbia	www.mozdaniudar.co.rs
StopAfib.org	www.stopafib.org
Stroke Foundation of Poland	www.fum.info.pl
SZÍV SN	www.szivsn.hu
The International FH Foundation	www.fh-foundation.org
World Heart Federation	www.world-heart-federation.org
World Stroke Organization (WSO)	www.world-stroke.org

Table of contents

Chapter 1
Foreword to the updated EU stroke report

Stroke is a devastating event that is responsible for 14% of all deaths in Europe annually. In many cases, the first and only manifestation of stroke is death. Surviving stroke can be considered to be worse than death, with stroke victims facing an uncertain future and a life that may be severely affected by disability. There are currently approximately 8 million stroke survivors in the European Union (EU). Stroke also places an incredible emotional and physical burden on caregivers, who are often close family members of stroke survivors. The financial burden of stroke is also staggering, currently costing the EU economy about €62 billion per year.

Many of these deaths, lives affected and costs 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 highlight actions to improve management of patients with the abnormal heart rhythm known as atrial fibrillation (AF) – a condition that increases the risk of stroke fivefold and that is responsible for at least 15–20% of all strokes caused by blood clots. Importantly, patients with AF are more likely to have a severe stroke than patients without AF and, if they do, these patients have a 50% likelihood of death within 1 year. Furthermore, the presence of AF increases the risk of permanent disability after a stroke by almost 50%. With AF estimated to affect about 10 million people in Europe alone, the scale of the problem is clear, especially as the elderly proportion of the population increases – and the proportion with AF increases with age. AF prevalence is expected to rise dramatically to 25–30 million by 2050.

Despite being a very common condition, AF often has no symptom – or symptoms may be vague or non-specific. As a consequence, AF is under-diagnosed and undertreated, which means that many affected individuals do not receive therapy to protect them against stroke. Furthermore, even patients diagnosed with AF, and known to be at risk of a stroke, often do not receive adequate stroke prevention therapy. As Members of the European Parliament, we consider this as a distressing and avoidable situation, given that AF-related strokes can be so devastating but are preventable with anticlotting therapy. This situation needs to be addressed urgently.

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

How will we help? Although the delivery of healthcare remains the responsibility of national governments, cooperation at the 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 sharing best practice, knowledge and education – for example, in cancer, Alzheimer's disease and organ transplantation.

Prevention of AF-related stroke requires new strategies to understand and manage AF, and improved delivery of therapies to prevent stroke. Physician education is required both to improve detection and diagnosis of AF and to optimize strategies to prevent AF-related

stroke. In addition, improved patient or caregiver education on the risk of AF-related stroke and the symptoms of AF, as well as equal access to therapy and information across the region, is paramount.

In this updated report, the aim is to build on the success of the initial 2009 report by continuing to raise awareness of the need for greater investment in preventing stroke, particularly in patients with AF. Importantly, this report reiterates a clear Call for Action, to which we draw your attention. Implementation of these recommendations at European and national levels will be crucial. This report continues to bring together the various strands of policy development, awareness-raising, and research and educational activities, and to focus them on improving AF diagnosis and management and ensuring effective AF-related stroke prevention. The EU can then continue to develop and promote 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 healthcare for these patients. As policy makers, we firmly believe that only through the coordinated actions of all participants, European and national, shall we see the highest number of AF-related strokes avoided and the greatest quality of life improvements achieved.

It is a privilege for us as Members of the European Parliament to participate actively in an initiative that will help to position this important issue firmly as a key priority for the European agenda. With support from our parliamentary colleagues, we seek to build on the work done to date and look forward to your support in driving this important initiative.

Liam Aylward, MEP (ALDE, Ireland);
Cristian Silviu Buşoi, MEP (ALDE, Romania);
Jim Higgins, MEP (EPP, Ireland);
Antigoni Papadopoulou, MEP (S&D, Cyprus);
Cecilia Wikström, MEP (ALDE, Sweden)

October 2012

Chapter 2
Executive summary

Non-communicable diseases (NCDs) are responsible for almost 90% of deaths in Europe.[1] Cardiovascular disease is the biggest killer in Europe, being responsible for 50% of all deaths.[1] Stroke is the second biggest cause of cardiovascular death, after ischaemic heart disease, killing an estimated 1.3 million people in Europe (14% of all deaths) and 6.2 million people worldwide (11% of all deaths) every year.

The number of new stroke cases in the European Union (EU) is predicted to rise from an estimated 1.1 million in 2000 to 1.5 million per year by 2025 as the proportion of elderly people in the population increases.[2] In line with this prediction, there were 1.3 million new stroke cases in the EU, Iceland, Norway and Switzerland combined in 2010.[3] This is an epidemic already in progress, and we must act if we are to avoid a crisis.

In 2010, there were 8 million stroke survivors living in the EU.[3] 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 the patients' quality of life,[4] but also that of their families and carers.[5] Furthermore, the economic burden of stroke is huge, accounting for 2–3% of the entire healthcare expenditure in the EU.[6]

Atrial fibrillation (AF) is the most common sustained abnormality of heart rhythm; in Europe, it is estimated that 10 million people have the condition.[7] This number is expected to rise dramatically to 25–30 million by 2050, representing a threefold increase.[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 because it can lead to the formation of blood clots in the heart, which can then migrate to the brain. As a result, AF accounts for approximately 1 in 5 ischaemic strokes (those caused by a clot blocking a blood vessel in the brain).[9] Previously undiagnosed AF is also a probable cause of many strokes of unknown origin (so-called 'cryptogenic' strokes); indeed, stroke may be the first manifestation of AF. The risk of stroke in patients with AF increases with age – AF is associated with approximately 36% of strokes in patients over 80 years of age[10] – and with the addition of other risk factors, such as high blood pressure, previous stroke and diabetes.[11]

AF-related strokes tend to be more severe, cause greater disability and have a worse outcome than non-AF-related strokes. AF-related strokes are also associated with a 50% likelihood of death within 1 year, compared with 27% for non-AF-related strokes.[9] Importantly, the burden of AF-related stroke will become more marked in the years to come because of the anticipated increase in the number of people with AF[7] as the proportion of elderly people in the population increases and as survival after conditions that predispose to AF (such as heart attack) improves.[12]

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[13] and EU policy as a key need in Europe.[14] The United Nations (UN) has also proposed a target to reduce premature mortality from NCDs (which includes AF-related stroke) by 25% by the year 2025.[15]

Anticlotting therapy is used to inhibit the formation of blood clots and, therefore, reduces the risk of AF-related stroke. When appropriately used and properly managed it is highly effective, lowering stroke risk by about two-thirds.[16] However, despite the existence of guidelines for its use and management, such therapy is both underused and misused in clinical practice, mostly owing to perceived drawbacks[17–19] associated with both vitamin K antagonists (VKAs), such as warfarin,[20,21] and aspirin.[22–25]

Stroke kills approximately 6.2 million people worldwide every year (11% of all deaths)

In 2010, stroke affected 8 million people in the EU

Approximately 10 million people in Europe have AF

The risk of stroke 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

AF-related stroke can be prevented, but many therapies are often underused with suboptimal outcomes as a result

Earlier detection and improved treatment of AF can help to prevent many strokes

Prevention of AF-related stroke, therefore, calls for improved delivery of established therapies, new strategies to understand and manage AF, and improved delivery of new therapies.

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.[10,26] In fact, AF often has no symptoms at all;[27] an estimated one-third of patients with AF are unaware that they have the condition[28,29] and, as a result, will not have access to the necessary prevention strategies. Thus, many preventable strokes occur every year, leading to thousands of avoidable early deaths and a devastating burden on individuals, families and society in terms of disability, medical and social care costs, and lost productivity (working hours) and tax revenues.

This updated report highlights the continuing and 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 should, at a minimum, 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 for the prevention of AF-related stroke
- Equal and appropriate access to therapy for patients with AF
- Improved adherence to updated guideline recommendations for the management of AF
- Continuing research into the causes, prevention and management of AF

Chapter 3
Call to action

The authors of this updated report, and all individuals and societies who endorse these recommendations, reiterate the call for EU action to improve the detection and management of AF and to promote more effective measures to prevent AF-related stroke across all Member States. Through these actions 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 prevention of atrial fibrillation-related stroke

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

The most prevalent cardiovascular disorders are ischaemic heart disease and stroke. AF, the most common sustained abnormal heart rhythm, is a major cause of stroke – in particular, of severe, disabling stroke. Most AF-related 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 (EHN) and the European Society of Cardiology (ESC) to reduce the burden of cardiovascular diseases substantially[13,14] – and the recently adopted UN target to reduce NCD mortality by 25% by the year 2025.[15]

When used correctly, therapy that helps to prevent blood clots has been shown to reduce the risk of stroke in patients with AF by more than 60%.[30–32] However, some of the drugs that help to prevent unwanted clotting, such as warfarin, are underused or used suboptimally in clinical practice. The reasons for this include the complexity of appropriate management of such therapy and a widely held belief that the risks of therapy may outweigh the benefits.[17–19] In addition, AF is often not diagnosed until the patient suffers a first stroke; even at that point, the condition may not always be diagnosed. This possibility increases the size of the problem, meaning that many clearly preventable strokes occur every year because of delayed diagnosis of AF, combined with 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.

Many clearly preventable strokes occur because of delayed diagnosis of AF and underuse of anticlotting therapy

In March 2011, the European Commission initiated a pilot European Innovation Partnership (EIP) on Active and Healthy Ageing in the context of its Innovation Union Strategy.[33] The pilot Partnership aims to increase the average healthy lifespan of European citizens by 2 years by the year 2020 through, among other strategies, reductions in the health burden linked to chronic diseases and NCDs.[34] This priority is further supported by the European Parliament, which adopted a resolution on the EU position and commitment in advance of the UN High-Level Meeting on the Prevention and Control of NCDs in September 2011.[35] In its resolution, the European Parliament calls on the European Commission and Member States to take a strong political stance to reduce the prevalence and incidence of NCDs, including cardiovascular diseases, in particular by tackling ischaemic heart disease and stroke.

AF is a major cause of severe, disabling stroke

We reiterate our call for the European Parliament and the European Commission to drive policy initiatives to improve early detection and management of AF, and to prevent AF-related stroke

In keeping with these overarching themes and objectives, AF management and prevention of AF-related stroke are gaining increasing prominence within the framework of NCD prevention and management, as the NCD epidemic becomes increasingly prominent within the EU health policy agenda. However, as part of the wider initiative for prevention of stroke and cardiovascular disorders in Europe, there is still a clear and substantial need for:

- Coordinated action at the EU level and potentially beyond
- An EU policy initiative calling for:
  - Improved diagnosis of AF prior to the first stroke
  - Appropriate and effective management of AF
  - Effective and well-tolerated methods to prevent AF-related stroke in patients who have already developed AF
  - Continuing research into the causes of AF

Such an initiative would be in line with the main priorities of the EU with regard to health – i.e. a focus on factors that determine health – thereby providing a path to health promotion and disease prevention.[14] It is also important to focus on reducing the societal and economic burden of chronic diseases so as to ensure the sustainability of healthcare systems in the context of an ageing population.

Principal recommendations

1. Create and raise awareness of the impact of AF and AF-related stroke
2. Develop coordinated strategies for early and adequate diagnosis of AF
3. Improve education of patients and carers about AF and prevention of AF-related stroke
4. Encourage the development and use of new approaches to the management of AF and the prevention of AF-related stroke
5. Improve awareness of physicians about AF management and prevention of AF-related stroke
6. Promote equity of access to therapy and information for all patients across the EU
7. Strongly advocate adherence to clinical guidelines for the management of patients with AF and prevention of AF-related stroke
8. Facilitate exchange of best practices between Member States
9. Boost research into the causes, prevention and management of AF

Principal recommendations

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

When an individual has developed AF, their risk of an ischaemic stroke (from a blood clot in the brain) is increased fivefold compared with the risk in individuals without the condition.[8,36] Because of the large number of people in the EU living with AF (~10 million),[7] the human and economic impact of AF and AF-related stroke is huge: the average medical cost alone of AF-related stroke per patient has been calculated to be approximately €12 000 in the first year after a stroke.[37]

AF-related stroke can be prevented. 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; better understanding of AF and its causes; and improvements in strategies for 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 help prevent AF-related stroke.

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 screening procedure, such as checking for an irregular pulse with electrocardiogram (ECG) confirmation, can have a crucial role in improving detection of AF in patients at risk. Increased awareness of the early signs of AF, and the early signs 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 should be encouraged and has been shown to be cost-effective.[38] Campaigns, such as the 'Know Your Pulse' campaign launched by the Arrhythmia Alliance in 2009,[39] promote awareness of the relevance of an irregular pulse as a sign of AF and of the importance of detecting abnormal heart rhythm, thus improving timely initiation of AF therapy and appropriate stroke prevention treatment.

3. Improve education of patients and carers about AF and prevention of AF-related stroke

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 reliable and accurate information about the risk of AF-related stroke and the methodology for its prevention. Pharmaceutical and technological developments, such as newer anticlotting drugs and patient-operated monitoring techniques for existing drugs, may make it easier to provide appropriate treatment to protect patients with AF against stroke. Improved 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 and its consequences.

We call on the EU to promote understanding, earlier detection and improved management of AF

EU-wide collaboration between existing patient organizations could help to collate and compare data from different countries in Europe. This collaboration would involve the exchange and dissemination of information about AF and its diagnosis and management, as well as about AF-related stroke prevention. Such collaboration would make it possible to identify best practices for the successful management of AF across the EU, leading to benchmarks for management that could 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 the initial development of AF. However, some factors that contribute to the development of AF, such as genetics and the natural ageing process, are not modifiable, so it will never be possible to eliminate AF entirely.[40]

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

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

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

management of AF and its symptoms. Effective use of anticlotting therapy is essential in the large majority of patients who have already developed AF in order to prevent complications (such as stroke) resulting from a circulating blood clot. The factors that place a patient with AF at highest risk of stroke include: congestive heart failure, high blood pressure, age of 75 years or older, diabetes and previous stroke.

The ideal anticlotting drug is effective and has: a favourable safety profile in a wide range of patients, including the elderly; a very low risk of interactions with food and other drugs; and a simple dosing regimen, with no need for routine coagulation monitoring or dose adjustment. Agents approaching this ideal are now available and the encouragement of their use could increase adherence to therapy and, potentially, improve outcomes in patients with AF.

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

5. Improve the awareness of physicians about AF management and prevention of AF-related stroke

Physicians may be so concerned about the risks of anticlotting therapy that they underestimate its benefits in reducing stroke risk.[41–43] Improving awareness of the substantially increased risk of stroke in patients with AF compared with those without AF is, therefore, important. Physician education is also needed to help in the recognition of undiagnosed ('silent') AF before complications such as stroke occur. Physicians need to 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. Physicians should be encouraged to undertake continuing professional education regarding the characteristics of the different anticlotting therapies now available and the correct management of patients in receipt of these agents. We call for a coordinated EU effort to improve physician education and awareness strategies, supported by adequate resources.

We call on the EU, via the Member States, to raise awareness of existing clinical guidelines for the management of AF and prevention of AF-related stroke

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

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

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 any underlying clinical conditions; to well-managed 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 clinical guidelines for the management of patients with AF and prevention of AF-related stroke

Several sets of guidelines exist for the management of AF, and the ESC published updated guidelines in 2012.[44] The degree to which guidelines are properly implemented varies widely between and within countries, as evidenced by analysis of anticlotting therapy in large cohorts of patients with AF. According to surveys in Italy, Germany and Spain, the proportion of patients with AF at high risk of stroke and receiving guideline-adherent anticoagulation was only approximately 25–57%.[45–47] In a Europe-wide survey, anticlotting therapy was in agreement with the guidelines in only 61% of patients.[48] Therefore, there is a need across much of Europe to improve adherence to guidelines on the prevention of AF-related stroke because non-adherence is associated with poor outcomes.[48]

The EU can encourage guideline adherence at a national level by calling for better implementation of the existing European Guidelines (for example, those developed by the ESC).[44,49] 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 appropriate anticlotting therapy and to ensure that such therapy is optimally delivered. This, in turn, will reduce the number of new cases of AF-related stroke. Improved guideline adherence would also enhance patient safety – in line with the communication on patient safety from the European Commission to the European Parliament and the Council, and the 2009 Council Recommendation on patient safety.[50–52]

8. Facilitate exchange of best practices between Member States

In 2009, this report recommended an EU initiative to harmonize the existing national guidelines into one set of unified European guidelines in order to work towards the goal of AF-related stroke prevention. In light of the publication of guidelines from the ESC in 2010,[49] as a second stage, coordination at a European level is needed between the various national professional bodies charged with implementing the guidelines. A tactical approach such as this would directly facilitate sharing of best practices and the development of a consistent policy on the prevention of AF-related stroke in patients across all Member States. It would also help to ensure that the principle of healthcare equality across the EU is implemented and that individual patients receive similar (and the best possible) care in all EU Member States. In line with the core mission of the ESC National Guidelines Coordinators,[53] 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 practices.

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 abnormal heart rhythm that affects mainly older people. The European Commission identified demographic ageing as one of the most serious challenges currently faced by European countries. In its communication 'Taking forward the Strategic Implementation Plan of the European Innovation Partnership on Active and Healthy Ageing', the Commission highlights that, according to recent projections, the number of Europeans aged 65 years and older will almost double over the next 50 years, from 87 million in 2010 to 148 million in 2060.[54]

Furthermore, a recent study projected that, with current mortality trends and AF incidence, AF could reach epidemic proportions by 2050, affecting approximately 25–30 million people in Europe.[7] 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.

The European Commission supports research on AF under the Seventh Framework Programme for Research and Technological Development (2007–2013) through the European Network for Translational Research in Atrial Fibrillation (EUTRAF) project,[55] which was allocated a total of €12 million for 5 years. The project aims to explore disease mechanisms and to develop better diagnostic means and new therapies in patients with AF through integrated research. The EU is currently negotiating the next Framework Programme for Research (2014–2020), named Horizon 2020.[56] Within the 'Societal Challenges – Health, Demographic Change and Wellbeing' initiative, research on chronic diseases, including cardiovascular disease, and risk factors is expected to receive EU funding.

We advocate an EU initiative to promote uniform adherence to guidelines for the management of AF, and to share and promote best practices among all Member States

It may be possible to utilize the resources of Horizon 2020, and/or to benefit from the Innovative Medicines Initiative (IMI) – the unique partnership between the European Commission and the European Federation of Pharmaceutical Industries and Associations. Research topics that the EU could support and help to coordinate include:

- Systematic analysis of the epidemiology of AF (i.e. the factors that determine the frequency and distribution of AF, including 'silent' AF) and its relationship to stroke
- Epidemiology of AF-related stroke; risk factors and outcomes
- Europe-wide assessment of the burden and severity of disease for all patients with stroke, including patient experience and assessment of quality of life. Such studies should place a particular emphasis on the greater burden of AF-related stroke and its contribution to the overall burden of stroke
- Research to identify individuals 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.

The European Commission committed almost €10 million to support the European Stroke Network (ESN) in their efforts to coordinate the largest ever multidisciplinary European stroke research programme (EUSTROKE).[57,58] The research programme started in March 2008 and will run until February 2013. To augment and complement the efforts of the ESN and results of EUSTROKE, an EU-wide coordinated research initiative is urgently needed, aimed at improving the management of AF, and understanding more fully its causes and epidemiology, and at preventing AF-related stroke.

Chapter 4
Atrial fibrillation: a major risk factor for stroke

Key points

- **AF is the most common sustained heart rhythm abnormality and is a major risk factor for stroke and death in the general population**
- **AF is a global problem; in Europe, it is currently estimated to affect approximately 10 million people and is projected to affect 25–30 million by 2050**
- **Risk factors for AF include high blood pressure, heart failure, cigarette smoking, obesity and diabetes**
- **The likelihood of developing AF increases with advancing age**
- **People aged 40 years and older have a 1 in 4 risk of developing AF over their remaining lifetime**
- **AF is often not detected until a serious condition such as stroke or heart failure develops**
- **Routine pulse-taking could have an important role in the detection of AF in at-risk patients**
- **AF increases the risk of stroke fivefold and is responsible for approximately 15% of all strokes**

AF is the most common sustained heart rhythm abnormality[59] and is a major risk factor for stroke and death in the general population.[9,59] AF occurs when the upper chambers of the heart (known as the atria) tremble rapidly and irregularly rather than contracting regularly and effectively.[60] This can result in irregular contraction of the lower chambers of the heart (the ventricles) and an erratic pulse rate.

AF can be subdivided into five classes, with most patients progressing to the more sustained forms over time:[49]

- First diagnosed
- Paroxysmal: often self-terminating within 48 hours, but continuing for less than 7 days
- Persistent: continuing for more than 7 days or requiring management to correct the arrhythmia
- Long-standing persistent: having already lasted for a year or more by the time a strategy to attempt to correct the arrhythmia is adopted
- Permanent: when strategies to correct the arrhythmia are not considered worthwhile by both the patient and the physician. If a strategy to correct the arrhythmia is undertaken, the AF is reclassified as long-standing persistent

The term 'non-valvular AF' is used to describe cases where rhythm disturbance is not associated with a problem with a valve in the heart;[61] most of the studies discussed in the following sections involve patients with AF that is non-valvular rather than valvular. AF may occur in isolation or in association with other disturbances of normal heart rhythm, most commonly atrial flutter.

Development of atrial fibrillation: causes and contributing factors

A report of the Framingham Heart Study, a large, long-term United States (US)-based study initiated in the early 1950s, found that

advancing age, high blood pressure, heart failure, previous heart attack, valvular disease (disease involving one or more heart valves), diabetes and cigarette smoking were risk factors for development of AF.[62] It has now been established that heart conditions such as heart failure, valvular heart disease and prior heart attack – as well as general cardiovascular risk factors such as diabetes, high blood pressure, obesity and cigarette smoking – are risk factors for the development of AF.[63] A recently completed study, which followed more than 14 000 individuals for an average period of 17 years or more, suggested that elevated levels of these risk factors could account for 50% of AF cases.[64] This means that a large proportion of AF incidence may be preventable if these modifiable risk factors are reduced. Table 1 shows the common coexisting conditions found in patients with AF in some recent global and European studies.[7,45,47,65–70]

High blood pressure, obesity, cigarette smoking and diabetes are among the common modifiable risk factors for the development of AF

The likelihood of developing AF increases with advancing age and with the presence of cardiovascular disease or cardiovascular disease risk factors. However, some patients seem to have genetic abnormalities that predispose to AF, and these abnormalities are most often seen in young patients who develop AF.[40,71]

Prevalence and incidence of atrial fibrillation

In Europe, AF is presently estimated to affect approximately 10 million people.[7] Table 2 shows results of studies investigating the prevalence of AF in various European countries.[7,38,45,47,68,72–77] As well as illustrating the huge burden of AF across Europe, the table also shows a variable prevalence of AF in different countries. Although this may reflect true variance of AF prevalence across Europe, it should be noted that some of the variance will be the result of differences in design between the studies. The studies looked at different age groups and used different methods of diagnosing AF (in some studies only hospital admissions were considered). Table 2 highlights the need for more studies to evaluate the true prevalence of AF in European populations. A study of global AF prevalence, excluding the US and Europe, also found variance between different countries and between hospital- and community-based studies.[78] The reported prevalence varied from 0.1% in India to 4.0% in Australia.

AF incidence and prevalence increase with age

The incidence of AF has been found to increase with each decade of age.[59] 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.[73] This revealed an incidence of 1.1 per 1000 person-years in people aged 55–59 years, rising to 20.7 per 1000 person-years in those aged 80–84 years.[73] In each age category, the incidence was higher in men than in women. Most recently, in 119 526 patients with AF seen over 5 days in the Spanish primary care

Table 1. Summary of common coexisting conditions in patients with AF in global and Europe-wide studies and in some individual European countries.

Patients with AF, %	Global:[65,66,a] 9288 patients	Europe:[67,b] 5203 patients	Sweden[68] 159 012 patients	Denmark[69] 121 280 patients	Germany[47] 183 448 patients	Spain[45] 3287 patients	UK[70] 79 844 patients	Iceland[7] 4905 patients
Heart failure	21.0	33.7	33.8	18.8	43.8	21.3	29.2	25.0
High blood pressure	78.0	63.8	43.2	39.7	86.8	92.6	50.2	25.0
Diabetes	22.0	18.1	17.0	9.1	44.0	33.7	16.6	9.0
Ischaemic heart disease[c]	19.0	32.8	33.5	Not reported	Not reported	20.9	Not reported	39.0

[a]35 countries.
[b]19 countries: Australia, Austria, Brazil, Canada, China, Denmark, Finland, France, Germany, Italy, Japan, Korea (South), Mexico, Netherlands, Norway, Poland, Spain, Sweden, UK.
[c]Ischaemic heart disease results from reduced blood supply to the heart, often evident as angina or heart attack.
AF, atrial fibrillation; UK, United Kingdom.

Table 2. Studies evaluating the prevalence of AF in Europe.

Country	Sample size	Patients with AF	Year	Diagnosis method	Age (years)	Women (%)	Prevalence of AF (%)
Netherlands (Rotterdam)[73]	6808	376	1990–1993	Single ECG	≥55 (mean 69)	60%	5.5%
Netherlands[74]	40 185 (from 18 practitioners)	1234	1996[a]	Medical file; ECG if irregular pulse	≥60	–	5.1%
UK (England and Wales)[75]	1.4 million (from 211 practitioners)	7218	1998	Medical records	All ages	–	Men 1.2%; Women 1.3%
UK (West Midlands)[38]	14 802 (at 50 health centres)	1068	2001	Medical file	≥65 (mean 75)	57%	7.2%
Iceland (Reykjavik)[7]	All inhabitants invited	4905	2008	Medical file	All ages	–	Men 2.3%; Women 1.5%
Spain[45]	199 526 (from 836 practitioners)	7260	2009–2010	Medical file	All ages (mean 53)	–	6.1%
Germany[47]	8.3 million (two statutory medical insurance funds)	183 448	2007	Medical file	All ages	44%	2.21%
Sweden[68]	National hospital discharge register	182 678	2005–2008	Medical file	All ages	–	2.0%
Switzerland (Geneva)[72]	3285 (invited sample from a previous random survey)	29	2005–2007	Single ECG	≥50	48%	0.9%
Portugal[76]	10 447 (invited sample)	261	2010[a]	Single ECG	≥40 (mean 59)	55%	2.5%
France[77]	–	–	2011[a]	Extrapolation of international epidemiological data	All ages	–	1.0–1.6%[b]

Adapted from Schmutz *et al*. Low prevalence of atrial fibrillation in asymptomatic adults in Geneva, Switzerland. Europace (published on behalf of the European Society of Cardiology) 2010;12(4):475–481 by permission of Oxford University Press.[72]
[a]Year of publication
[b]Calculated based on a population of France in 2011 of 63 460 768 people (http://www.insee.fr/fr/themes/detail.asp?ref_id=bilan-demo&page=donnees-detaillees/bilan-demo/pop_age2.htm) accessed September 2012.
AF, atrial fibrillation; ECG, electrocardiogram; UK, United Kingdom.

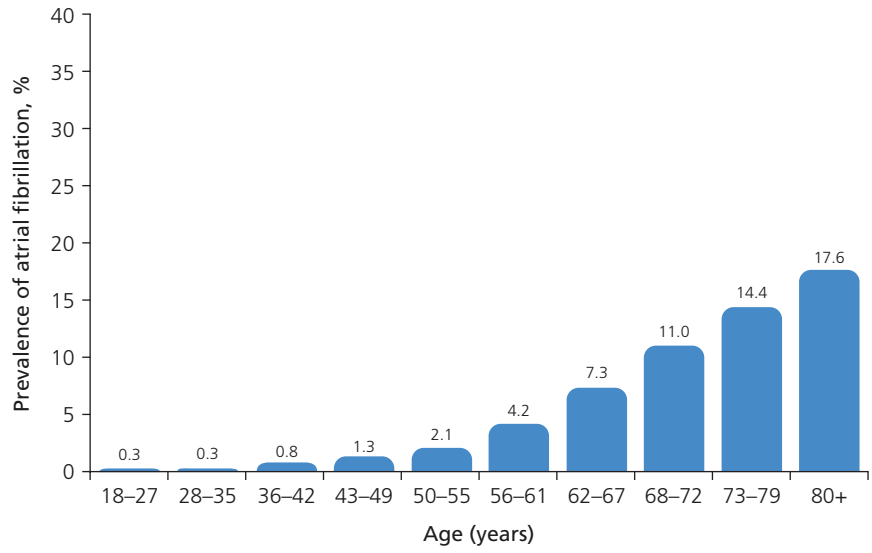
setting, the prevalence of AF increased from 0.3% at age 18–27 years to 2.1% at age 50–55 years, rising further to 17.6% at age 80 years or older (Figure 1).[45]

AF prevalence is increasing

The prevalence of AF also appears to be increasing over time. In France, the number of hospitalized patients with a diagnosis of AF increased by 26% from 2005 to 2008.[77] Similarly, data from a United Kingdom (UK) primary care database demonstrated an increase in AF prevalence from 0.84% in men and 0.83% in women in 1994 to 1.49% and 1.29%, respectively, in 2003.[79] Based on one cross-sectional study of almost 18 000 adults diagnosed with AF between July 1996 and December 1997 in California, it was estimated that approximately 2.1 million people in the US had AF.[80] 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 2A).[80] More recently, a study based on the population of Reykjavik, Iceland, in 2008 estimated, based on recent trends in mortality and AF incidence in the general population, that the number of people with AF will approximately triple by 2050 (Figure 2B).[7] The authors of this study also estimate that there are currently approximately 10 million people with AF in Europe and predict that this figure will rise to 25–30 million by 2050. 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.[81]

AF affects approximately 10 million people in Europe

Figure 1. Prevalence of atrial fibrillation by age in the Spanish primary care setting.



Redrawn with permission from Barrios *et al.* 2012.[45]

The prevalence and incidence of AF rises as population age increases

Lifetime risk of atrial fibrillation

AF is often present without symptoms

Another report of the Framingham Heart Study investigated the lifetime risk of AF in individuals who were free of the condition at first examination. The study sample included 3999 men and 4726 women who were followed up from 1968 to 1999.[82] For men and women aged 40 years and older, the remaining lifetime risk of developing AF was found to be 1 in 4. Similar data are available from a European population.[73]

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

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;[83] for breast cancer, the remaining lifetime risk is 1 in 8 for women aged 40 years.[84]

Signs and symptoms of atrial fibrillation

A simple and easily identifiable sign of AF is an irregular pulse, and the symptoms of AF may include palpitations, chest pain or discomfort, shortness of breath, dizziness and fainting.[85] In AF-related emergency admissions to hospital, AF most often presents as difficulty with breathing, chest pain and palpitations.[86] However, many people with AF have no symptoms, or have vague, non-specific symptoms. 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.[10]

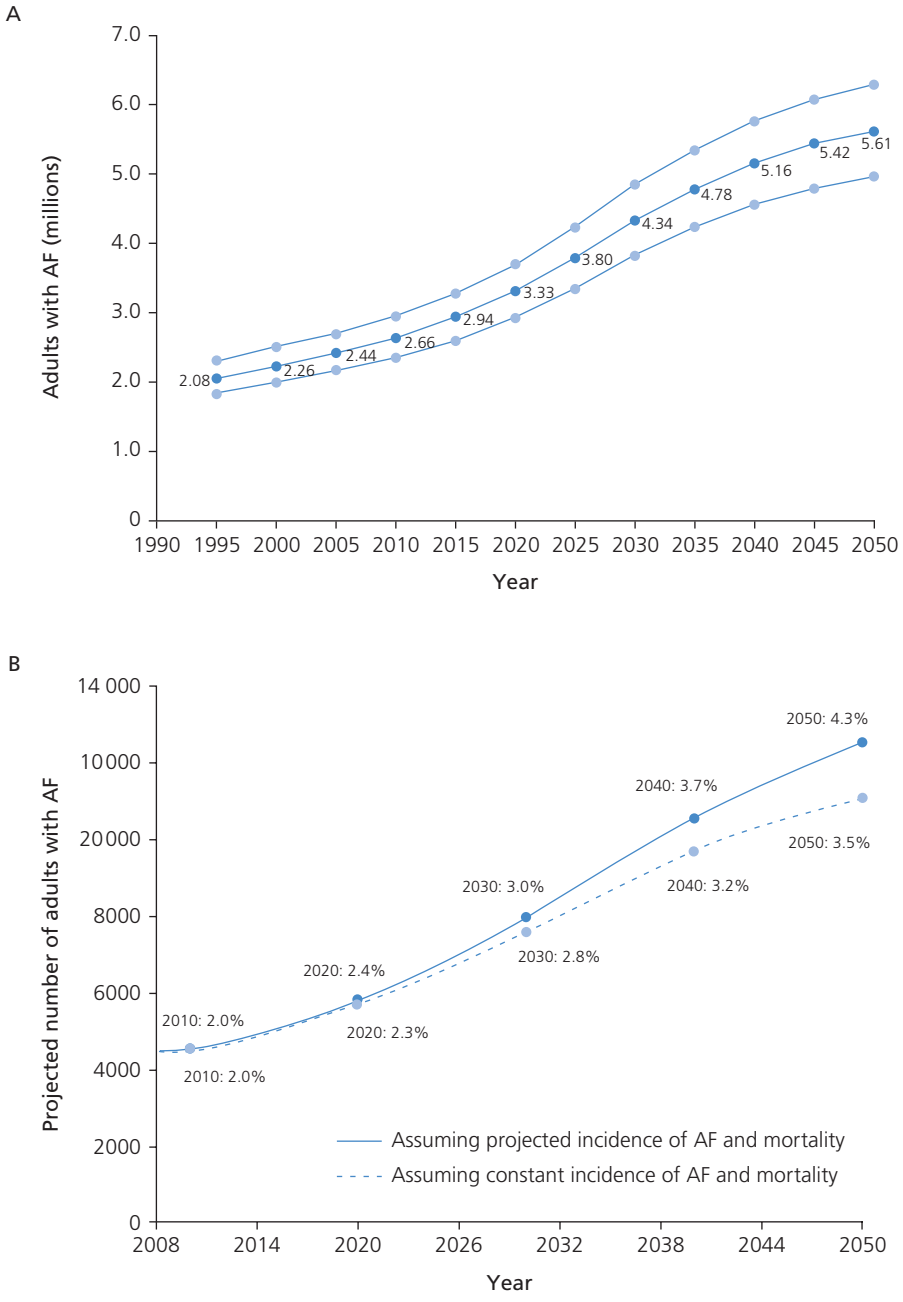
There is an average delay of 2.6 years between the onset of symptoms and a diagnosis of AF

Physicians may encounter AF when patients consult them about other conditions, related or unrelated to the heart. Unfortunately, however, AF is often not detected until an individual presents with a serious condition such as stroke or heart failure.[86] Even 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.[87] This indicates that many patients with AF are not being managed effectively and are at risk of serious long-term consequences, such as stroke.

Detection and diagnosis of atrial fibrillation

The National Institute for Health and Clinical Excellence (NICE) in the UK recommends assessment for the presence of AF in

Figure 2. Projected number of adults with AF in the US and in Iceland.



A: Projected number of adults with AF in the US between 1995 and 2050. The upper, middle and lower curves represent upper, middle and lower boundaries of estimate.
B: Projected number of adults with AF in Iceland between 2008 and 2050.
Adapted from Go *et al*. (copyright © [2001] American Medical Association. All rights reserved)[80] and from Stefansdottir *et al*. Trends in the incidence and prevalence of atrial fibrillation in Iceland and future projections. *Europace* (published on behalf of the European Society of Cardiology) 2011;13(8):1110–1117 by permission of Oxford University Press.[7]
AF, atrial fibrillation.

individuals with breathlessness, palpitations, fainting or dizziness, chest discomfort, stroke, or transient ischaemic attack (TIA; a brief stroke, described in more detail in Chapter 5, 'Stroke: a significant cause of poor health and death', page 27).[88] NICE has produced some useful information on AF for patients and their carers that gives a brief overview of the main treatments used for the condition.[85] Management of AF is discussed in more detail in Chapter 8, 'Prevention of atrial fibrillation-related stroke' (page 47).

The often silent, asymptomatic nature of AF means that approximately one-third of individuals with this arrhythmia are undiagnosed and may be at risk of AF-related stroke.[28,29] A UK community health review of 788 individuals aged 85 years identified AF as being underdiagnosed.[29] AF was identified in 109 of the 85-year-olds who received an ECG, of whom 30 had not been diagnosed previously. This means that 4% overall had undiagnosed AF and approximately one-third of all the individuals with AF were undiagnosed. A multicentre study – the Screening for AF in the Elderly (SAFE) study – in primary care in the UK aimed to determine whether active screening was more effective than routine care at detecting AF in the community.[89] The SAFE study involved 50 primary care practices and almost 15 000 patients aged 65 years or older, identified randomly from computerized lists of patients in the target study group. Active screening identified previously undiagnosed AF in 1.63% of the patients over the course of 1 year and 59% more cases of AF than routine care. These figures may well be underestimated because patients with paroxysmal AF, with a normal heart rhythm at time of screening, would not have been detected. Increased detection and diagnosis of AF are, therefore, imperative to initiate timely and effective treatment and thus prevent many of the complications related to AF, particularly AF-related stroke.

Active screening can identify more new cases of AF than routine clinical care

Increased detection and improved treatment of AF are needed to prevent AF-related stroke

Systematic versus opportunistic screening

As well as determining the value of active screening versus routine practice, a substudy of the SAFE study compared systematic with opportunistic active screening.[38,89] Of the 15 000 patients enrolled, 5000 were assigned to the control group (which received routine clinical care) and 10 000 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. Patients with an irregular pulse were given an information sheet and were 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.

Both systematic and opportunistic screening identified approximately 60% more cases of AF than routine care.[89] 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.[38]

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.[38] This is also realistic, given that many patients are elderly and so are also likely to have other conditions necessitating periodic primary care visits. In light of this, the 2012 guideline update from the ESC recommends pulse checks for all patients aged 65 years and older followed by an ECG in those with an irregular pulse.[90] 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 after detection of an irregular pulse.[86] Furthermore, The Arrhythmia Alliance, The Heart Rhythm Charity, launched the 'Know your Pulse' campaign in 2009.[39] The campaign aims to promote awareness among the general public of the importance of pulse checking and to provide tools, such as an online application, to help individuals check their own pulse.

The role of ambulatory monitoring

Paroxysmal AF episodes can be short and infrequent, adding to the difficulties in diagnosing the condition. In some instances, therefore, it may be useful to use a heart monitor to record the pulse over an extended period of time. In a population of 478 patients with ischaemic stroke in Germany, AF was newly diagnosed on initial ECG at presentation in 5% of patients.[91] After 3 months of follow-up, during which patients were subject to continuous bedside ECG monitoring or wore a monitoring device for 24 hours at least

once, the number of patients with newly diagnosed AF more than doubled to 11%. These results provide some evidence for routine adoption of monitoring for AF in patients after stroke.

Following the SAFE study, several recommendations were made for future research that could help define further the optimum patient pathway (Table 3).[38]

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. Furthermore, the difficulties in diagnosing the condition mean that current evaluations of AF prevalence in Europe may be severely underestimated. The following chapters will discuss AF as a risk factor for stroke. The irregular trembling rather than effective beating of the atria leads to blood stasis or pooling within the atria.[49,60] This can result in blood clots developing within the atria (usually the left atrium); these clots can subsequently break away and travel to vessels in the brain, thus causing a stroke. AF is responsible for approximately 15% of all strokes,[92] and increases the risk of stroke fivefold compared with individuals with a normal heart rhythm.[8] Paroxysmal AF carries the same risk of stroke as permanent AF,[49,93] and therapy to prevent AF-related stroke should be considered after the 48-hour time period described above has expired.[49] Although there are differences in the mechanisms of the two rhythm disturbances,[10] patients with atrial flutter are also at increased risk of developing AF and patients with persistent atrial flutter can experience alternating periods of AF and atrial flutter;[94] therefore, therapy for prevention of stroke is recommended in the same way as for patients with AF.[49]

Table 3. Some of the recommendations for further research, based on the findings of the Screening for AF in the Elderly (SAFE) study.[38]

- How the implementation of a screening programme for AF influences the uptake and maintenance of anticoagulation therapy in patients aged 65 years and older
- The role of computer software in assisting with the diagnosis of cardiac arrhythmias
- How best to improve the performance of healthcare professionals in interpreting ECGs
- Development of a robust economic model for prevention of AF-related stroke, incorporating the treatment effect of newer drugs compared with standard care

AF, atrial fibrillation; ECG, electrocardiogram.

AF increases the risk of stroke fivefold and is responsible for approximately 15% of all strokes

Chapter 5
Stroke: a significant cause of poor health and death

Key points

- Approximately 8.2 million people in Europe have suffered at least one stroke in their lifetime
- Latest data show that approximately 1.3 million individuals in Europe suffer a stroke each year
- The number of strokes per year is predicted to rise dramatically as the life expectancy of the population increases, especially AF-related stroke
- In 2008, stroke was responsible for almost 14% of all deaths in Europe
- The overall economic cost of stroke to Europe was over €64 billion in 2010

What is stroke?

A stroke occurs when the brain is damaged as a result of a restricted blood supply or leakage from a blood vessel within the brain. There are two main types of stroke: haemorrhagic and ischaemic. A haemorrhagic stroke is caused by bleeding from a blood vessel in the brain. Ischaemic strokes are more common, accounting for approximately 85% of all strokes,[4] and are caused by a blood clot in the brain. A blood clot that formed elsewhere in the body and has travelled to the brain 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. AF-related strokes, caused by blood clots formed in the atria, are cardioembolic ischaemic strokes.

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 approximately 4–5%.[95,96] Studies have shown that, in the 90 days after a TIA, the risk of stroke exceeds 10%.[96]

Prevalence and incidence of stroke in Europe and the EU

In 2008, there were approximately 1.3 million deaths from stroke in Europe, accounting for almost 14% of all deaths.[1] In 2010, the prevalence of stroke (i.e. total number of new cases plus the number of stroke survivors) in the EU member states plus Iceland, Norway and Switzerland was estimated to be 8.2 million.[3]

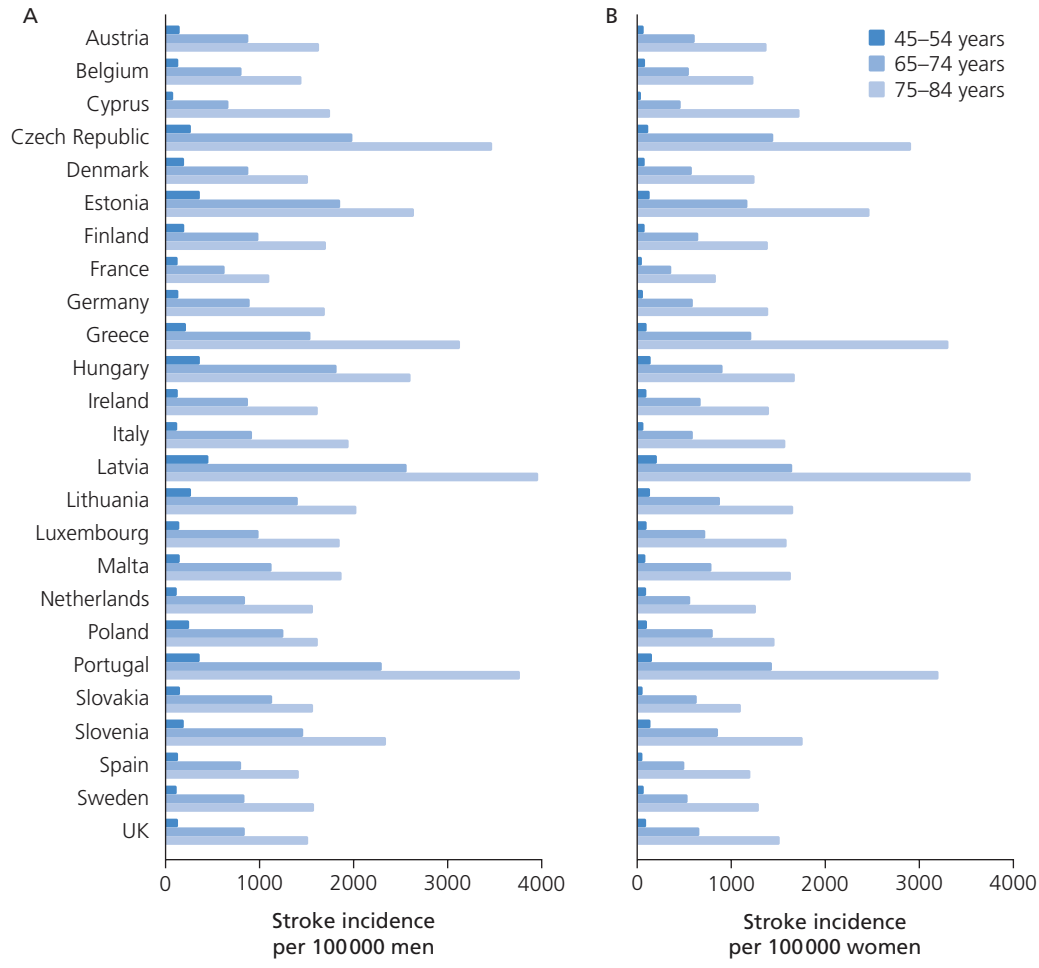
8.2 million people in the EU plus Iceland, Norway and Switzerland have suffered a stroke, and approximately 1.3 million new or recurrent strokes occur each year

For countries within the EU, a study based on data from the World Health Organization (WHO) estimated the incidence of stroke (initial and recurrent strokes) to be 1.1 million in 2000.[2] Furthermore, it has been predicted that stroke incidence within the EU will increase to 1.5 million per year by 2025, mostly as a result of the increasing proportion of elderly individuals.[2] In line with this prediction, the incidence of stroke in the EU plus Iceland, Norway and Switzerland was 1.3 million in 2010.[3]

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

The incidence of stroke in individual countries in the EU was also estimated by the WHO in 2006 (Figure 3).[2] This estimation showed that, for both men and women, the number of individuals who experience stroke increases substantially with age. For example, in Belgium, the incidence of stroke in men aged 75–84 years was 10 times that in men aged 45–54 years; in women aged 75–84 years, the incidence of stroke was nearly

Figure 3. The number of individuals who experience stroke increases substantially with age.



Estimates of stroke incidence (A) per 100 000 men and (B) per 100 000 women at selected ages in the EU (from the World Health Organization).
Data taken from Truelsen *et al.* Stroke incidence and prevalence in Europe: a review of available data. *Eur J Neurol* 2006;13:581–598, John Wiley & Sons, Inc.
EU, European Union; UK, United Kingdom.

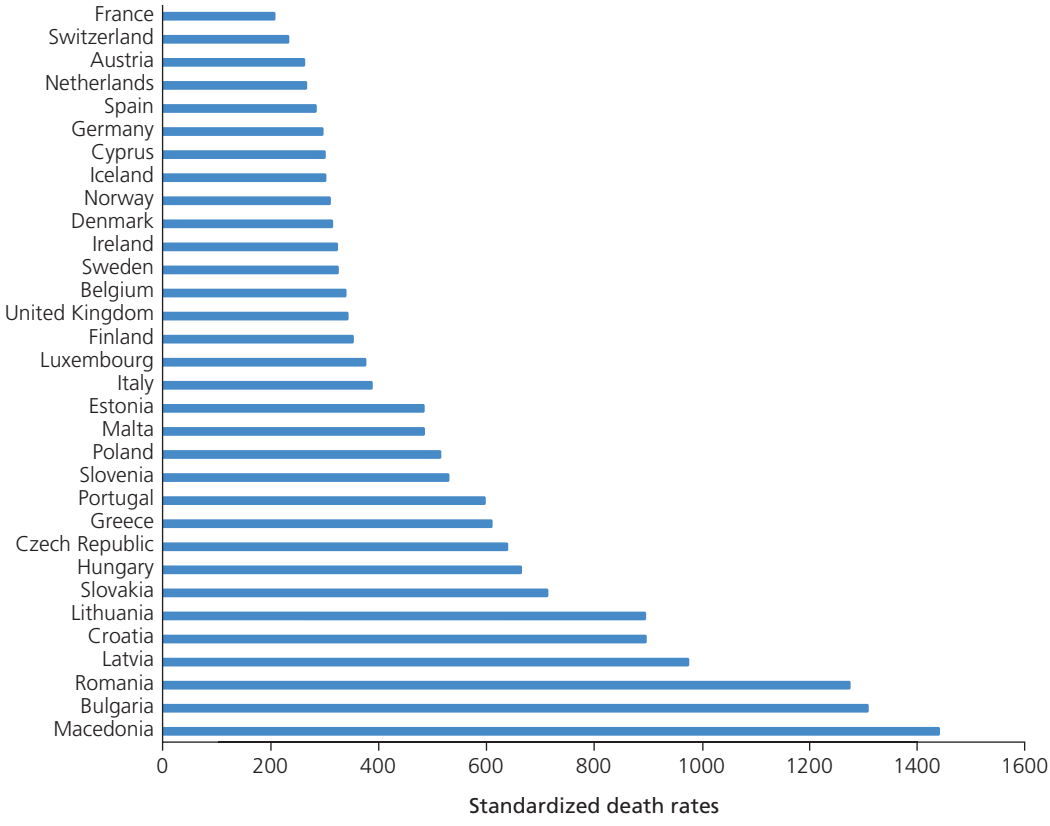
15 times that in women aged 45–54 years. Furthermore, these data showed that stroke incidence was higher in men than in women across most countries and age ranges.

Although strokes in young adults are relatively uncommon, approximately 25% of strokes occur in people aged younger than 65 years,[97] and a national survey of stroke patients in the US estimated that 3.7% of strokes occurred in patients aged 15–45 years.[98]

Death and poor health in patients who have had a stroke

As discussed previously, stroke accounts for nearly 14% of all deaths in Europe.[1] Stroke is generally thought of as a problem that affects the elderly; however, the death rate from stroke in individuals in Europe aged up to 60 years was estimated to be 16.9 per 100 000 of the population in 2008.[1] This figure rose substantially in individuals aged 60–79 years to 402.2 per 100 000.[1] In the EU in 2009, stroke was identified as the second biggest cause of death in people aged 65 years and older (behind ischaemic heart disease), with a standardized death rate of 397.4 per 100 000, and was the biggest cause of death in this age group in Bulgaria, Greece, Luxemburg, Portugal, Slovenia and Macedonia. Figure 4 shows deaths owing to stroke in individuals aged 65 years and older per 100 000 inhabitants in 2009.[99]

Figure 4. Deaths owing to stroke in individuals aged 65 years and older per 100 000 inhabitants in 2009.



Data taken from Buchow *et al*. 2012.[99]

Additionally, stroke is a major cause of long-term disability worldwide – in 2004, the WHO estimated that 5 million stroke sufferers were left permanently disabled.[4] Young individuals are not exempt from the devastating effects of stroke. A long-term study assessing outcomes in young adults aged 15–45 years after stroke found that, after 6 years, only 49% were still alive, were not disabled, had not suffered from recurrent vascular events or had not undergone major vascular surgery; most survivors reported emotional, social or physical effects that lessened their quality of life.[100]

Stroke can affect almost all human functions, making it difficult for many patients to get out of bed, walk short distances or perform basic activities of daily life. As well as impairing speech and physical function,[4] stroke can also adversely affect mental health.[101]

Because the onset of stroke is sudden, the affected individual and their family are often poorly prepared to deal with the consequences of stroke.[101] The development of chronic disability can severely affect the 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.

In 2004, 5 million stroke sufferers worldwide were 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

Stroke costs in Europe were over €64 billion in 2010

In the EU plus Iceland, Norway and Switzerland, the estimated total economic cost of stroke in 2010 was over €64 billion (1 billion is defined as 1000 million).[3] Approximately 66% of this amount was from direct healthcare costs, 26% resulted from direct non-medical costs (such as special accommodation and informal care) and approximately 8% was from indirect costs (such as loss of productivity or early retirement).[3]

AF is responsible for approximately 15% of all strokes

The total costs attributable to stroke in 2010 are shown in Figure 5A for individual European countries.[3] Healthcare costs attributable to stroke were approximately €42 billion, and costs unrelated to healthcare were approximately €22 billion.

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

The *per capita* costs (cost per resident) associated with stroke in 2010 for individual European countries are shown in Figure 5B. These data show that the amount spent on stroke per year varies greatly within Europe, from €27 per person (Romania) to €255 per person (Luxembourg). These figures demonstrate the tremendous financial burden to society posed by stroke in Europe.

Risk factors for stroke

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

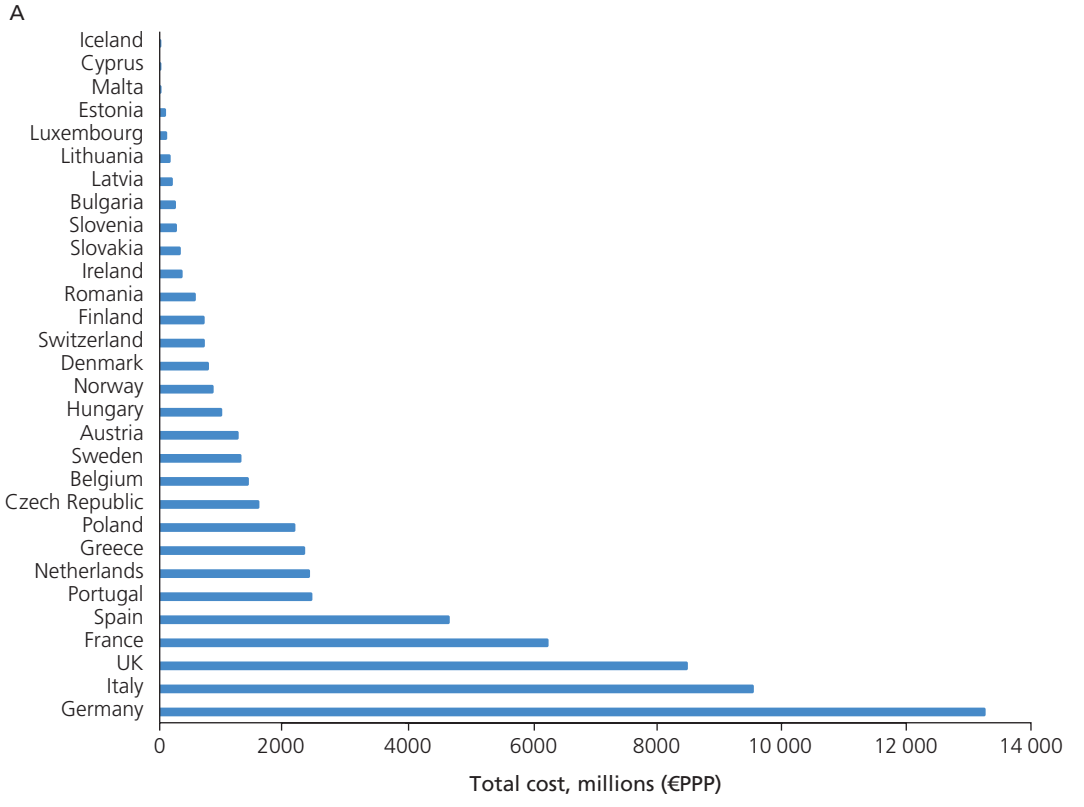
AF is the most common sustained heart rhythm abnormality[59] and is a major risk factor for ischaemic stroke and death in the general population.[9,59] Other established risk factors for stroke include high blood pressure, diabetes, heart disease and lifestyle factors, such as smoking, excessive alcohol consumption, poor diet and insufficient physical activity.[102] The five major modifiable risk factors – the 'big five' – that merit targeting in the prevention of stroke have been identified as:[103]

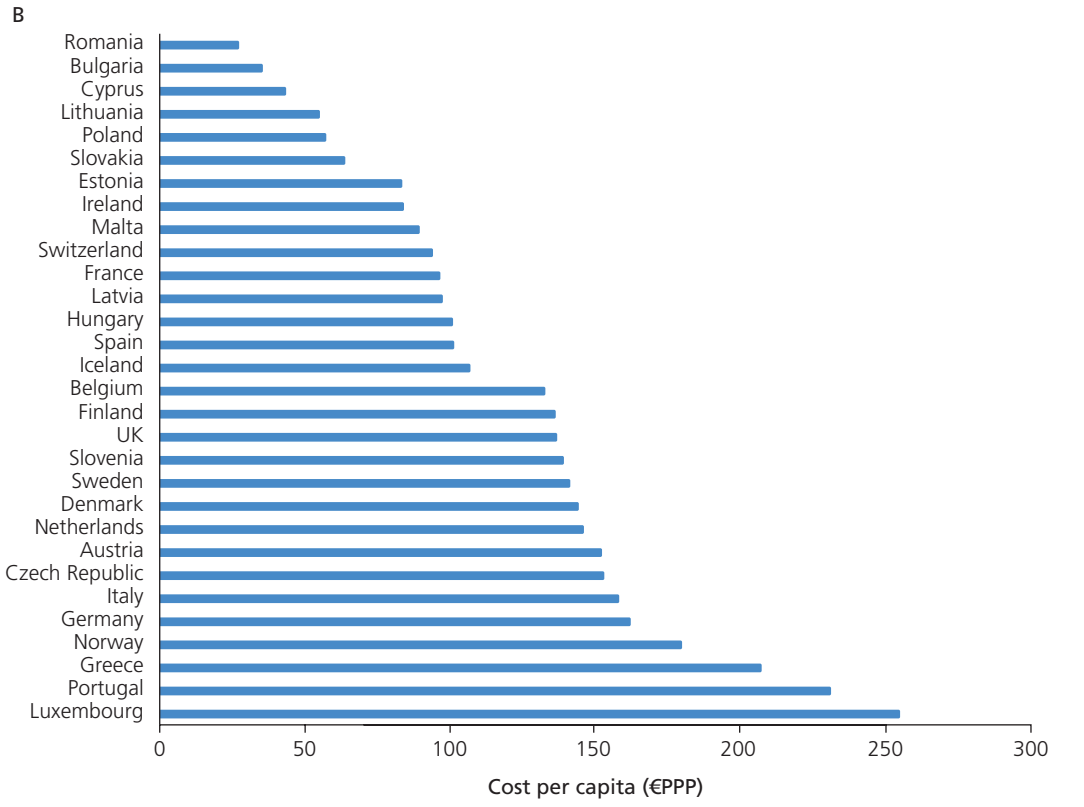
- High blood pressure
- Smoking
- Lack of physical exercise
- Diabetes
- AF

Owing to its high prevalence, hypertension or high blood pressure is the leading modifiable risk factor for stroke,[104] accounting for approximately one-third to one-half of all strokes.[105] AF, by comparison, is estimated to be responsible for approximately 15% of all strokes[92] (20% of all ischaemic strokes[9]), and patients with AF have a 3–4% risk per year of developing stroke.[106] 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 6).[8,36] Furthermore, whereas the relative importance of high blood pressure is the same for both haemorrhagic and ischaemic strokes, AF is a significant risk factor for ischaemic stroke.[107] This was highlighted in a study of 692 patients who had had ischaemic stroke (69%) or TIA (31%) in Germany, where the prevalence of AF approached 30% in these patients.[91] As stated above, the prevalence of stroke in Europe in 2010 was approximately 8.2 million.[3] If AF is responsible for approximately 15% of all strokes, the prevalence of AF-related stroke in Europe could be approximately 1.2 million. Moreover, many patients with AF also have high blood pressure (Table 1), so a holistic approach to management is required (see section on 'Management of other conditions that increase the risk of atrial fibrillation stroke risk: a holistic approach', page 56 in Chapter 8).

Some variation in stroke epidemiology owing to ethnicity 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, of stroke, among Afro-Caribbean populations. In the UK, the death rate from stroke is higher among individuals of South Asian origin than among the Caucasian population.[108] As ethnic diversity increases in the EU, appreciation of the risk factors in different ethnic populations should be high on the agenda. In addition, some conditions such as high blood pressure and diabetes, while being risk factors for stroke, increase the risk of developing AF.[62,103] AF is itself a significant stroke risk factor, and coexisting conditions such as diabetes and high blood pressure further increase the risk of

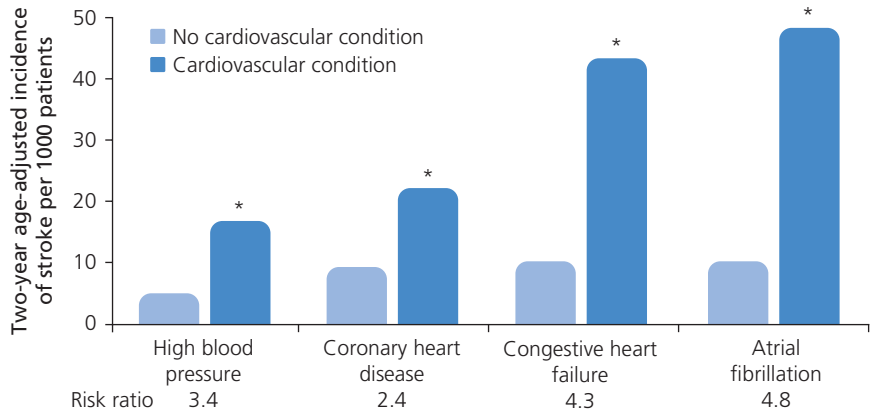
Figure 5. Costs attributable to stroke in Europe in 2010.





A: Total costs; B: cost per capita. Data taken from Gustavsson *et al.* (2011).[3]
Direct healthcare cost is estimated to be 66% of the total cost of stroke.[3]
PPP, purchasing power parity; UK, United Kingdom.

Figure 6. Two-year age-adjusted incidence of stroke in the presence and absence of cardiovascular conditions.



Atrial fibrillation confers a fivefold increase in the risk of stroke; in patients with high blood pressure, stroke risk is increased threefold. Adapted with permission from Wolf *et al.* Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991;22(8)983–988.[8]
*$p<0.001$.

stroke in patients with AF.[109] Risk factors for the development of AF were discussed in Chapter 4, 'Atrial fibrillation: a major risk factor for stroke' (page 19), and risk factors for stroke in patients with AF are discussed in Chapter 6, 'Characteristics of stroke and stroke risk factors in patients with atrial fibrillation' (page 33).

Therefore, stroke is clearly a costly health problem in Europe and a massive burden on patients, their carers, families and friends, and society. This burden falls disproportionately on the elderly because they are at the highest risk. Early diagnosis and effective management of AF would help to reduce the burden of stroke in the EU as discussed in Chapter 4, 'Atrial fibrillation: a major risk factor for stroke' (page 19). Furthermore, the prevention of stroke with pharmacological or non-pharmacological therapies in patients at high risk of stroke has the potential to significantly reduce this high economic burden.[110] For example, in patients with AF, a population that is 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.[111] The cost-effectiveness of anticoagulant therapy in patients with AF is discussed further in the section 'Cost of VKA therapy for prevention of AF-related stroke' in Chapter 8 (page 55), and the cost-effectiveness of the non-VKA oral anticoagulants (OACs) is also discussed later in Chapter 9 section 'Cost-effectiveness versus vitamin K antagonists' (page 64).

Chapter 6
Characteristics of stroke and stroke risk factors 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 5-year mortality from stroke**
- **The risk of permanent disability after stroke is almost 50% higher in patients with AF than in patients without AF**
- **A history of stroke in patients with AF increases the likelihood of another stroke by at least 2.5-fold**
- **Prior stroke, advanced age and high blood pressure increase the risk of stroke in patients with AF**
- **Patients in the EU may currently be receiving inconsistent advice and therapy owing to a lack of consensus on AF risk stratification and optimal prophylaxis**

A thromboembolism occurs after formation of a blood clot, followed by circulation of all or part of the blood clot in the bloodstream, resulting in ischaemic stroke or transient ischaemic attack (TIA; a clot within the brain), pulmonary embolism (a clot within the lungs) or systemic embolism (a clot within other arteries in the body).

Thus, strategies for the prevention of AF-related stroke require the use of 'anticlotting' (also referred to as antithrombotic or 'blood thinning') drug therapy. Strategies for prevention of AF-related stroke are discussed in Chapter 8, 'Prevention of atrial fibrillation-related stroke' and Chapter 9, 'Non-vitamin K antagonist oral anticoagulants for prevention of atrial fibrillation-related stroke', pages 45 and 57, respectively. Paroxysmal AF carries the same risk of stroke as permanent AF;[49,93] therefore, patients with paroxysmal or permanent AF should receive stroke prevention therapies according to their overall risk of stroke.[49] Risk factors for stroke in patients with AF and stratification schema devised to assess the individual risk of stroke are described in this chapter.

Increased severity of stroke

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

In addition to a high risk of stroke, patients with AF suffer from more severe strokes and have a poorer prognosis after the event than do patients without AF.[112] The increased severity of strokes in patients with AF is thought to be because such strokes are predominantly cardioembolic.[112]
A cardioembolic stroke is caused by a blood clot in the heart – all or part of which breaks away and becomes trapped in an artery in the brain.[112] Because they are formed in heart chambers (rather than in arteries or veins), cardioembolic clots are often large and, therefore, tend to block larger arteries.[113] Blockage of the larger arteries in the brain, compared with blockage of smaller arteries characteristic of other types of stroke, results in a larger infarction (i.e. greater damage) and thus a 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 at

discharge and increased length of hospital stay than patients with non-cardioembolic stroke.[114] Moreover, the mean costs of acute care were higher for cardioembolic stroke (€4890 per patient) than for non-cardioembolic stroke (€3550).[114] In addition to being more severe, cardioembolic strokes are associated with a higher risk of recurrence than other types of stroke.[115] AF is the cause of 50% of cardioembolic strokes (Figure 7).[116] This proportion may be even higher if patients with rheumatic heart disease and prosthetic valves are excluded.

The Copenhagen Stroke Study analysed in detail the characteristics and consequences of stroke in patients with AF compared with those without AF, reporting a 70% increase in in-hospital mortality in the presence of AF.[112] The increased severity of AF-related strokes compared with that of other strokes suggests that patients with AF will experience a greater impairment in quality of life than patients without AF. Patients with AF are, therefore, a key target population for reducing the overall burden of stroke on society.

Reducing AF reduces the prevalence and burden of stroke

Increased death rate

The death rate from stroke is significantly higher in patients with AF than in those without AF. In a large Italian study of patients who had suffered a first stroke, AF increased the 5-year mortality from stroke almost twofold (Table 4) and was an independent predictor of 30-day and 1-year mortality even after adjusting for other outcome predictors, such as age, sex and vascular risk factors.[9] The Austrian stroke registry also demonstrated an almost doubled death rate from stroke in the presence, compared with the absence, of AF (25% vs 14%).[117]

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

In view of the increasing prevalence of AF,[7] 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

As discussed previously, AF-related stroke is more severe and is associated with more ill health than stroke unrelated to AF.[9,19,112,118] In the European Stroke Community Project, the presence of AF increased the risk of remaining disabled after a stroke by almost 50%.[19]

AF increases the risk of permanent disability after a stroke by almost 50%

Data from the Copenhagen Stroke Study were used to investigate the impact of stroke on morbidity. Loss of ability to perform normal daily activities after a stroke, and decline in

Figure 7. The main cause of cardioembolic stroke is non-valvular atrial fibrillation.

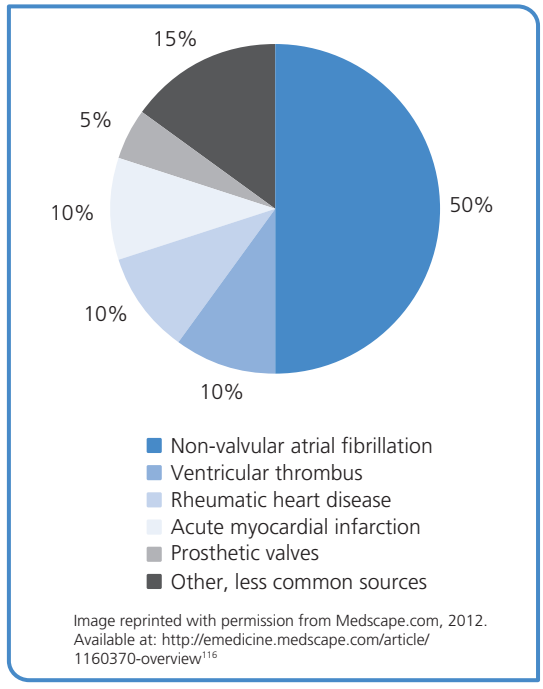


Image reprinted with permission from Medscape.com, 2012. Available at: http://emedicine.medscape.com/article/1160370-overview[116]

Table 4. Annual mortality rates from first stroke over a 5-year period (1994–1998) in patients with (n=869) and without (n=2661) AF.

	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

Rates are rounded to the nearest decimal place. Patients were included in the Italian prospective, population-based L'Aquila registry. Patients were followed up until 31 December 2001. Rates are the percentage of patients who were alive at the beginning of each year. Modified with permission from Marini *et al.* 2005. Contribution of atrial fibrillation to incidence and outcome of ischemic stroke: results from a population-based study. Stroke 2005;36(6):1115–1119.[9]
AF, atrial fibrillation.

neurological function – including level of consciousness, partial paralysis of the arm, hand and/or leg, and difficulty in swallowing – were significantly greater in patients with AF than in patients without AF, both immediately after the stroke and after rehabilitation.[112] In addition, AF was associated with a 20% increase in the length of hospital stay and a 40% decrease in the likelihood of a patient being discharged to their own home. In the European Stroke Community Project, patients with AF were more likely to be discharged to an institution after stroke.[19]

Furthermore, a recent systematic review and meta-analysis of 14 studies reported that AF was associated with a significant increase in the risk of dementia; this association seemed to be driven by those particular studies (7 in all) that were restricted to patients with stroke.[119] Therefore, this paper presents another aspect of AF-related stroke that is generally not considered.

Risk factors for stroke in patients with atrial fibrillation

Factors reported to further increase the risk of stroke in patients with AF include:[70,109,120–122]

- Prior stroke or TIA
- Advanced age
- High blood pressure
- Heart failure
- Diabetes
- Vascular disease
- Female sex

A history of stroke or TIA is the strongest independent predictor of stroke in patients with AF, increasing the risk of another stroke at least 2.5-fold.[70,109] Increasing age also has a significant effect on the risk of stroke among patients with AF, with more than twice the risk in patients aged 80–89 years compared with those aged 60–69 years.[70] High blood pressure also increases the risk of stroke approximately twofold in patients with AF.[70,109]

Although stroke and AF are both more prevalent in men than in women,[2,73] an analysis from the Euro Heart Survey for AF identified that the risk of thromboembolism for women with AF is more than twice that for men with AF.[120] However, not all studies have demonstrated such a significant difference between the sexes.[109,121] In a registry of patients with AF in Sweden, the overall rate of ischaemic stroke was 47% higher in women with AF than in men with AF.[122] Despite this, in patients younger than 65 years without other stroke risk factors, there was a similar risk between men and women with AF.[122]

Vascular disease is also an independent risk factor for AF-related stroke;[123–125] in a recent, large study in Denmark, vascular disease increased the risk of thromboembolism by approximately 10% in patients with AF.[124] In a separate study of patients in the Loire Valley in France, vascular disease was also found to be an independent predictor of stroke in younger patients with AF (<65 years).[125]

Although some of these risk factors can be controlled, such as high blood pressure, others cannot be controlled (e.g. sex and age). 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 system of classifying the level of stroke risk is needed. Several different models have attempted to grade the risk of stroke among patients with non-valvular AF according to the presence of coexisting conditions (e.g. previous stroke, TIA or blood clot; heart failure; high blood pressure; diabetes) and other factors, such as age and sex, that are known to increase the risk of stroke in patients with AF.[120] Well-known risk stratification schemes are summarized in Table 5.[11,61,88,94,120,126,127]

Previous stroke increases the risk of another stroke at least 2.5-fold in patients with AF

The schemes vary somewhat in the specific risk factors they incorporate and the methods of scoring and evaluation.

The American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) scheme,[61] groups

patients into low-, moderate- and high-risk groups based on combinations of risk factors (Table 5). Although not all physicians use risk stratification schemes, the most well-known risk stratification scheme is $CHADS_2$ (Congestive heart failure, Hypertension; Age ≥75 years; Diabetes; Stroke or TIA),[11,129] which provides an individual cumulative score with points given for individual risk factors, as outlined in Table 6.[11,129] Originally, in the 'classical' $CHADS_2$ classification, scores of 0, 1–2 and ≥3 described low, moderate and high risk of stroke, respectively.[129] These classifications were later 'revised' with scores of 0, 1 and ≥2 representing low, moderate and high risk of stroke, respectively (Table 5).[120] A drawback of $CHADS_2$ is that it does not include the other, less well-validated risk factors for stroke, such as vascular disease and female sex.[120] Thus $CHADS_2$ may underestimate stroke risk and could, therefore, result in an excess of patients being inappropriately allocated to low and moderate risk categories.

The $CHADS_2$ scheme has been expanded to include the more recently established risk factors for stroke: vascular disease, female sex and age 65–74 years.[120] This risk factor-based scheme can be expressed as the acronym CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, Stroke or TIA – Vascular disease, age 65–74 years, female sex [Table 6]), and it has been validated in an analysis from the Euro Heart Survey[120] and using large, real-world cohorts of patients not receiving anticoagulation therapy in the UK and Denmark.[69,70] Although kidney failure may also increase the risk of AF-related stroke,[90,130,131] it is not included in any of the stroke risk stratification schemes. Patients with severe renal failure are also at increased risk of

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

Table 5. Summary of the main systems for stratifying the risk of stroke in patients with atrial fibrillation.

Risk scheme	Low risk	Moderate risk	High risk
$CHADS_2$ (2001)[11,120,a]	Score 0 (original); 0 (revised)	Score 1–2 (original); 1 (revised)	Score 3–6 (original); 2–6 (revised)
Framingham (2003)[127,b]	Score 0–7	Score 8–13	Score 14–31
NICE guidelines (2006)[88]	Age <65 years with no history of embolism, hypertension, diabetes, or other clinical risk factors	Age ≥65 years with no high risk factors; age <75 years with hypertension, diabetes, or vascular disease	Previous ischaemic stroke, TIA or systemic embolic event; age ≥75 years with hypertension, diabetes, or vascular disease; clinical evidence of valve disease or heart failure; impaired left ventricular function on echocardiography
ACC/AHA/ESC guidelines (2006)[61]	No risk factors	Patient with only one risk factor: age ≥75 years; hypertension, diabetes, heart failure, or impaired left ventricular function	Previous stroke, TIA, systemic embolism; mitral stenosis; prosthetic heart valve; two or more of: age ≥75 years, hypertension, diabetes, heart failure, or impaired left ventricular function
ACCP guidelines (2012)[94]	$CHADS_2$ score = 0	$CHADS_2$ score = 1	$CHADS_2$ score ≥2
Rietbrock modified (2008)[126,c]	NA	NA	NA
CHA_2DS_2-VASc (2009)[120,d]	Score = 0	Score = 1	Score = 2–9

Reproduced from 'Performance of stroke risk scores in older people with atrial fibrillation not taking warfarin: comparative cohort study from BAFTA trial.', Hobbs *et al.* vol. 342, pp d3653, copyright 2011 with permission from BMJ Publishing Group Ltd.[128]

[a]Scoring system based on previous stroke or TIA (2 points), age ≥75 (1 point), hypertension (1 point), diabetes (1 point), congestive heart failure (1 point).

[b]Scoring system based on age (max 10 points), female (6 points), raised systolic blood pressure (max 4 points), diabetes (5 points), previous stroke or TIA attack (6 points).

[c]Scoring system based on age (max 6 points), female (1 point), diabetes (1 point), history of stroke/TIA (6 points).

[d]Scoring system based on congestive heart failure (1 point), hypertension (1 point), age ≥75 (2 points), diabetes (1 point), stroke/TIA/thromboembolism (2 points), vascular disease (1 point), age 65–74 (1 point), female (1 point).

ACC, American College of Cardiology; ACCP, American College of Chest Physicians; AHA, American Heart Association; $CHADS_2$, Congestive heart failure; Hypertension; Age ≥75 years; Diabetes; Stroke or TIA; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, Stroke or TIA – Vascular disease, age 65–74 years, female sex; ESC, European Society of Cardiology; NA, not available; NICE, National Institute for Health and Clinical Excellence; TIA, transient ischaemic attack.

Table 6. Comparison of the $CHADS_2$[11,129] and CHA_2DS_2-VASc[120] risk stratification schemes.

Risk factor	$CHADS_2$ score	CHA_2DS_2-VASc score
Congestive heart failure/left ventricular dysfunction	1	1
Hypertension	1	1
Age ≥75 years	1	2
Diabetes mellitus	1	1
Stroke/TIA/thromboembolism	2	2
Vascular disease	NI	1
Age 65–74 years	NI	1
Sex (1 point for female)	NI	1
Maximum	6	9

NI, not included; TIA, transient ischaemic attack.

death and serious bleeding and they are deliberately excluded from clinical trials; furthermore, their risk assessment and management is complex.[90,131,132]

The BAFTA Investigators, on the basis of their BAFTA validation study of contemporary AF-related stroke risk scores, have recommended a simple pragmatic policy of automatically defining all patients with AF older than 75 years of age as being at high risk of stroke – i.e. it is not necessary to determine the risk score in these patients.[128] This may help to reduce the inevitable physician inertia that follows multiple steps in determining management options. This simple clinical rule corresponds with the ESC 2012 guideline recommendations based on the CHA_2DS_2-VASc scheme (i.e. prophylaxis with an oral anticoagulant [OAC; an anticlotting therapy] because an age of 75 years or older results in a CHA_2DS_2-VASc score of 2).[90] These guidelines are discussed later in Chapter 10, 'Guidelines for the prevention of atrial fibrillation-related stroke', page 67.

Because the use of any antithrombotic ('blood thinning') therapy is associated with a risk of bleeding, it is important to identify patients who are truly at a low risk of stroke who may not benefit overall from preventive therapy. When patients participating in the Euro Heart Survey were stratified using various schema, the CHA_2DS_2-VASc scheme put the smallest proportion of patients into the low-risk stratum and the greatest proportion into the high-risk stratum (CHA_2DS_2-VASc 0 = low-risk, 1 = intermediate risk and 2 = high-risk [Table 5 and Figure 8]), in contrast to others.[120] In an analysis of 47 576 patients with a $CHADS_2$ score of 0 or 1 from a Danish registry, CHA_2DS_2-VASc provided substantial improvement over $CHADS_2$ in identifying patients truly at low risk of thromboembolism.[133] The 1-year stroke rate of patients with AF at increasing $CHADS_2$ and CHA_2DS_2-VASc score are compared in Table 7.[69] However, stroke risk is not stable over time. In a study of patients with 'lone' AF (i.e. without underlying coexisting disease [CHA_2DS_2-VASc = 0]), after a mean of 12 years of follow-up, 43% were no longer in the low risk category.[134] Patients with a CHA_2DS_2-VASc score of 0 should, therefore, be regularly monitored for the development of additional stroke risk factors.

Tools to assess anticoagulant-associated bleeding risk in patients with AF at risk of stroke have also been developed. Based on data on risk factors for major bleeding from the Euro Heart Survey in addition to data from systematic reviews, a new, simple bleeding risk score – HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile International Normalized Ratio, Elderly, Drugs/alcohol concomitantly) – has been derived for patients with AF:[135]

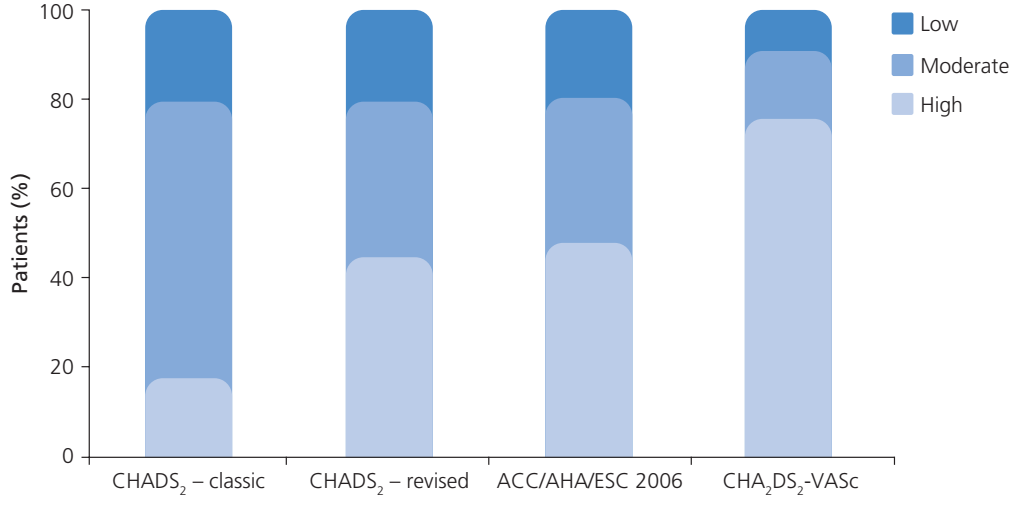
- High blood pressure (uncontrolled with therapy): 1 point
- Abnormal renal/liver function: 1 point each – maximum 2 points
- Stroke (previous history, particularly lacunar): 1 point
- Bleeding history or predisposition (e.g. anaemia): 1 point

- Labile international normalized ratio (INR; unstable/high INRs or in therapeutic range <60% of time): 1 point
- Elderly (>65 years): 1 point
- Drugs/alcohol (concomitant use of drugs such as antiplatelet agents and non-steroidal anti-inflammatory drugs or alcohol): 1 point for drugs plus 1 point for alcohol excess – maximum 2 points

Two other bleeding risk schema have been derived for assessment of patients with AF: HEMORR$_2$HAGES (Hepatic or Renal Disease, Ethanol Abuse, Malignancy, Older Age [>75 years], Reduced Platelet Count or Function, Re-Bleeding, Hypertension, Anemia, Genetic Factors, Excessive Fall Risk and Stroke)[136] and ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation).[137] The HAS-BLED score was further validated using 7329 patients with AF enrolled in a clinical trial[138] and has also been validated based on data from 965 patients with AF from an outpatient clinic in the UK.[139] Recent studies have also reported the HAS-BLED score to be a better predictor of bleeding risk than HEMORR$_2$HAGES and ATRIA, in patients with AF, including the risk for intracranial haemorrhage (the most feared type of bleeding).[138,140,141]

The HAS-BLED score demonstrates that there are several common risk factors for both stroke and bleeding, such as high blood pressure, advanced age and previous history of stroke, meaning that clinical decision making regarding anticoagulant therapy is often a difficult balancing act. However, in a study of more than 170 000 patients with AF in Sweden, the risk of ischaemic stroke increased more than the risk of bleeding with both higher HAS-BLED and CHA$_2$DS$_2$-VASc scores.[68] This study and another study, involving more than 130 000 patients with AF in Denmark, analysed the balance between ischaemic stroke risk reduction and associated intracranial bleeding risk resulting from anticoagulant therapy (giving intracranial bleeding 50% more weight than ischaemic stroke).[68,142] In both studies, although the outcome was negative with a CHA$_2$DS$_2$-VASc score of 0, irrespective of bleeding risk, there was a neutral or positive benefit of vitamin K antagonist (VKA) treatment in patients with a CHA$_2$DS$_2$-VASc score of 1 or more. Therefore, the benefit of stroke risk reduction outweighs the risk of bleeding associated with anticoagulant therapy in nearly all patients, with the exception of those at very low risk who can be identified using the CHA$_2$DS$_2$-VASc score.

Figure 8. Percentage of patients with atrial fibrillation from the Euro Heart Survey 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. Data taken from Lip *et al.* 2010.[120]
ACC, American College of Cardiology; AHA, American Heart Association; CHADS$_2$, Congestive heart failure; Hypertension; Age ≥75 years; Diabetes; Stroke or TIA; CHA$_2$DS$_2$-VASc, Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, Stroke or TIA – Vascular disease, age 65–74 years, female sex; ESC, European Society of Cardiology; TIA, transient ischaemic attack.

Table 7. Stroke rates from a Danish registry as a function of $CHADS_2$ and CHA_2DS_2-VASc score.

	1-year stroke rate (%)	
Score	$CHADS_2$	CHA_2DS_2-VASc
0	1.67	0.78
1	4.75	2.01
2	7.34	3.71
3	15.47	5.92
4	21.55	9.27
5	19.71	15.26
6	22.36	19.74
7	–	21.50
8	–	22.38
9	–	23.64

Data from Olesen *et al.* 2011.[69]

Recent ESC guidelines state that it is reasonable to use the HAS-BLED score to assess bleeding risk in patients with AF on the basis that a score of ≥3 indicates high risk.[90]

The guidelines recommend that 'some caution and regular review' of patients with HAS-BLED ≥3 is needed after antithrombotic therapy initiation.[90] The HAS-BLED score is also a useful tool to identify modifiable factors, which can then be addressed by the physician and the patient, meaning that bleeding risk could be reduced over time. However, the HAS-BLED score should not be used on its own to exclude patients from receiving OAC therapy.

Different risk stratification schemes, therefore, 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.

Risk estimates from different risk stratification models vary, potentially resulting in inconsistent advice and therapy across the EU

Uniform acceptance of guidelines published by the ESC, which advocate use of the CHA_2DS_2-VASc and HAS-BLED schema,[90] could address many such inconsistencies.

Chapter 7
The high cost of atrial fibrillation and atrial fibrillation-related stroke for individuals and society

Key points

- **AF alone can impose a significant burden on patients and can markedly affect their quality of life**
- **Stroke is a devastating event that exerts a huge toll – not only on the patient but also on the patient's family, who are often completely unprepared for the consequences**
- **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 and clinical consequences associated with stroke are greater for AF-related stroke than for non-AF-related stroke**

Being diagnosed with atrial fibrillation

The typical 'journey' for a patient diagnosed with AF involves the following:[143]

- Fear and confusion – an anxious search for an explanation of symptoms, often over an extended period of time, before a diagnosis is finally made
- Turmoil – unpredictable, recurrent and invasive symptoms, emotional distress, fear of stroke, and loss of hope, especially when treatments fail
- Despondency – uninformed and unsupported, symptoms dismissed or not considered, fear of death and stroke, and uncertainty as to what the future holds
- Relief and hope – diagnosis, validation, control and hope

Results from one study found that one-third of patients with AF suffer depression and anxiety; symptoms of depression were the strongest independent predictor of quality of life.[144]

Beyond the numbers – living with atrial fibrillation

AF affects patients and their families in many different ways, and to a greater or lesser extent. For those who suffer an AF-related stroke, the impact of the condition is profound – not only for the patients but also for their families and others who suddenly find an unexpected burden of care thrust upon them.

The following are a few personal recollections that can hopefully provide some sense of what it is like to live with AF and its consequences.

M's story

"In 2003, I was working in my home office when my heart felt like it skipped some beats and started racing, pounding and flopping. I got dizzy and light-headed, and I thought I was going to pass out. My right leg was ice cold, and the vision in my right eye was blurry.

At the emergency room, they said I'd had blood clots and had had a close call with a stroke, due to AF. I'd never heard of AF. I got prescriptions for a β-blocker and warfarin (a blood thinner), and they said, 'you'll be fine'. But I wasn't fine.

AF episodes occurred frequently, leaving me emotionally drained, feeling like a limp dish-rag and wanting to do nothing but sleep. My family wouldn't let me go anywhere by myself for fear I'd be by myself and have a stroke (and die). Everywhere I went, I had to make sure I had a mobile phone and β-blocker with me, even when just going to the mailbox.

Worst for me was the warfarin, which meant no yard work, no kitchen knives and no shaving my legs. I constantly 'ping-ponged' between the risk of developing clots and the risk of having a bleed. I had more than just bruising: I was black, blue and purple all over – all over my arms, legs, torso and even face. I often heard 'if you just eat right, you'll be fine'. I did eat right, but I wasn't fine. I was never stable on warfarin, apparently for genetic reasons.

Once you've had blood clots, AF becomes terrifying – the fear is constant. I was literally a stroke walking around waiting to happen. However, after 22 months, I had a procedure – a minimally invasive surgical ablation – and I have now been AF-free for 7 years."

J's story

"When I was 20, I woke up one morning with a pounding in my chest, with no previous warnings at all. All day it was on and off and my heart was going about 240 bpm (beats per minute). Eventually I went to my local A&E but after a few hours they let me go, even though I still had a heart rate of about 120 bpm. The following day, I woke up and was fine until midday, when I nearly collapsed: my dad took me straight to my local hospital, where I stayed for 2 weeks before being sent to a larger hospital to be seen by an arrhythmia specialist. At the main hospital, they diagnosed a supraventricular tachycardia ([SVT] *any arrhythmia originating in the upper portion of the heart – see Glossary*), but this time I couldn't do anything without triggering it, which was very frightening and not good for my self-confidence at all!

To try to cure the SVT, I had a catheter ablation which, unfortunately, wasn't successful. I stayed in hospital for a month and then, a month after returning home, I went back in for a second ablation, which was successful. I was off work for 9–10 months in total and, at first, I was scared to even walk down my stairs. I didn't leave the house for a good 3–4 months, even after my successful operation. When I was in hospital, the staff had to encourage me to get up from my bed. I had many days when I just cried and thought 'why me?' and I struggled to even leave my bed because I was so frightened. Worse – I was still having the odd missed beat, which frightened me in case it meant the arrhythmia was coming back.

I eventually got my confidence back after 10 months (a long, hard time), got back to work and started to feel normal again. But, to my great disappointment, after 2 months back in work, my heart went into another arrhythmia one afternoon, which was later diagnosed as AF. This led to me leaving the job and finding a new, less stressful job, although I was determined that the AF was not going to beat me anymore. So now it doesn't frighten me, but I know it will always be there.

This is a very brief summary of my experiences with SVT and AF. Please believe me when I say it is not very nice at all. It is possible to overcome the mental strain it causes and to learn to live with AF – it just may take time."

E's story

"My AF started about 10-plus years ago when I woke up one morning and found that I couldn't stand up for very long without feeling very faint. I ended up at A&E, where I spent several hours, but the AF resolved on its own. The hospital staff said it was due to my age (52) and wouldn't happen again. Well, about 3 weeks later, it did happen again, so back to A&E and this time I was admitted and they changed my drugs from atenolol to sotalol. Once again, my AF reverted on its own and I went home. However, I ended up back in A&E the day before Christmas Eve for an ECG *(electrocardiogram)* and, as the ECG showed changes, they kept me in all over Christmas. I had an angiogram, which was negative so that at least was reassuring.

I still felt awful: tired, depressed and short of breath, and my previously controlled blood pressure was fluctuating widely. When they told me that this was the best life was going to be, and I would just have to get used to it, I was horrified. Luckily, we were able to see a top cardiologist who put me back on atenolol and I then had a long struggle getting my blood pressure back to normal. About 3 months later, the AF started again and, from then on, I ended up in A&E about every 6 weeks, sometimes having a cardioversion, sometimes nothing – neither of which worked for very long.

Eventually cardioversion didn't work and the AF stubbornly stayed put; I had been in hospital about 5 days when they decided to do an ablation. This got rid of the flutter, but the AF didn't go away. I had another cardioversion about 6 weeks later. I think

I then went 3 months before the AF started playing up again – that was quite a long time ago.

In 2006, I had a pulmonary vein isolation (*a kind of ablation – see Glossary*) done under general anaesthetic. I felt pretty rough when I woke up and was kept in an extra day but it took me about 3 months to get back to feeling normal. However, the procedure worked and I was relatively free from AF, or at least I could cope with the level I was experiencing, for the next 18 months. I thought all my problems were solved, but then suddenly, about 3 weeks after my 60th birthday, I went back into AF and the saga began again.

Since then, I have had two more ablations. Neither worked for very long and of course my tablets kept getting changed to try and ease the AF. However, things did gradually improve and now I am okay; certainly, I've had no more hospitalizations for the AF (although I am still aware of it at times), and life is now good. I will be on warfarin and medication for my blood pressure for life."

K's story – the personal impact of AF-related stroke

"We hear people use the terms 'stroke victim', 'cancer victim' and 'road accident victim' all the time. People who suffer from any of these things are obviously victims but you rarely, if ever, hear anything about the person who looks after them being a victim. However, when you suddenly, without warning, find yourself in shock, in at the deep end, with no knowledge, caring for someone, that carer is a victim in their own right. Overnight, I became an authority on a subject, an illness, that I never wanted to know about and never thought I would have to learn about. That doesn't mean you want sympathy or that you wouldn't gladly look after your beloved, but caring for someone, especially when you don't know what the long-term outcome of their condition will be, is frightening, wearing, exhausting and life-changing.

When my husband had a stroke 2.5 years ago, it was without any doubt life-changing for both of us. It might sound dramatic but when I think about it now, 2.5 years later, that image of finding my husband that day, 1st March 2008, is still shocking. The details of everything that happened in those first few hours and weeks after the stroke are as sharp as if it had happened yesterday. When I woke in the morning, those few seconds in that dopey half-asleep state were the only peace I got because as soon as my brain kicked in, the panic was overwhelming. The days consisted solely of twice-daily hospital visits, catching the doctors on their rounds so I could ask questions and answering endless phone calls from well-meaning friends and family. And then it was more phone calls to my husband's employers, consultants, GP, physiotherapists and so forth. When John came out of hospital, all of my 'spare time' was spent on the computer researching stroke and, latterly, when it was diagnosed, AF – something I'd never even heard of. Doing all this when you feel beside yourself with worry is doubly exhausting. When it happened, I only told a handful of people because it was so exhausting having to go through the whole scenario. It felt like I was ringing people just to give them bad news and talking about it was emotionally draining and depressing – I nearly always came off the phone in tears, feeling like I'd been wrung out. My mother used to constantly say to me 'you've got to be strong for John, you know' and I'd think 'what about me?' I'm human and I have a breaking point.

I don't consider myself to be a carer in the real sense of the word because my husband went back to work after a year and we do count ourselves very lucky that our outcome was so good, but I know I've changed and that our lives aren't the same. A stroke, by definition, means a part of the brain has died, so how can that someone ever be the same person again? And, really importantly, their partner needs to go through a period of mourning because you have, in essence, lost at least a part of the person you once had and that's something I don't think anyone who hasn't been there realizes.

As soon as AF was diagnosed as the cause of the stroke, I went completely into overdrive. Getting John's heart back in rhythm became my complete focus, I didn't really think about anything else. His treatment for AF had started with trying different drugs and every new one gave us a bit of hope but none of them provided a long-term solution. Finding the right doctor was obviously crucial and it goes without saying that it is paramount to have confidence in your doctor and to feel comfortable about asking questions and, very importantly, to understand the answers.

A cardioversion quite early on put John's heart back into rhythm but only for a few days. He said he suddenly felt unwell and had some discomfort in his chest, and when I listened, his heart had gone back into an irregular beat. We were absolutely devastated. I have never, ever been so frightened as I was when John went down for his first ablation procedure. By the time he came back from the lab 8 hours later, I was frantic with worry! There's a risk of stroke when they do an ablation and the risk is bigger if you've already had a stroke, and that was my greatest

worry – not that the procedure wouldn't work but that another stroke would happen. By then, John had made considerable progress and the thought of going back to square one – or worse – was unthinkable.

From my experience of the last few years, people in general haven't heard of AF. We've all heard of stroke; most of us probably know or know of someone who's had one. I certainly didn't need the FAST campaign that was running at the time on TV to know that John had had a stroke. By contrast, everyone everywhere knows what finding a lump can mean and, however scared you would be to find a lump, you would go to the doctor. We knew, completely by accident, that before the stroke, my husband's heart wasn't in rhythm. We were lying in bed watching TV one evening and I could hear his heartbeat was really irregular. What we didn't know was what that meant or what it could cause and unbelievably, stupidly, neither of us investigated it. It wasn't until we were in A&E about 6 weeks later and the doctor asked me if my husband had a heart condition that I remembered the incident.

Everyone needs to be as knowledgeable about checking for an irregular heartbeat as they are about checking for a lump. I always knew that of the two things, stroke and AF, the AF was treatable (probably/hopefully) but there is no going back from a stroke. How can there be? If we had known about AF, the stroke could probably have been prevented. We're just thankful that our story has turned out as well as it has. One thing I don't do anymore, which I used to do every day, is listen to his heart. After three ablations, his heart has now been in rhythm for 10 months and I literally can't bear to listen anymore in case I hear the unbearable.

I will say that, as important as it is to only look to the next day when you're in crisis, it is sometimes good to look back and see how far you have come. And if a major health scare teaches you anything, it's that you 'don't sweat the small stuff anymore' because nothing else will ever be that frightening again."

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

These are just a few patient experiences – there are approximately 10 million people living with AF in the EU alone – all with their own experience of the huge toll that AF exerts, and its impact on their families.

Other patient stories can be found at:
http://www.stopafib.org/stories.cfm
http://www.atrialfibrillation.org.uk/case-studies/

Significant impact of atrial fibrillation-related stroke 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 effect that a state of health has on health-related quality of life on a scale of 0 to 10, where 10 represents perfect health and 0 represents death. Murphy *et al*. found that mild stroke yielded a higher utility score (9/10) than severe stroke (4/10).[145] AF-related strokes result in lower utility scores than other types of stroke, which is consistent with AF-related strokes being more severe than strokes in patients without AF. 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'.[146]

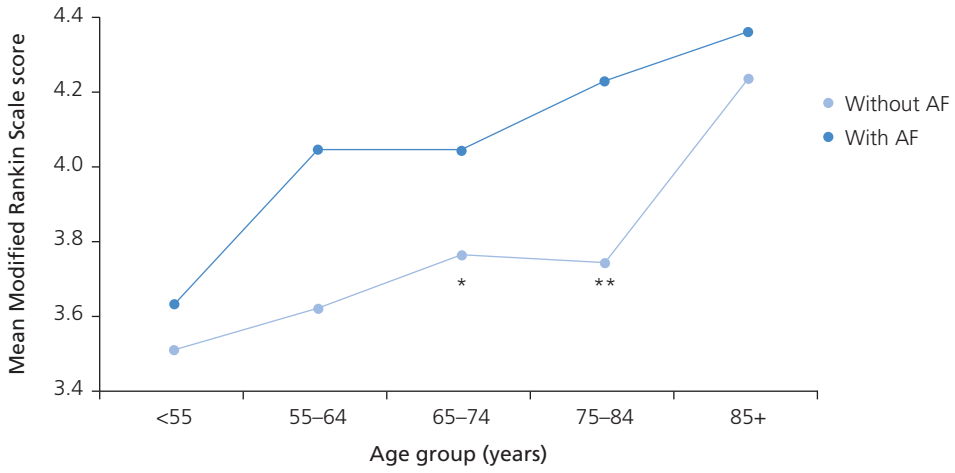
In addition to general utility scores, other scores assess the impact of a state of health on a specific aspect of quality of life (such as neurological function). The modified Rankin Scale (mRS) is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke (Table 8).[147] Dulli *et al.* compared the mean mRS scores of patients after an AF-related versus a non-AF-related ischaemic stroke (Figure 9).[148] As for utility scores, mRS scores indicate that AF-related stroke has a greater negative impact on quality of life than non-AF-related stroke.

Table 8. The modified Rankin Scale.[147]

Grade	Description
0	No residual symptoms
1	Some symptoms but no significant disability and able to carry out all usual activities
2	Slight disability and unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability requiring some help but able to walk unassisted
4	Moderately severe disability, being unable to walk and attend to own bodily needs without assistance
5	Severe disability, being bedridden and incontinent and requiring constant nursing care and attention

Adapted with permission from van Swieten *et al.* Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988;19(5):604–607.[147]

Figure 9. Disability after AF-related and non-AF-related ischaemic stroke, based on modified Rankin Scale score.



Data from 1061 patients with ischaemic stroke. *p*-values refer to differences between patients with AF-related versus non-AF-related stroke. Redrawn from Figure 2 from the article *Neuroepidemiology* 2003;22:118–123 and reprinted with permission from S. Karger AG, Basel.[148]
*$p<0.05$; **$p<0.0005$.
AF, atrial fibrillation.

AF also increases the risk of medical complications after stroke. Compared with those without AF, patients with AF suffer more frequently from pneumonia, pulmonary oedema (accumulation of fluid in the lungs) and neurological complications after stroke.[117]

AF increases the risk of medical complications after stroke

Heavy burden on carers, families and society

Approximately one-third of patients who experience a stroke return to their home with some level of permanent disability.[4] As discussed in the previous chapter, in the European Stroke Community Project, the presence of AF increased the risk of remaining disabled after a stroke by almost 50%.[19] Patients then rely on informal carers, typically family members, to help with their normal daily activities and to arrange the required additional assistance from healthcare services. In addition to giving practical help, carers have to manage the often considerable cognitive, behavioural and emotional changes in the patient. These changes include mood swings, personality changes, irritability, anxiety, memory loss and depression.[4,149] 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

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."

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 couldn't understand. I was scared of him, I didn't want to see him anymore. I was ashamed of him… he doesn't remember much about it. He doesn't look like Daddy anymore."

After a stroke, patients with AF are almost 50% more likely to be permanently disabled than patients without AF

the patient and distress at not having time to attend to all of the patient's needs.[4,149]

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

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.[98,150] 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 huge overall burden on society.

High economic cost

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

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.[151] The total economic cost of stroke is probably even greater than this, because these calculations generally omit costs incurred by the patient and carers, which can be difficult to estimate. The total cost of stroke in the EU plus Iceland, Norway and Switzerland in 2010, including healthcare costs, direct non-medical costs (e.g. nursing care) and indirect costs (e.g. costs borne by patients and carers, loss of productivity, etc.), was calculated to be over €64 billion.[3]

Because stroke in patients with AF is more severe than stroke in patients without AF,[112] it is likely to incur greater costs. In a French study, the mean total cost of a severe stroke was €34 809 per patient – more than three times higher than the mean cost of a mild stroke (€10 530 per patient).[152] Similarly, in Sweden, the estimated costs for the first year of care after a severe stroke (approximately €8500–59,000) were considerably higher than those for a mild stroke (approximately €6200–20,000).[153]

There is also direct evidence for the increased cost of stroke in patients with AF. In the Berlin Acute Stroke Study, the average direct cost of stroke per patient was significantly higher in patients with AF (€11 799) than in patients without AF (€8817).[37] The additional costs for AF-related stroke were driven by acute hospital treatment costs and the cost of nursing care at home. The effect of AF on stroke-related inpatient costs was also recently analysed over a 3-year period in Sweden.[154] Among stroke survivors, the inpatient costs over this period were on average €818 higher in patients with AF than in patients without AF (€10 192 vs €9374) after controlling for additional risk factors and death rates.[154] Because AF is responsible for approximately 15% of all strokes,[92] the increased cost of AF-related strokes compared with other strokes represents a significant economic burden for the EU. Fifteen per cent of the overall burden of stroke in Europe in 2010 (€64 billion)[3] represents an annual cost of approximately €10 billion for AF-related stroke. However, this is likely to be a considerable underestimation of the real burden, because – being more severe and more costly – AF-related strokes are likely to account for a larger proportion of the overall cost of stroke.

Analyses of the cost burden may also neglect to take into account the increased risk of dementia in patients with AF-related stroke.[119] The precise long-term cost impact of managing this particular patient group is unknown, but it no doubt contributes in some capacity to the underestimation of the total cost burden of AF-related stroke.

Strong rationale for prevention of atrial fibrillation-related stroke

In conclusion, AF alone can impose a severe burden on patients' lives. Furthermore, 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. As AF-related stroke is preventable, there is a clear opportunity to reduce not only a significant proportion of stroke deaths but also the human and economic burden associated with both acute- and aftercare following the more severe and disabling strokes associated with AF. Therefore, it is imperative that effective management of AF and prevention of stroke be provided for this high-risk population.

Chapter 8
Prevention of atrial fibrillation-related stroke

Key points

- For direct treatment of AF, several drugs are available to stabilize the abnormal heart rhythm and/or reduce a rapid heart rate
- It is strongly recommended that patients diagnosed with AF also receive therapy to reduce the risk of blood clots forming, and thereby reduce the risk of cardiogenic thrombi migrating to the brain
- Currently available anticlotting therapies are effective in the prevention of AF-related stroke, but the limitations associated with vitamin K antagonists (VKAs) and aspirin led to the development of alternative oral anticoagulants (OACs)
- High blood pressure and diabetes, which commonly affect patients with AF, also require management to reduce the risk of stroke

General management of a patient with AF involves reduction of a rapid heart rate, sometimes accompanied by restoration and maintenance of a normal heart rhythm, along with management of coexisting cardiovascular conditions such as diabetes and high blood pressure. 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. Even when strategies are employed to correct the abnormal heart rhythm, AF recurrences are likely, and drugs to reduce the risk of blood clots and, hence, stroke are also required. These strategies are discussed in more detail in this chapter.

Strategies for stabilizing heart rhythm

AF is most commonly managed using 'rhythm control' or 'rate control' strategies.[155] In rhythm control, drugs (known as anti-arrhythmic drugs) are used to reduce the irregularity of the heart's rhythm; in rate control, drugs are used to reduce a rapid heart rate.[155] Examples of drugs used for rhythm or rate control include amiodarone, dronedarone, digoxin and β-blockers. Non-pharmacological methods used to treat AF include electrical cardioversion (a process by which an abnormal heart rhythm is terminated by the delivery of electric current to the heart), and catheter or surgical ablation (procedures used to block faulty electrical pathways in the heart).

Pharmacological methods for stabilizing heart rhythm

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

Effective management of AF resulting in restoration of the normal heart rhythm could, in theory, prevent stroke by stopping the formation of blood clots in the heart. In practice, large studies comparing rate control with rhythm control have found no difference between the two strategies for clinical outcomes such as hospitalization or death (any cause or cardiovascular causes).[156–158] In fact, some studies demonstrated higher event rates with rhythm control than with rate control. Furthermore, these studies failed to demonstrate a reduction in the risk of stroke with rhythm control compared with rate control.[156–158] Studies of anti-arrhythmic drugs (such as amiodarone) compared with placebo specifically designed to look at these outcomes had not been carried out[159] until a fairly recent study of the newer anti-arrhythmic drug dronedarone.[160] In a phase III study of 4628 patients with paroxysmal or persistent AF

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

(the ATHENA study), over a follow-up period averaging 21 months, dronedarone was shown to reduce the incidence of death or hospitalization owing to cardiovascular events compared with placebo.[160] In a *post hoc* analysis of the ATHENA data, dronedarone was also associated with a reduced risk of stroke compared with placebo, particularly in patients with multiple risk factors for stroke.[161] However, studies have demonstrated that dronedarone is not safe in patients with heart failure[162] or with permanent AF,[163] because treatment resulted in a higher risk of death owing to cardiovascular causes compared with placebo in these patients. A comparison of available anti-arrhythmic drug options, including dronedarone, found amiodarone to be most effective for maintenance of a normal heart rhythm but resulting in the highest incidence of adverse events.[164] Recently, the 2012 update to the European Society of Cardiology (ESC) guidelines stated that dronedarone is appropriate for maintaining sinus rhythm in patients with paroxysmal or persistent AF; it should not be given to patients with moderate or severe heart failure, and should be avoided in patients with less severe heart failure, if appropriate alternatives are available.[90]

Because a clear benefit of rhythm control over rate control is yet to be demonstrated, and owing to the potential for adverse events caused by the use of anti-arrhythmic drugs, a rate control strategy is usually adopted first.[49,155] Rhythm control is sometimes undertaken in younger patients and for relief of AF symptoms when these are not alleviated by the rate control strategy.[49]

Non-pharmacological methods for stabilizing heart rhythm

Electrical cardioversion

Electrical cardioversion is effective at returning the heart to normal sinus rhythm quickly, but without additional therapy most patients (70–80%) revert back to AF within a year; anti-arrhythmic drugs are usually required to maintain sinus rhythm.[165] Furthermore, it is well known that there is an increased risk of thromboembolism after cardioversion.[90] In patients with AF lasting 48 hours or longer, OAC therapy is, therefore, recommended both before and after cardioversion, regardless of the method used (i.e. electrical or pharmacological).[90] Current guidelines also recommend that in patients with risk factors for stroke or AF recurrence, OAC therapy should be continued for life.[90]

Catheter ablation

Catheter ablation is carried out by an electrophysiologist in a specialist catheterization laboratory and involves inserting a catheter-based energy source into the heart via the blood vessels (through small incisions in the groin, arm or neck area). This energy source is then used to ablate the tissue in key areas responsible for the irregular heartbeat (usually the areas around the pulmonary veins), creating a 'conduction block'.[166] A number of different energy sources can be used for the ablation (e.g. radiofrequency, cryothermy [intense cold], laser energy).[49] The findings of a recent Danish study are reported in the 2012 ESC guidelines update, comparing catheter ablation with anti-arrhythmic drug therapy as a first-line rhythm control strategy in patients with AF.[90] After 2 years, significantly more patients were AF-free in the catheter ablation group, with significant improvements in quality of life also reported compared with drug therapy at 1 and 2 years. Indeed, current ESC guidelines recommend considering catheter ablation instead of anti-arrhythmic drugs as a first-line therapy in patients with symptomatic paroxysmal AF, taking into consideration patient choice, benefit and risk.[90] However, AF recurrences during long-term follow-up have been reported with catheter ablation;[90,167] paradoxically, there is also a small risk of thromboembolism in the days and weeks after the ablation.[168] Reports suggest that there are fewer complications when OAC therapy is continued; therefore, current ESC guidelines recommend undertaking catheter ablation while continuing low-level anticoagulation (international normalized ratio [INR] 2.0–2.5).[90] Long-term OAC therapy should also be continued in all patients with a CHA_2DS_2-VASc score of 2 or more, irrespective of the apparent success of the procedure. However, the guidelines acknowledge that experience with non-VKA OACs for peri-procedural anticoagulation is limited.[90]

Surgical ablation

Because surgical procedures for rhythm control involve making incisions or ablating tissue from the outside of the heart on the external wall of the atria, to disrupt the faulty electrical pathways, these have to be carried out by a cardiothoracic surgeon.[166] The earliest form of this is the Cox-Maze III procedure, in which a complex series of incisions is made in the atrial walls in a maze-like pattern (Dr James Cox first developed this technique in the 1980s). It is also often referred to as the 'cut and sew' Maze procedure.[166] Although Cox-Maze III is extremely successful at eliminating the arrhythmia, with reports of freedom from AF in 75–95% of patients up to 15 years after the procedure,[49] it is also very complex and requires open heart surgery. As a consequence, it is often reserved for those patients who are undergoing open heart surgery for another procedure such as valve replacement. It is also associated with an increased mortality risk and other complications and is, therefore, not routinely used in patients with AF.[49] The Cox-Maze IV procedure is similar to Cox-Maze III but is a surgical ablation with a an energy source to isolate or ablate the problem tissue on the external wall of the atria (again, the target is usually the tissue around the pulmonary veins). Sinus rhythm is restored in around 85% of patients at 1 year, with slight variations in success rates depending on the energy source used.[49] However, this also requires open heart surgery. By contrast, the mini-maze procedure involves surgical ablation, which can be carried out via small incisions in the chest wall, and so is considered to be minimally invasive.[166] Reported success rates for the mini-maze procedure are generally between 50% and 90% depending on the type of AF (www.stopafib.org/mini-maze-success-rates.cfm). Although these surgical procedures are more invasive and associated with more complications than catheter ablation, they are more successful at preventing AF recurrence because they can more easily achieve complete isolation of the 'problem areas' responsible for the irregular impulses.[49,169] They also enable other procedures that help reduce stroke risk to be carried out (e.g. occlusion or excision of the left atrial appendage [LAA]; see the section 'Invasive strategies for preventing thrombus formation: LAA closure' in this chapter and Chapter 13, 'New developments for the management of atrial fibrillation and the prevention of atrial fibrillation-related stroke', page 87).[49]

Irrespective of the success rates seen, patients who have undergone surgical or catheter-based ablation should not automatically stop receiving oral anticoagulation; reversal of atrial remodelling resulting from the arrythmia takes place after surgery and is often complicated by further arrhythmia.[49] According to the ESC guidelines, anti-arrhythmic and anticoagulation drugs should be continued for at least 3 months after surgery, and withdrawal is based on clinical, ECG and echocardiographic assessment at 3-, 6- and 12-month follow-up.[49]

In summary, even when a rhythm control strategy is adopted to restore or sustain a normal heart rhythm, anticlotting therapy is still required in patients at risk of stroke, because unpredictable recurrences of AF are likely.

Strategies for preventing formation of blood clots

Anticlotting drug therapy

Strategies for the prevention of AF-related stroke generally require the use of antithrombotic drug therapy to prevent the formation of blood clots in the fibrillating atrium. It is, therefore, recommended that patients with AF who are at an increased risk of stroke (i.e. CHA_2DS_2-VASc score ≥1) should receive some form of antithrombotic therapy, specifically OAC therapy in the first instance (see Chapter 10, 'Guidelines for prevention of atrial fibrillation-related stroke', page 67).[90]

Patients with AF and an increased risk of stroke should receive antithrombotic therapy

There are two main classes of anticlotting drugs (also known as antithrombotic drugs or 'blood thinners') currently used in the prevention of AF-related stroke:[170]

- The major class is anticoagulants, which interrupt the pathway of biochemical reactions that result in the formation of a blood clot (the coagulation pathway; Figure 10)
- Antiplatelet drugs, although much less effective than anticoagulants, are also used in certain circumstances. These inhibit the aggregation of platelets (components of the blood that contribute to clot formation and form a significant part of the blood clot)

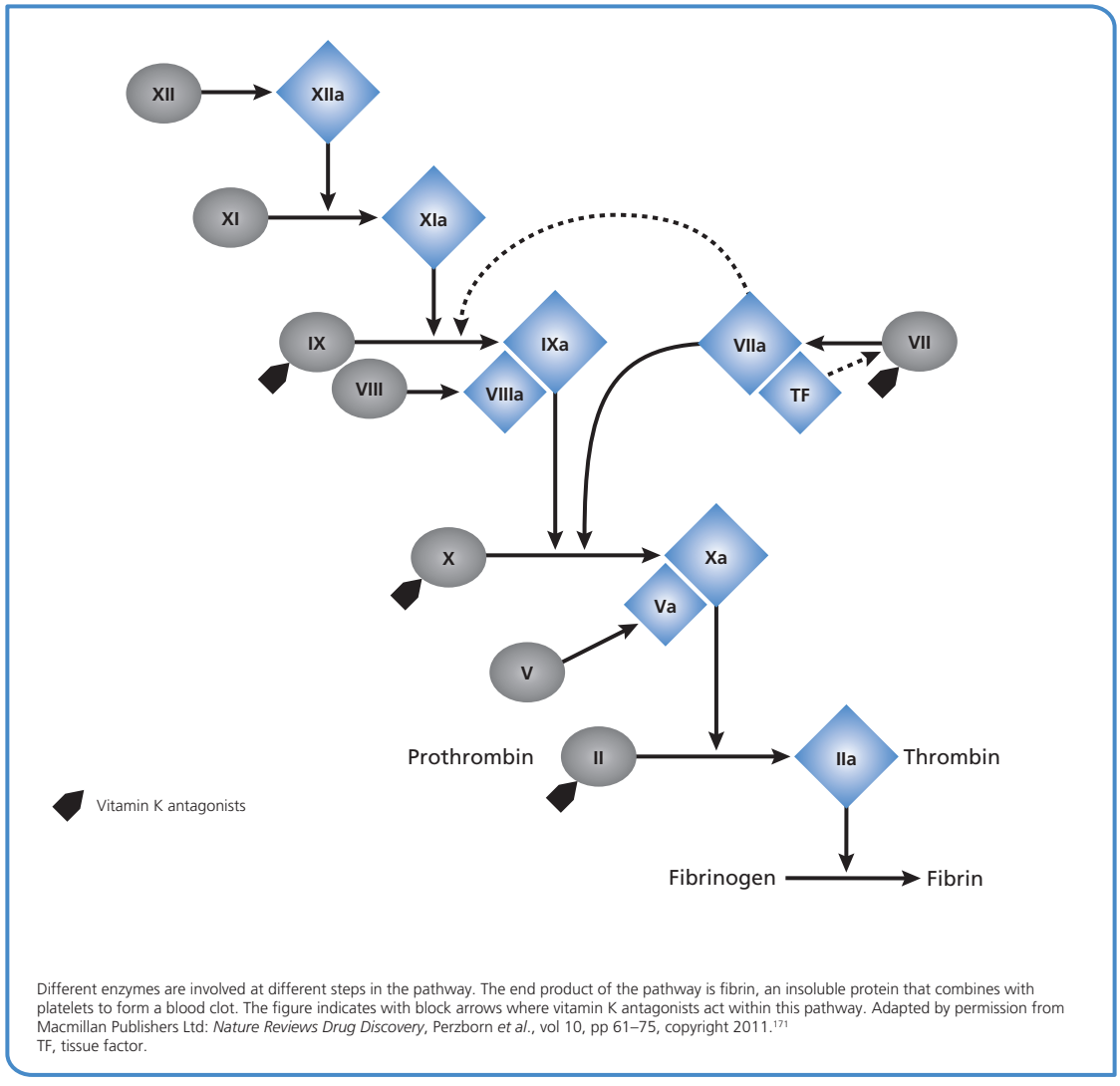
Because these agents diminish the ability of the blood to form clots, their use is also associated with a risk of bleeding. Use of these drugs, therefore, requires careful assessment by physicians of both stroke and bleeding risk on an individual patient basis (see section 'Approaches to risk stratification', page 35 in Chapter 6 'Characteristics of stroke and stroke risk factors in patients with atrial fibrillation'). The most feared type of bleeding resulting from the use of antithrombotic drugs is bleeding within the brain (known as intracranial haemorrhage).

VKAs, which are a type of OAC, and aspirin, an antiplatelet agent, are currently the most widely used drugs in the prevention of AF-related stroke. Alternative non-VKA OACs are also now available; these are discussed in Chapter 9, 'Non-vitamin K antagonist oral anticoagulants for prevention of atrial fibrillation-related stroke' (page 57).

Vitamin K antagonists

VKAs, such as warfarin, exert their anticoagulant effects by inhibiting the vitamin K-dependent synthesis of four proteins that play key roles in the coagulation pathway (Figure 10).[170] This pathway is a series of enzyme reactions, which also involves platelets, and ultimately produces fibrin, an insoluble protein that forms blood clots. The effects of VKAs can be significantly modified by genetic factors[172] and interactions with other drugs and food,[173] including amiodarone, an anti-arrhythmic drug discussed

Figure 10. Simplified diagram of the coagulation pathway – a series of enzyme reactions involved in the formation of a blood clot.



Different enzymes are involved at different steps in the pathway. The end product of the pathway is fibrin, an insoluble protein that combines with platelets to form a blood clot. The figure indicates with block arrows where vitamin K antagonists act within this pathway. Adapted by permission from Macmillan Publishers Ltd: *Nature Reviews Drug Discovery*, Perzborn *et al.*, vol 10, pp 61–75, copyright 2011.[171]
TF, tissue factor.

in this chapter (in the section on 'Strategies for stabilizing heart rhythm', page 47).[174] Furthermore, there is a narrow window between the dose of VKA that achieves therapeutic efficacy and the dose that produces an unacceptable increase in bleeding risk (i.e. a narrow therapeutic range).

Thus, the management of patients receiving VKAs may be challenging, and regular monitoring is required. For monitoring, the patient's prothrombin time (a measure of clotting ability) is divided by a reference prothrombin time; the resulting value is then converted to an INR. The use of INR standardizes results by correcting for differences between thromboplastin (Neoplastin) reagent preparations.[49] An INR range of 2.0–3.0 (target 2.5) is typically recommended for patients receiving VKA therapy.[49] If the INR is too high, a patient is at increased risk of bleeding; too low, and the risk of a blood clot is increased. The relationship between INR measurement and the risk of ischaemic stroke and haemorrhagic stroke (bleeding from a vessel in the brain) is illustrated in Figure 11.[175] Although ischaemic stroke risk declines to a minimum at an INR between 2.0 and 3.0, the risk of haemorrhagic stroke progressively increases above this point. If a patient's INR is found to be outside the target range, the dose of VKA should be adjusted accordingly.

Because VKAs interact with food and drugs, maintaining the patients INR within the target range can be challenging. The resulting need for regular monitoring and dose adjustment can be a significant barrier to effective anticoagulation in everyday 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 and a 26–33% reduction in mortality.[30–32,176] Figure 12 shows the results from a meta-analysis of six randomized studies.[31,177–183] The implication is that one stroke is prevented for every 37 patients treated per year.[31]

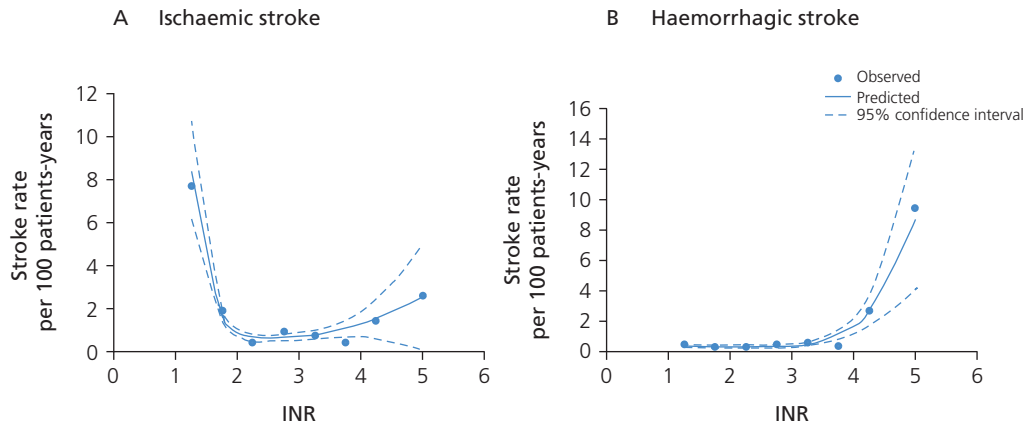
Patients on VKAs need regular INR monitoring and dose adjustment to keep their INR within the target range

Importantly for patients with AF, it has been shown that, when the INR is monitored regularly and – where necessary – adjusted appropriately, VKAs are effective in preventing both mild and severe strokes.[184,185]

Antiplatelet agents

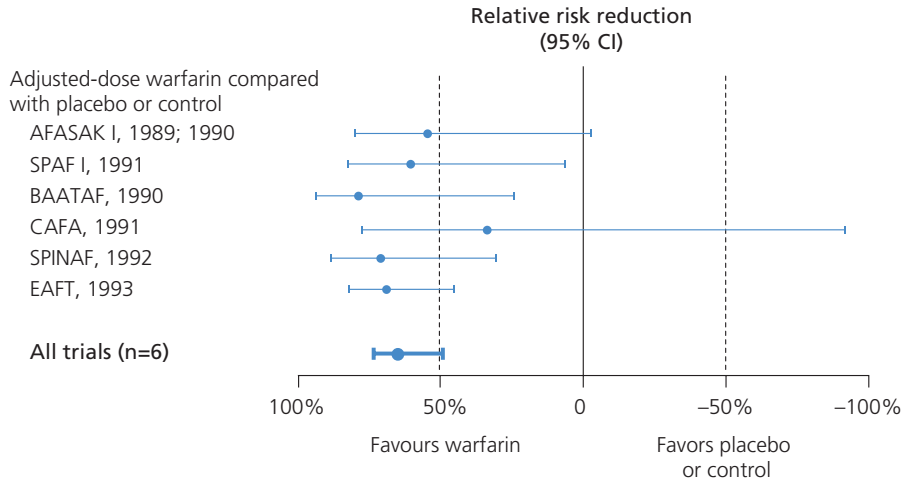
Aspirin and clopidogrel are antiplatelet agents that inhibit the aggregation of platelets,[186] which in turn reduces the risk of a blood clot forming and helps prevent a stroke. In addition, aspirin reduces blood vessel constriction.[187] Antiplatelet drugs are more

Figure 11. The 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) a blood clot (INR <2.0) or (B) bleeding such as haemorrhagic stroke (INR >3.0).
Redrawn with permission from *Eur J Intern Med*, vol. 20, Amouyel *et al.* INR variability in atrial fibrillation: a risk model for cerebrovascular events, pp 63–69, copyright 2009, with permission from Elsevier.[175]
INR, international normalized ratio.

Figure 12. Results from a meta-analysis of six randomized studies,[177–183] showing that warfarin provides a greater reduction in the risk of stroke in patients with atrial fibrillation than placebo or control.



The relative reduction in stroke risk and 95% CIs are shown for each individual trial. This interval is the region in which there is 95% confidence the relative risk reduction. Adapted with permission from Figure A & C: Hart RG, Pearce MA and Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;146:857–867 used with permission from the American College of Physicians.
AFASAK, Atrial Fibrillation, ASpirin, and Anticoagulation study; BAATAF, Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA, Canadian Atrial Fibrillation Anticoagulation; CI, confidence interval; EAFT, European Atrial Fibrillation Trial; SPAF, Stroke Prevention in Atrial Fibrillation; SPINAF, Stroke Prevention in Nonrheumatic Atrial Fibrillation.

effective in the prevention of blood clots that are rich in platelets, such as those due to atherosclerosis.[170] Dual therapy with clopidogrel and aspirin is currently indicated for secondary prevention of atherothrombotic events in patients who have had a heart attack (myocardial infarction), ischaemic stroke or with established peripheral arterial disease, and in patients with unstable angina.

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%).[31] Clinical trials directly comparing aspirin with VKA therapy in the prevention of AF-related stroke have shown VKAs to be significantly superior, providing a relative risk reduction (RRR) of approximately 50% compared with aspirin.[188,189] A meta-analysis of eight studies comparing VKA therapy with aspirin therapy demonstrated that, although results from some of the individual trials were inconclusive, warfarin therapy overall was clearly superior to aspirin therapy (Figure 13).[31,177,180,182,190–195] This analysis found that warfarin reduces the risk of all strokes by 38% compared with aspirin.

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

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.[22–24,196]

Aspirin is now a guideline-recommended option only in patients who refuse the use of any OAC (whether VKA or non-VKA) or cannot tolerate anticoagulants for reasons unrelated to bleeding.[90] There is doubt as to whether patients at low risk of stroke receive any benefit from aspirin.[197,198]

A clinical study (the ACTIVE-A trial) investigated the effects of dual antiplatelet therapy, clopidogrel in combination with aspirin, for the prevention of stroke in patients for whom VKA therapy was unsuitable.[199] This study showed that, compared with aspirin and placebo, clopidogrel in combination with aspirin significantly reduced the risk of stroke in patients with AF, but was also associated with a significantly greater rate of major bleeding and intracranial bleeding. Aspirin and clopidogrel combination therapy has also been compared with VKA therapy for prevention of AF-related stroke in the ACTIVE-W study.[200] This study was stopped early because of the

clear superiority of VKA therapy compared with the aspirin plus clopidogrel combination. Patients on combination therapy experienced significantly more strokes, although major bleeding events were similar between the two groups. Again, according to ESC guidelines, combination therapy with aspirin (75–100 mg daily) and clopidogrel (75 mg daily) is recommended as a consideration only for patients at low risk of bleeding who have refused to take any OAC.[90]

Antithrombotic therapy in clinical practice

Owing to the practical difficulties in maintaining the INR within the target range, there are concerns that the efficacy and the risk of bleeding observed with VKAs in the controlled clinical trial setting are not reflective of, and may not always be achieved in, clinical practice.[201] Patient management is also usually stricter and, therefore, may be of a higher standard in clinical trials. In addition to monitoring highly motivated patients closely, clinical trials often recruit relatively few elderly patients and frequently exclude those with a high risk of bleeding.[32,201]

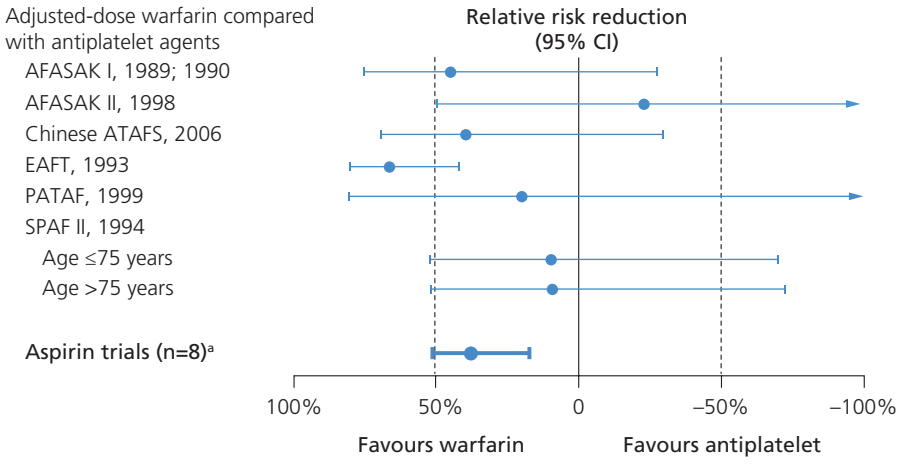
Three investigations in the routine clinical practice setting in the UK and Italy demonstrated reductions in the risk of stroke of 26%, 48% and 66% in patients with AF receiving VKAs – including elderly patients – compared with those not receiving VKAs.[202–204] Despite an increased risk of bleeding, the overall rates of ill health and death were significantly lower in patients receiving VKAs than in those not receiving VKAs.[203,204] However, the risk reduction observed in the UK study (26%) was substantially lower than in clinical trials.[203] Furthermore, an analysis of the process and quality of OAC use in clinical practice has highlighted major management differences between care in a specialist anticoagulation clinic and routine medical care, with less time within the therapeutic INR range being achieved in routine medical care.[203,205]

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

A recent 'real-world' study, using data from more than 132 000 patients with AF in Denmark, compared no treatment with treatment with aspirin or VKA.[142] In patients at high risk of stroke, those not receiving any treatment were at an 86% higher risk, and those receiving aspirin at an 81% higher risk, of thromboembolism, compared with the patients treated with VKAs. Compared with VKA treatment, the risk of bleeding was 16% lower with no treatment and only 7% lower

Patients enrolled in clinical trials may not reflect those encountered in routine clinical practice

Figure 13. Results from a meta-analysis of randomized studies,[177,180,182,190–195] showing that warfarin provides a greater reduction in the risk of stroke in patients with atrial fibrillation than aspirin.



The relative reduction in stroke risk and 95% CIs are shown for each individual trial. Adapted with permission from Figure A & C: Hart RG, Pearce MA and Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;146:857–867 used with permission from the American College of Physicians.
[a]Two trials included are not shown individually.[193,195]
AFASAK, Atrial Fibrillation, ASpirin, and Anticoagulation; ATAFS, Antithrombotic Therapy in Atrial Fibrillation; CI, confidence interval; EAFT, European Atrial Fibrillation Trial; PATAF, Prevention of Arterial Thromboembolism in Atrial Fibrillation; SPAF, Stroke Prevention in Atrial Fibrillation.

with aspirin treatment. Therefore, although use of aspirin resulted in an appreciable risk of bleeding, it offered little protection against thromboembolism.

Until recently, VKAs alone were the only recommended oral anticoagulant for patients with AF at moderate or high risk of stroke

This study also looked at the overall benefit of VKA treatment by balancing ischaemic stroke prevention against bleeding resulting from treatment.[142] This analysis was based on intracranial haemorrhage, the most feared type of bleeding – giving it 50% more weight than ischaemic stroke to account for the generally more devastating effects of brain haemorrhage. Depending on HAS-BLED score, there was a neutral or positive benefit of VKA treatment in patients with a CHA_2DS_2-VASc score of 1 or above. The outcome was negative with a CHA_2DS_2-VASc score of 0, irrespective of bleeding risk. Thus, although the efficacy and safety profiles of VKAs do appear to be somewhat less favourable in routine medical practice than in clinical trials, the benefits still outweigh the risks in most patients, except those at very low risk of stroke (CHA_2DS_2-VASc score of 0).

Studies support the use of anticoagulation in all patients with AF except those at very low risk of stroke

Prior to the availability of non-VKA OACs, only VKAs had been recommended as anticoagulant therapy in patients with AF and a moderate or high risk of developing stroke.[49] This is despite the major drawbacks associated with VKA therapy, including: unpredictable interactions with food and other drugs, which often necessitate significant lifestyle changes; the inconvenience and burden of INR monitoring; the need for dose adjustment; and the perceived risk of bleeding, particularly in the elderly. Despite the fact that guideline-adherent management is associated with improved outcomes,[48] the drawbacks of VKAs mean that guidelines are not always followed and patients may give up therapy. Thus, many patients with AF and a moderate to high risk of stroke do not receive anticoagulant therapy and, therefore, remain unprotected.[48,206] Current guidelines and adherence to these guidelines are discussed in more detail in Chapter 10, 'Guidelines for prevention of atrial fibrillation-related stroke' (page 67) and Chapter 11, 'Guidelines: theory versus practice' (page 71).

Case study: an elderly woman receiving warfarin

Mrs W, a 75-year-old woman, was admitted to hospital with pneumonia in 2009. 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 that 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. However, treatment with an OAC that does not require routine coagulation (e.g. INR) monitoring; can be given at a fixed daily dose; and is only minimally affected, if at all, by changes in diet or other medications would clearly have been preferable.

Cost of VKA therapy for prevention of AF-related stroke

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.[207] The cost of prevention thus appears to be favourable, compared with an average direct cost of €11 799 for treating an AF-related stroke in the EU (see section on 'High economic cost' in Chapter 7, page 46).[37] 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.[111] Although VKA therapy imposes an added economic burden on healthcare resources, the cost remains considerably lower than that of managing the consequences of blood clots, such as stroke.

Numerous other studies have provided further evidence that anticoagulation with VKAs is cost-effective in patients with AF at a moderate or high risk of stroke compared with no therapy or aspirin.[121,208] Management of complications after suboptimal anticoagulation is the major driver of cost.[208]

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; 1 year in perfect health is considered to be equal to 1.0 QALY, whereas 1 year at anything less than perfect health would equate to a QALY value of less than 1.0. The expression of cost per QALY gained thus enables comparisons to be made of different interventions in different disease areas. A review of cost-effectiveness studies in patients with AF reported that, in most cases, VKA therapy was more effective and less costly (i.e. dominant) compared with no antithrombotic therapy or associated with a low cost per QALY gained, particularly in patients considered to be at moderate to high risk of stroke.[208] 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 dominant compared with no therapy, or US$8000 per QALY gained versus aspirin therapy[209] – well below the range of acceptable cost-effectiveness of £20 000–30 000 per QALY established by National Institute for Health and Clinical Excellence (NICE) in the UK.[210]

The cost of preventing AF-related stroke is less than the direct cost of treating stroke

It should be noted that the cost-effectiveness of VKA therapy is dependent on achieving a marked reduction in the risk of thromboembolism. Practical difficulties in maintaining INR values within the therapeutic range may result in VKA therapy being less cost-effective in clinical practice than in controlled clinical trials. INR monitoring in clinical practice may also incur additional costs – to the patient, carer and society – not captured in cost-effectiveness studies. A study of the cost to society associated with attending anticoagulation 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.[211] Although not all patients in Europe who receive anticoagulation therapy regularly attend anticoagulation 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 the standard of patient management may be higher in clinical trials

Thus, cost-effectiveness is likely to be maximized when clinical practice is optimal. 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.

Invasive strategies for preventing thrombus formation: LAA closure

In patients with non-valvular AF, more than 90% of blood clots form in the LAA (part of the left atrium).[118] Closure of the LAA has, therefore, been targeted as a means of reducing the risk of blood clots and stroke in patients with AF. As mentioned previously, the LAA is often surgically removed or stapled as a concurrent procedure during open heart surgery and low rates of stroke have been reported in these patients.[90]

More recently, several new occlusion devices have been developed that allow the LAA to be blocked off in a minimally invasive manner. Such devices are designed to be placed inside

the heart via catheters at the opening of the LAA, or to be placed on the outside of the heart to 'clip' the LAA shut. These are discussed in more detail in Chapter 13, 'New developments for prevention of atrial fibrillation-related stroke' (page 87).

Despite positive findings, the level of evidence surrounding the efficacy and safety of LAA closure is not sufficient to recommend it for any patients other than those in whom long-term OAC therapy is contraindicated.[90]

Management of other conditions that increase the risk of atrial fibrillation-related stroke: a holistic approach

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

AF commonly coexists with other conditions, such as high blood pressure and diabetes, which themselves can predispose to blood clots and stroke. The risk in patients with several of these conditions is cumulative – 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.

Blood pressure control is particularly important in the management of AF, because uncontrolled blood pressure independently increases the risk of stroke 2–3-fold[8,212] and accounts for approximately one-third to one-half of all strokes (ischaemic and haemorrhagic).[105] AF in patients with diabetes is also associated with a 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.[213]

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

The outlook for prevention of atrial fibrillation-related stroke

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 anticoagulant 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, such as the risk of major bleeding events like intracranial haemorrhage and inconvenient INR monitoring. Nevertheless, they remain a frontline therapy in this indication. Thus, in the immediate term, improved detection of asymptomatic AF, and increased use and optimization of anticoagulation therapy, are important to reduce the incidence of strokes, especially severe strokes, in patients with AF.

The advent of effective, fixed-dose therapies with a good safety profile and widely accepted cost-effectiveness is likely to lead to considerable improvements in the management of patients with AF. Non-VKA OACs and recently published clinical trial results are discussed in more detail in Chapter 9, 'Non-vitamin K antagonist oral anticoagulants for prevention of atrial fibrillation-related stroke' (page 57).

Chapter 9
Non-vitamin K antagonist oral anticoagulants for prevention of atrial fibrillation-related stroke

Key points

- **Apixaban, rivaroxaban and dabigatran have all been shown to be at least as effective as warfarin for the prevention of AF-related stroke and systemic embolism**
- **The non-vitamin K antagonist (VKA) oral anticoagulants (OACs) have improved safety profiles compared with warfarin**
- **The characteristics of the non-VKA OACs mean simplified dosing and no need for routine coagulation monitoring or dose adjustment**
- **The non-VKA OACs offer a consistent benefit in high-risk patients, such as those with renal impairment, and patients with a prior stroke**

Limitations of the VKAs and the lack of effectiveness of aspirin restrict their use in the prevention of AF-related stroke (see Chapter 8, 'Prevention of atrial fibrillation-related stroke', page 47). These limitations have led to an ongoing search for alternative therapies that are more effective, more convenient and have better safety profiles than previously existing therapies.

Anticoagulant agents

The characteristics of an ideal anticoagulant for long-term use in a chronic condition such as AF include:[214]

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

VKAs are taken orally but interact with many foods and drugs, have a narrow therapeutic window, and require regular coagulation monitoring and dose adjustment. They, therefore, meet few of the criteria for an ideal therapy for prevention of AF-related stroke.

A recent Italian study provides an interesting insight into patient preference concerning anticoagulant therapy.[215] A total of 255 patients aged 23–91 years (mean age 64 years; 35% with AF) in the waiting room of an anticoagulation clinic were interviewed about their preference for the characteristics of a 'hypothetical' new anticoagulant therapy. They were asked for their preferences concerning: (1) route and frequency of administration; (2) monitoring frequency; (3) interactions with drugs or food; (4) need for dose adjustment; and (5) risk of causing some or minor bleeding. They were also questioned about their monthly 'willingness to pay' (i.e. what level of 'out-of-pocket' cost they would be prepared to pay each month) for each of these characteristics.

As expected, patients generally favoured tablets to injections, fewer doses (once vs twice daily), less monitoring (once vs twice monthly) and an agent with no associated risk of bleeding. Overall, there was no significant preference regarding food and drug interaction, or requirement for dose adjustment. Monthly patient willingness to pay was €79 for tablets

compared with injections; €41 for once- versus twice-daily tablets; €20 for once-monthly versus twice-monthly monitoring; and €25 for agents without risk of minor bleeding events. For an agent that required only once- versus twice-monthly monitoring, younger patients (≤65 years) were prepared to pay more than older patients (€22.1 vs €16.0 per month), as were those who were working compared with those who were not (€25.1 vs €13.6 per month). Furthermore, patients who had been on stable OAC therapy for some time considered drug/food interactions to be more important than did those who had only recently started OAC therapy.[215] This last point no doubt reflects the experience of patients who have been on VKA therapy for some time with the associated inconvenience of drug/food interactions.

The search for non-VKA OACs has, therefore, focused on compounds that meet more of the criteria for an ideal anticoagulant. Several non-VKA OACs are either in development or have recently completed development. In the coagulation pathway (Chapter 8, Figure 10, page 50) there are several potential targets for non-VKA OACs. The agents that are currently most advanced in their development directly target single proteins in the coagulation pathway (Factor Xa or thrombin).[214] Those agents that are in phase III development or have been recently licensed are discussed in this chapter.

Oral direct Factor Xa inhibitors

Factor Xa is the primary site for amplification in the coagulation pathway (Chapter 8, Figure 10, page 50).[216] Inhibition of Factor Xa achieves effective anticoagulation by inhibiting thrombin generation, while allowing the vital functions of existing thrombin to continue, thus potentially maintaining haemostasis as needed.[216] Oral direct inhibitors of Factor Xa include rivaroxaban, apixaban and edoxaban.

Rivaroxaban

ROCKET AF was a randomized, double-blind phase III study that compared the efficacy and safety of once-daily rivaroxaban (20 mg, or 15 mg for patients with moderate renal impairment) with dose-adjusted warfarin for the prevention of stroke in 14 264 patients with AF and a history of stroke, transient ischaemic attack (TIA) or systemic embolism or at least two other risk factors for stroke.[217] Patients were followed-up for a median of 707 days.

In the intention-to-treat analysis, rivaroxaban showed comparable benefits to warfarin for the primary efficacy endpoint (the composite of stroke and non-CNS systemic embolism [2.1% vs 2.4% per year; $p<0.001$ for non-inferiority]).[217] The intention-to-treat analysis followed all patients randomized in the trial until its completion, whether or not they completed the full course of therapy or switched to other options. In the prespecified on-treatment analysis, rivaroxaban was superior to warfarin, showing a 21% RRR for stroke and systemic embolism, (1.7% vs 2.2% per year, respectively; $p=0.02$). These results indicate that, as expected, the treatment benefits compared with warfarin were sustained for as long as patients received rivaroxaban. For the principal safety measure, rivaroxaban showed similar rates of major and non-major clinically relevant bleeding events, compared with warfarin (14.9% vs 14.5% per year; $p=0.44$). Rates of major bleeding were also comparable between rivaroxaban and warfarin (3.6% vs 3.4% per year; $p=0.58$). Patients treated with rivaroxaban had fewer intracranial haemorrhages (0.5% vs 0.7% per year; $p=0.02$), critical organ bleeding events (0.8% vs 1.2% per year; $p=0.007$) and bleeding-related deaths (0.2% vs 0.5% per year; $p=0.003$) compared with those treated with warfarin. However, rivaroxaban-treated patients showed increased rates of major bleeding resulting in a haemoglobin drop of 2 g/dl or more (2.8% vs 2.3% per year; $p=0.02$) and major bleeding requiring transfusion (1.6% vs 1.3% per year; $p=0.04$) compared with warfarin. Patients receiving rivaroxaban experienced more major gastrointestinal bleeding events than patients treated with warfarin (3.15% vs 2.16%; $p<0.001$), which would have contributed to the rate of major bleeding resulting in a haemoglobin drop of 2 g/dl or more.

Rivaroxaban-treated patients had fewer myocardial infarctions (0.9% vs 1.1% per year; $p=0.12$), although these results were not statistically significantly different. There was also a non-significant trend for a lower rate of all-cause mortality with rivaroxaban compared with warfarin (1.9% vs 2.2% per year; $p=0.07$).

Apixaban

The larger ARISTOTLE phase III, randomized, double-blind study compared apixaban (5 mg twice daily or 2.5 mg twice daily for patients with ≥2 risk factors likely to lead to increased drug exposure) with dose-adjusted warfarin, in 18 201 patients with AF and at least one additional risk factor for stroke.[218] Patients were followed up for a median of 1.8 years. In the intention-to-treat population, apixaban treatment significantly reduced the rate of the primary efficacy endpoint (the composite of stroke and systemic embolism) compared with warfarin (RRR 21%; 1.27% vs 1.60% per year; p=0.01). Compared with warfarin, apixaban also significantly reduced the rate of major bleeding (the principal safety outcome [2.13% vs 3.09% per year; p<0.001]) and intracranial haemorrhage events (0.33% vs 0.80% per year; p<0.001). Rates of gastrointestinal bleeding were comparable between the two groups (0.76% vs 0.86% per year; p=0.37). The rate of all-cause mortality was also significantly lower in patients treated with apixaban than in patients treated with warfarin (3.52% vs 3.94% per year; p=0.047).

Another phase III study (AVERROES) investigated whether apixaban was more effective than aspirin in preventing AF-related stroke in patients who had failed or were unsuitable for VKA therapy.[219] Apixaban was shown to significantly reduce the risk of stroke or systemic embolism compared with aspirin with no significantly increased risk of major haemorrhage.

Edoxaban (DU-176b)

A phase II study has compared the Factor Xa inhibitor edoxaban with warfarin in patients with AF.[220] Patients receiving 30 mg or 60 mg once-daily doses of edoxaban had a similar incidence of major and non-major clinically relevant bleeding to those assigned to warfarin, while patients receiving the 30 mg or 60 mg twice-daily doses experienced significantly more bleeding compared with those on warfarin. A phase III study (ENGAGE AF-TIMI 48) has also been initiated to evaluate the safety and efficacy profile of two doses of edoxaban versus warfarin.[221] Results are expected in 2013.[222]

Oral direct thrombin inhibitors

Dabigatran etexilate is an oral direct thrombin inhibitor (Chapter 8, Figure 10, page 50). This class of drug blocks the action of thrombin in converting fibrinogen to fibrin in the coagulation pathway.

RE-LY was a phase III, three-arm study, in which patients were randomized to dabigatran doses of 110 mg or 150 mg twice daily or dose-adjusted warfarin.[223] RE-LY was a blinded study with regards to the dabigatran dose given, and open label with regards to warfarin. The study enrolled 18 113 patients with AF and at least one additional risk factor for stroke, with follow-up for a median of 2 years.

In an intention-to-treat analysis, the rate of the primary efficacy endpoint, the composite of stroke or systemic embolism, was similar between patients receiving the dabigatran 110 mg twice-daily dose and patients receiving warfarin (1.53% vs 1.69% per year; p=0.34).[223] Dabigatran 150 mg twice daily significantly reduced the rate of stroke and systemic embolism compared with warfarin, showing an RRR of 34% (1.11% vs 1.69% per year; p<0.001). Compared with warfarin, the 110 mg twice-daily dose resulted in a significantly lower rate of major bleeding (2.71% vs 3.36% per year; p=0.003), and the dabigatran 150 mg twice-daily dose a similar rate of major bleeding (3.11% vs 3.36% per year; p=0.31). The rate of gastrointestinal bleeding was higher with the 150 mg dose of dabigatran than with warfarin (1.51% vs 1.02% per year; p<0.001). The rate of intracranial bleeding was significantly lower with both dabigatran doses (110 mg, 0.23% per year; 150 mg, 0.30% per year), compared with warfarin (0.74% per year, p<0.001 for both comparisons). A non-significant lower rate of all-cause mortality was observed with both dabigatran doses (110 mg, 3.75% per year [p=0.13 vs warfarin]; 150 mg, 3.64% per year [p=0.051 vs warfarin]), than with warfarin (4.13% per year). Rates of dyspepsia were significantly higher with both dabigatran doses (110 mg, 11.8%; 150 mg, 11.3%) compared with warfarin (5.8%; p<0.001 for both comparisons).[223]

There were higher rates of myocardial infarction with dabigatran (110 mg, 0.72% per year [p=0.07 vs warfarin]; 150 mg 0.74% per year

[*p*=0.048 vs warfarin]), compared with warfarin (0.53% per year).[223] A later *post hoc* reanalysis of the RE-LY study was carried out after further events were identified during routine clinical site closure visits.[224] This led to the addition of 32 new myocardial infarction events (four clinical and 28 silent myocardial infarctions).[224] Although observed myocardial infarction rates were still higher with both dabigatran doses, the statistical significance previously seen with the higher dose was no longer evident. However, a subsequent meta-analysis of seven dabigatran studies indicated that there was a significant 33% higher risk of myocardial infarction or unstable angina with dabigatran treatment compared with placebo or the control agents used in these studies (1.19% vs 0.79%; *p*=0.03).[225]

Rivaroxaban, apixaban and dabigatran are at least as effective as warfarin for the prevention of AF-related stroke and systemic embolism, with an improved safety profile

Advantages of the non-vitamin K antagonist oral anticoagulants

In patients at risk of AF-related stroke, there is a 62–68% lower stroke risk with warfarin therapy than with no treatment.[30,31,176] Apixaban, rivaroxaban and dabigatran have all been shown to be at least as effective, if not more effective, than warfarin for the prevention of AF-related stroke and systemic embolism.[217,218,223,224] Importantly, this efficacy is accompanied by the improved safety profiles of these drugs. Major bleeding was either reduced or comparable with warfarin therapy for all three of these non-VKA OACs. Although, with rivaroxaban and the higher dabigatran dose, extracranial bleeding such as gastrointestinal bleeding was higher than with warfarin, all three of the drugs reduced the levels of intracranial bleeding (bleeding inside the brain) – the most feared bleeding event resulting from anticoagulation treatment. Rivaroxaban also demonstrated a reduced rate of fatal bleeding in the ROCKET AF study.[217] In addition, there was a trend towards reduced all-cause mortality with all three drugs, compared with warfarin treatment, which reached statistical significance with apixaban in ARISTOTLE.[217,218,223,224]

All three of the non-VKA OACs reduced the levels of intracranial bleeding compared with warfarin

A separate analysis of the ROCKET AF trial was carried out to identify predictors of intracranial haemorrhage.[226] Among the significant predictors of intracranial haemorrhage were advanced age, prior stroke or TIA, and black or Asian race. In this study, randomization to rivaroxaban, rather than warfarin, was protective against intracranial haemorrhage.

Patients with reduced kidney function

Whereas warfarin is almost entirely metabolized by the liver,[227,228] the non-VKA OACs are excreted unmetabolized (i.e. as unchanged active drug) via the kidneys into the urine to varying degrees. This means that patients with reduced kidney function, also called renal impairment, could be exposed to higher drug levels if elimination of active drug via the kidneys into the urine is sufficiently reduced. The proportion of orally administered drug that is actually absorbed also needs to be considered; being approximately 50% for apixaban, around 7% for dabigatran and ≥80% for rivaroxaban.[171,229–231] The proportion of absorbed, active drug that is eliminated via the kidneys is about 50% for apixaban (estimated, based on approximately 25% of the orally administered dose being eliminated renally), more than 80% for dabigatran and 33% for rivaroxaban.[171,229,231,232]

To account for the partial renal elimination of rivaroxaban, patients with moderate renal impairment (creatinine clearance [CrCl] 30–49 ml/min) in ROCKET AF received a reduced dose of rivaroxaban of 15 mg once daily, compared with the 20 mg once-daily dose received by patients with mild impairment or healthy renal function (CrCl of more than 50 ml/min).[217] A subanalysis of the trial found that the treatment effect of rivaroxaban versus warfarin was consistent between patients with moderate renal impairment receiving the lower dose and patients with normal kidney function receiving the 20 mg once-daily dose.[233] This was the finding for prevention of stroke and systemic embolism, for major and non-major clinically relevant bleeding (principal safety measure), major bleeding alone, and intracranial haemorrhage.

In the ARISTOTLE trial of apixaban, the treatment effect for apixaban versus warfarin was consistent irrespective of renal function for the reduction of stroke and systemic embolism.[218] A more detailed subanalysis of

the ARISTOTLE trial in patients with varying degrees of renal function (estimated glomerular filtration rates >80 ml/min, between >50 and 80 ml/min, and ≤50 ml/min) confirmed that the relative efficacy and safety of apixaban versus warfarin was consistent irrespective of renal function.[234] The relative reduction in major bleeding with apixaban was highest in patients with an estimated glomerular filtration rate ≤50 ml/min.

In the RE-LY trial of dabigatran, the treatment effect for both dabigatran doses versus warfarin was also consistent irrespective of renal function for the reduction of stroke and systemic embolism.[223] In an analysis of factors affecting bleeding in patients in the RE-LY trial, decreasing renal function (CrCl ≥80 ml/min, 50–79 ml/min or <50 ml/min) did not have a significant impact on the relative effects of dabigatran and warfarin on major bleeding.[235] Despite this, cases of markedly increased dabigatran plasma levels associated with renal impairment in elderly patients have been reported.[236]

Abnormal kidney function is a risk factor for bleeding included in the HAS-BLED bleeding risk stratification scheme; although it is not included in stroke risk stratification schemes, it also increases the risk of AF-related stroke.[131,135,237,238] Such considerations emphasize the need for customizing anticoagulant therapy to each patient's overall clinical presentation. Patients should have their renal function tested before initiating treatment and if a decline in function is suspected during treatment.[239] Prescribing information for the non-VKA OACs is discussed in more detail in the section 'Prescribing the non-vitamin K antagonist oral anticoagulants in clinical practice' page 62.

Patients who have already had a stroke

A prior stroke is recognized as a risk factor for both stroke and anticoagulant-related bleeding, being given two points in both the $CHADS_2$ and CHA_2DS_2-VASc stroke risk stratification schemes, and one point in the HAS-BLED bleeding risk stratification scheme (see Chapter 6, 'Characteristics of stroke and stroke risk factors in patients with atrial fibrillation', page 33).[11,120,135] This makes management decisions for these patients difficult. Furthermore, the risk of death from a recurrent stroke has been shown to be almost twice the risk following a first ever stroke,[240] emphasizing the importance of secondary stroke prevention.

Analyses of patients with a prior stroke or TIA have been carried out for the ROCKET AF (52% of patients),[241] ARISTOTLE (19% of patients)[242] and RE-LY (20% of patients)[243] trials of rivaroxaban, apixaban and dabigatran, respectively. The benefits of the three drugs for stroke and systemic embolism prevention compared with warfarin were maintained in patients with prior stroke or TIA.[241–243] Results for major bleeding and intracranial haemorrhage were also consistent in patients with or without a prior stroke. These results are particularly reassuring because, despite their high stroke risk, it appears that these patients are currently often not prescribed anticoagulation with VKAs. The reasons for this apparent underuse are not well defined but may include concerns over the patient's ability to attend regular international normalized ratio (INR) monitoring or to comply with prescribed therapy.[244,245] Additionally, physicians may be overly concerned about VKA-induced major bleeding. In a systematic review of 29 studies of patients with prior stroke or TIA, 25 studies reported under-treatment, with 21 reporting treatment levels below 60%.[244] Described in this chapter are some advantageous characteristics of the non-VKA OACs, which should help increase the use of anticoagulants in patients with AF at risk of stroke.

Patients at different levels of stroke risk

In the RE-LY trial, 31.9% of patients had a $CHADS_2$ score of 0–1, 35.6% a score of 2 and 32.5% a score of 3–6.[223,246] A subanalysis of the RE-LY trial demonstrated, as expected, that both stroke and bleeding risk increased with increasing $CHADS_2$ score.[246] The effects of the study drug compared with warfarin were maintained across these $CHADS_2$ risk groups (non-significant interaction); the dabigatran 150 mg twice-daily dose was associated with lower rates of stroke and systemic embolism and similar rates of bleeding; the dabigatran 110 mg twice-daily dose was associated with similar rates of stroke and systemic embolism and lower rates of bleeding. Both dabigatran

doses significantly reduced the rate of intracranial haemorrhage compared with warfarin in each $CHADS_2$ risk group. Similarly, the ARISTOTLE trial of apixaban enrolled 34.0%, 35.8% and 30.2% with $CHADS_2$ scores of 1, 2 and 3 or more, respectively.[218] Again, the treatment effect from apixaban versus warfarin was consistent with the overall trial results for these $CHADS_2$ risk groups.

The ROCKET AF study of rivaroxaban enrolled a higher risk cohort with 87.1% having a $CHADS_2$ score of 3–6; the remaining patients had a score of 2.[217] As with RE-LY and ARISTOTLE, the treatment effect of rivaroxaban versus warfarin was maintained for stroke, systemic embolism and major bleeding for each individual $CHADS_2$ score from 2 to 6.

The non-VKA OACs offer a consistent benefit in high-risk patients such as those with renal impairment, or with a prior stroke

Elderly patients

Advanced age is also a significant risk factor for both stroke and major bleeding.[11,120,135] In ROCKET AF, the treatment effect seen with rivaroxaban compared with warfarin was consistent between patients aged 75 years or older and those below 75 years, with respect to stroke, systemic embolism, major bleeding and intracranial haemorrhage.[247]

In the RE-LY trial of dabigatran, there was a significant treatment interaction with age for major bleeding.[235] Dabigatran 110 mg twice daily was associated with a lower risk of bleeding than warfarin in patients below 75 years, and a similar risk of bleeding in patients aged 75 years or older. The dabigatran 150 mg twice-daily dose was associated with a similar risk of bleeding to warfarin in patients below 75 years but an increased risk of bleeding in patients aged 75 years or older. It should be noted, however, that this age-related interaction was only evident for extracranial bleeding and not for intracranial bleeding.

VKA-experienced/-naïve patients

Research has shown that patients who have previously received VKA therapy often respond differently to subsequent VKA therapy compared with patients receiving it for the first time.[248,249] A subgroup analysis of VKA-experienced and VKA-naïve patients in the RE-LY trial concluded that prior exposure to VKA had no impact on the relative efficacy and safety of dabigatran compared with VKA.[250] A more recent subanalysis of ROCKET AF data also reported that the efficacy and safety of rivaroxaban in both VKA-experienced and VKA-naïve patients was consistent with the overall trial results.[251] Furthermore, a similar number of strokes/systemic embolic events and major bleeding events occurred in the first 30 days after randomization in VKA-experienced patients assigned to either rivaroxaban or VKA.

Prescribing the non-vitamin K antagonist oral anticoagulants in clinical practice

Rivaroxaban and dabigatran, but not apixaban or edoxaban, currently have marketing authorization in the EU for prevention of AF-related stroke.[239,252] Dabigatran is available for patients with non-valvular AF at risk of stroke with one or more of the following: prior stroke/TIA or systemic embolism; a left ventricular ejection fraction of less than 40% (a sign of heart failure); symptomatic heart failure; age 75 years or older; or age 65–74 years with diabetes, coronary artery disease, or hypertension.[239] Patients under the age of 80 years are to receive 300 mg of dabigatran (150 mg twice daily) and patients aged 80 years or older 220 mg daily (110 mg twice daily). Rivaroxaban is available for patients with non-valvular AF with one or more risk factors such as: congestive heart failure, hypertension, age 75 years or older, diabetes, or prior stroke or TIA. There is no required dose adjustment for age with rivaroxaban; the dose is 20 mg once daily except in patients with moderate (CrCl 30–49 ml/min) or severe (CrCl 15–29 ml/min) renal impairment, where the dose is 15 mg once daily.[252] Dabigatran is contraindicated in patients with severe renal impairment and, although there is no dose adjustment for moderate renal impairment, these patients should be kept under close surveillance with the 110 mg twice-daily dose considered for patients at high risk of bleeding.[239] Although rivaroxaban and dabigatran have far fewer drug interactions than warfarin, there are a small number of important drug interactions outlined in the labels of each drug.[239,252] The European Society of Cardiology (ESC) guidelines for treatment

of patients with AF at risk of stroke with the non-VKA OACs is discussed in Chapter 10, 'Guidelines for prevention of atrial fibrillation-related stroke' (page 67).

Therefore, management of patients receiving rivaroxaban or dabigatran is very different from management of warfarin-treated patients. As well as knowledge of the availability of these drugs as a potential option for patients at risk of AF-related stroke, physician education on how to manage patients in receipt of these drugs is also required. Physicians need to be aware of the dose adjustments required, for example in patients with moderate renal impairment treated with rivaroxaban and when dabigatran-treated patients reach 80 years of age. Patients' renal function will need to be tested before initiating therapy, especially in elderly patients – and re-assessed periodically if a decline in renal function is suspected – and their treatment will need to be adjusted accordingly. Physicians will also need to be aware of the drug interactions of the non-VKA OACs. Because patients in receipt of the non-VKA OACs do not require routine coagulation monitoring at anticoagulation clinics, physicians will need to assess compliance with therapy during practice visits. Patients with AF are often elderly and, therefore, likely to also have other conditions necessitating periodic primary care visits, so practitioners should be strongly encouraged to discuss their anticoagulation treatment during these visits.

Prescribing decisions with the non-VKA OACs

Studies directly comparing the non-VKA OACs with each other have not been carried out. However, the absolute reductions in stroke and systemic embolism risk were similar across all three trials (0.3–0.6% per year).[217,218,223,224] Although it is tempting to use indirect comparisons of the non-VKA OACs to help make choices regarding which drug to use, the differences in design and patient characteristics between RE-LY, ROCKET AF and ARISTOTLE mean that such an approach is fraught with difficulty, and any conclusions cannot be considered reliable, a view consistent with the approach taken in the recently updated ESC guidelines (discussed in Chapter 10, 'Guidelines for prevention of atrial fibrillation-related stroke', page 67).[90,253–255] In fact, because of these differences, as part of its new technology appraisal of rivaroxaban, National Institute for Health and Clinical Excellence (NICE) concluded that it would not consider indirect comparisons of rivaroxaban and dabigatran.[255] As described previously, a major difference between the studies was the stroke risk of the patients enrolled, particularly the substantially higher proportion of patients with prior stroke/TIA enrolled in the ROCKET AF trial. Mean $CHADS_2$ scores were 2.1, 3.5 and 2.1 for RE-LY, ROCKET AF and ARISTOTLE, respectively.[217,218,223] In addition, the RE-LY trial was open label for warfarin making the data difficult to compare with ARISTOTLE and ROCKET AF, both of which had a double-blinded trial design for both study drug and warfarin but with differences in the prespecified statistical analyses. Treatment decisions should, therefore, be based on individual patient circumstances and the characteristics of each drug,[256] rather than attempts at indirectly comparing efficacy and safety data across the three quite different trials.

Patient management with the non-VKA-OACs

As described in the previous chapter, difficulties in maintaining a therapeutic INR mean that warfarin may not always be as effective in routine practice as in the clinical study environment.[203] In contrast to warfarin, the non-VKA OACs have no food and few drug interactions.[257] The anticoagulation effect of the non-VKA OACs has been found to be predictable and their dose does not need to be periodically adjusted in order to maintain a therapeutic level. These attributes may make non-VKA OACs easier to manage in practice. Providing patients with more information on the benefits of non-VKA OACs could also lead to improved clinical outcomes (see Chapter 12, 'Current challenges for the prevention of atrial fibrillation-related stroke', page 77). Post-approval studies of the efficacy and safety of the available non-VKA OACs in routine practice for prevention of AF-related stroke are ongoing.[66,258,259]

The next chapters describe clinical guidelines for preventing AF-related stroke (Chapter 10, 'Guidelines for prevention of atrial fibrillation-related stroke', page 67), particularly those from the ESC, and how the limitations associated with warfarin mean that guideline adherence is currently not always optimal (Chapter 11, 'Guidelines: theory versus practice', page 71). This means that many eligible patients do not receive anticoagulation and remain at risk of AF-related stroke. The improved safety profile of the non-VKA OACs could encourage more physicians to prescribe anticoagulants to patients with AF who are at risk of stroke. In addition to the safety profile, the non-VKA OACs have other advantageous characteristics, which could overcome the limitations of warfarin and potentially improve guideline adherence. Because the anticoagulation effect of the non-VKA OACs is predictable, and they appear to have a wider therapeutic window, they can be given at fixed doses with no requirement for inconvenient routine coagulation monitoring.[257] Patients who have previously had a stroke may find attending routine monitoring clinics particularly difficult, especially if the first stroke was disabling. In addition, patients in receipt of the non-VKA OACs would not have to endure restrictions to their diet, which might be the case if they were receiving warfarin.[257] These characteristics may improve patients' willingness to both adopt and comply with anticoagulation therapy. However, one concern is that, without routine monitoring, a point of patient–physician contact is lost; therefore, different ways to inform patients and discuss their treatment may need to be established.

Advantageous characteristics of the non-VKA OACs could increase anticoagulant use in patients with AF at risk of stroke, reducing the burden of AF-related stroke

Although the half-life of warfarin (the amount of time it takes for blood levels of a drug to halve) is about 40 hours (moderately shorter or longer for VKAs other than warfarin), its effects last for 2–5 days.[228] If warfarin is withdrawn, it takes a while for the INR to fall because warfarin acts indirectly on the production of vitamin K-dependent coagulation factors, which need to be replenished by the liver. The non-VKA OACs are direct-acting and have half-lives ranging from 7 to 14 hours,[257] meaning their effect wears off more quickly than that of warfarin.

These are important considerations when patients experience a bleeding event or require a surgical procedure – anticoagulants must be withdrawn and the anticoagulation effect may need to be reversed. Although vitamin K can be given to patients receiving VKAs as an antidote to reduce the time it takes for the anticoagulation effect to wear off, its reversal effect on warfarin action can take many hours and, therefore, would not be useful on its own in acute emergency situations.[228,260] As with most anticoagulants, no specific antidotes for the non-VKA OACs are currently available, although early studies testing possible antidotes are being undertaken.[261–263] In addition, because the effects of these drugs wear off much more quickly than with warfarin, the need for a specific antidote is not as compelling. When acute bleeding situations arise, supportive measures should be used; if needed, blood products can be used for patients receiving either VKA or non-VKA anticoagulants.[228,239,252] Concentrates of coagulation factors (prothrombin complex, or activated prothrombin complex) can be used in VKA-treated patients[228] and may also be considered in certain patients treated with non-VKA OACs.[239,252]

When a patient requires elective surgery, warfarin therapy must be withheld for 4–5 days before surgery to allow the INR to fall below 1.5 (when surgery can be conducted safely).[228] High-risk patients need to be 'bridged' with parenteral anticoagulants while they are not in receipt of warfarin. Dabigatran should be stopped 1–3 days before surgery (depending on renal function);[239] rivaroxaban should be stopped 24 hours before surgery.[252] Some experts have recommended stopping rivaroxaban 48 hours before procedures associated with a high risk of bleeding, or if the patient is at high risk of bleeding.[264]

Cost-effectiveness versus vitamin K antagonists

When considering the costs of the non-VKA OACs for prevention of AF-related stroke, they are compared with the cost of the current standard therapy of warfarin. As well as the acquisition costs of the different drugs, the direct healthcare costs of clinical events such as

stroke, TIA, systemic embolism, major or minor bleeding, and intracranial haemorrhage must also be considered, as must the costs of routine INR monitoring associated with warfarin. As described in the previous chapter, cost-effectiveness is often expressed as cost per quality-adjusted life-year (QALY) gained, allowing comparisons of different interventions in different disease areas.

As part of its new technology appraisals, NICE examined cost-effectiveness analyses carried out by both manufacturers and by an Evidence Review Group (ERG) for prevention of AF-related stroke.[255,265]

Dabigatran

NICE concluded that, based on a sequential dosing strategy where AF patients aged <80 years were switched from a 150 mg twice-daily dose to 110 mg twice-daily when they reached 80 years of age, dabigatran was a cost-effective alternative to warfarin across the whole patient group.[265] This sequential regime resulted in an incremental cost of £18 900 per QALY gained for dabigatran compared with warfarin use, with the 'most plausible' incremental costs for the whole population eligible for dabigatran within the threshold of £20 000–£30 000 per QALY considered acceptable by NICE.[210,265] This was estimated to rise above the upper £30 000 threshold if a warfarin-treated patient spent ≥75% of time within the therapeutic INR range, but NICE concluded that there was not enough evidence to exclude the minority of people with very good INR control while on warfarin from being recommended dabigatran. These results were based on an annual cost of monitoring for warfarin therapy of £242 per person (range £115–279 per person based on different assumptions by the ERG), although NICE were aware that there was uncertainty around INR monitoring costs.

A Danish study was also based on the sequential treatment path for dabigatran described previously.[266] A theoretical cohort of 10 000 patients with AF at moderate to high risk of stroke was used, based on patients under 80 years enrolled in the RE-LY study, with a mean starting age of 69 years. This study estimated that the cost per patient for their remaining lifetime would be €16 886 for a warfarin-treated patient and €18 752 for a dabigatran patient, with the main reason for the difference being the cost of the medication. The warfarin costs were based on an estimated annual cost of routine coagulation monitoring of €513. The study estimated the mean QALYs per patient to be 8.32 for warfarin and 8.59 for dabigatran, meaning the incremental cost per QALY gained was €6950 for dabigatran over warfarin. This rose to €29 019 for centres where warfarin-treated patients spent a mean time in therapeutic range of at least 72.6%, which would still be considered cost-effective. Dabigatran was estimated to be both more effective and cheaper than warfarin therapy if cost of routine coagulation monitoring exceeded €744 per year.

Rivaroxaban

In a separate appraisal of rivaroxaban for prevention of AF-related stroke, NICE concluded that rivaroxaban was cost-effective, with the incremental cost over warfarin (between £2870 and £29 500 per QALY gained) below the NICE threshold of £20 000–30 000 per QALY gained.[255] Again, this was based on annual anticoagulation monitoring costs for warfarin of £242 per person; however, NICE did acknowledge that this estimate was likely to be conservative. As a result, the incremental cost for rivaroxaban compared with warfarin 'would be no more than' £29 500 per QALY'.[255] The analysis also accounted for a level of INR control closer to the level seen in the UK (from an overall mean of 55% in ROCKET AF to the mean of 61% seen in those trial centres in Western Europe).[217,255]

Although European studies are not yet available, a study of rivaroxaban from a US payer's perspective has recently been published.[267] This Markov model, based on patients with AF aged 65 years with a $CHADS_2$ score of 3, estimated that rivaroxaban-treated patients would live for 10.0 QALYS and warfarin-treated patients 9.8 QALYs. The incremental cost of rivaroxaban was $27 498 per QALY gained, with an 80% probability of being cost-effective at a threshold of $50 000,[267] a common threshold used in US cost-effectiveness studies.[268] These cost-effectiveness findings were most sensitive to changes in the hazard

decrease of intracranial haemorrhage and stroke with rivaroxaban, cost of the drug, and time horizon.[267]

Therefore, when the costs of stroke and bleeding events are considered, together with the monitoring costs associated with VKA therapy, dabigatran and rivaroxaban are a cost-effective alternative to VKA therapy at thresholds commonly set by payer organizations.

Apixaban

One US cost-effectiveness model has been published, comparing the cost-effectiveness of apixaban with aspirin in patients unsuitable for VKA therapy and based primarily on the results of the AVERROES trial.[269] The base-case assumption was of a cohort of 70-year-old patients with AF with a $CHADS_2$ score of 2 and a low risk of bleeding. In the 1-year model, the total costs per patient were $3454 for apixaban and $1805 for aspirin, whereas QALYs gained were the same in both treatment arms (0.96). In the 10-year model, however, total costs per patient were lower for apixaban ($44 232 vs $50 066 for aspirin), with apixaban yielding an additional 0.36 QALYs compared with aspirin (6.87 vs 6.51, respectively). Therefore, although there were several limitations to the study, it did suggest that apixaban was more costly and less effective than aspirin initially, but that apixaban became cost-effective and eventually economically dominant as the time horizon was extended.

Data comparing cost-effectiveness of apixaban with VKA therapy are currently lacking. One recently published study evaluated the reduction in medical costs (driven by clinical outcomes) associated with the use of individual non-VKA OACs, including apixaban, instead of warfarin from the US payer perspective.[270] This evaluation was based on the ARISTOTLE, RE-LY and ROCKET AF trial results.[217,218,223,224] Over 1 patient-year, the medical cost reduction associated with non-VKA OAC use instead of warfarin was estimated to be –$179 for dabigatran, –$89 for rivaroxaban and –$485 for apixaban, indicating that apixaban was associated with the greater cost reduction relative to warfarin. However, this was not a cost-effectiveness analysis and did not take into account drug costs and warfarin monitoring costs. The findings of another Markov model evaluating the cost-effectiveness of apixaban against dabigatran (both doses) and rivaroxaban for prevention of AF-related stroke from a UK perspective have been presented.[271] The following endpoints were used in the model: stroke (ischaemic and haemorrhagic), intracranial haemorrhage (excluding haemorrhagic stroke), other major bleeding events, clinically relevant non-major bleeding events, myocardial infarction and treatment discontinuations. For a lifetime horizon, the investigators reported incremental cost-effectiveness ratios ranging between £4426 and £12 762 per QALY for apixaban compared with the other non-VKA OACs. However, this analysis is subject to several of the limitations of indirect comparisons discussed earlier.

The outlook for the non-VKA OACs for prevention of AF-related stroke

As well as demonstrated efficacy and improved safety compared with warfarin, the non-VKA OACs offer fixed dosing with no need for routine coagulation monitoring. The non-VKA OACs may, therefore, help obviate most concerns regarding VKA therapy and mitigate any physician misconceptions regarding anticoagulant therapy. This should expand the proportion of eligible patients with AF at risk of stroke who receive oral anticoagulation, and thus reduce the overall burden of AF-related stroke.

Chapter 10
Guidelines for prevention of atrial fibrillation-related stroke

Key points from the 2012 update to the European Society of Cardiology guidelines

- The 2012 update to the European Society of Cardiology (ESC) guidelines strongly recommends a clinical practice shift towards increased focus on the identification of 'truly low-risk' patients with AF (i.e. age <65 years and lone AF [irrespective of sex] or CHA_2DS_2-VASc score 0) who do not need any antithrombotic therapy, instead of trying to focus on identifying 'high-risk' patients
- For all patients with a CHA_2DS_2-VASc score of 2 or more, oral anticoagulant (OAC) therapy is recommended
- For patients with a CHA_2DS_2-VASc score of 1 (except female patients under the age of 65 with lone AF), oral anticoagulation should be considered
- Rivaroxaban, dabigatran and apixaban (if approved) are now recommended over vitamin K antagonist (VKA) therapy for patients with AF at risk of stroke
- Antiplatelet therapy is not the preferred therapeutic option for AF-related stroke prevention for any patients with AF, and should only be considered if patients refuse all OACs (whether a VKA or one of the non-VKA OACs)

Summary of guidelines

Several sets of guidelines exist for the prevention of AF-related stroke. Those developed jointly by the ACC, AHA and ESC in 2006 represent American–European consensus guidelines.[61] In 2011, focused updates dealing with specific new drugs were issued by the ACC Foundation, the AHA and the Heart Rhythm Society (HRS), and were incorporated into the text of the 2006 ACC/AHA/ESC guidelines.[10] The American College of Chest Physicians (ACCP) produces international guidelines that are regularly updated; the current version (9th edition) was published in 2012.[94] Both the ACC/AHA/ESC and the ACCP guidelines were based on expert consensus from an international faculty and have been endorsed by major societies in both Europe and North America. In 2012, the AHA and the American Stroke Association issued a Science Advisory for the use of antithrombotic agents in non-valvular AF,[272] and the Canadian Cardiovascular Society published a AF guidelines focused update for stroke prevention and rate and rhythm control.[273] This chapter focuses on recent European guidelines produced by the Task Force for the Management of Atrial Fibrillation of the ESC.[49,90]

Guidelines endorsed by major societies exist for the prevention of AF-related stroke

Guidelines from the European Society of Cardiology

The European guidelines for the prevention of AF-related stroke, published by the ESC in 2010,[49] were updated in 2012 in collaboration with the European Heart Rhythm Association.[90] These guidelines are summarized in Table 9.

The 2012 ESC guidelines strongly recommend a clinical practice shift towards increased focus on the identification of 'truly low-risk' patients with AF (i.e. age <65 years and lone AF [irrespective of sex] or CHA_2DS_2-VASc score 0) who do not need any antithrombotic therapy, instead of trying to focus on identifying 'high-risk' patients. Therefore, the emphasis is now on identifying the small proportion of patients for whom the risk of bleeding outweighs the benefits of prophylaxis. OAC therapy is recommended for all other patients (Table 9).

In the ESC guidelines, antiplatelet therapy is not a preferred therapeutic option for patients with AF at any stroke risk level

Thus, for most patients, ESC guidelines recommend either oral anticoagulation or no prophylaxis. Antiplatelet therapy should be considered only when patients refuse to use any OAC drug. In these cases, therapy with aspirin and clopidogrel can be considered if a patient is at low risk of bleeding, or aspirin monotherapy could be used as a 'less effective' option.

Guidelines recommend oral anticoagulation for all patients with AF except those truly at 'low risk' of stroke

Use of the CHA_2DS_2-VASc stroke risk stratification scheme (Table 6) is recommended to identify patients at low risk (CHA_2DS_2-VASc score 0, i.e. patients younger than 65 years with lone AF). Female patients with AF who are under 65 years of age with lone AF (but CHA_2DS_2-VASc score 1 due solely to sex) are also considered to be at low risk and not to require antithrombotic therapy (Figure 14).

As described previously in Chapter 6, the CHA_2DS_2-VASc scheme is better than $CHADS_2$ at identifying patients truly at low risk of thromboembolism.[133] Compared with $CHADS_2$, CHA_2DS_2-VASc categorizes the smallest proportion of patients as low risk (Figure 8);[120] therefore, incorporation of this scheme into the guidelines increases the number of at-risk patients with AF recommended to receive anticoagulation. The ESC guidelines and the 2012 ACCP guidelines also recommend that patients with atrial flutter should receive antithrombotic therapy as recommended for patients with AF.[49,94] Patients with paroxysmal AF should also receive OAC therapy according to their stroke risk.[49]

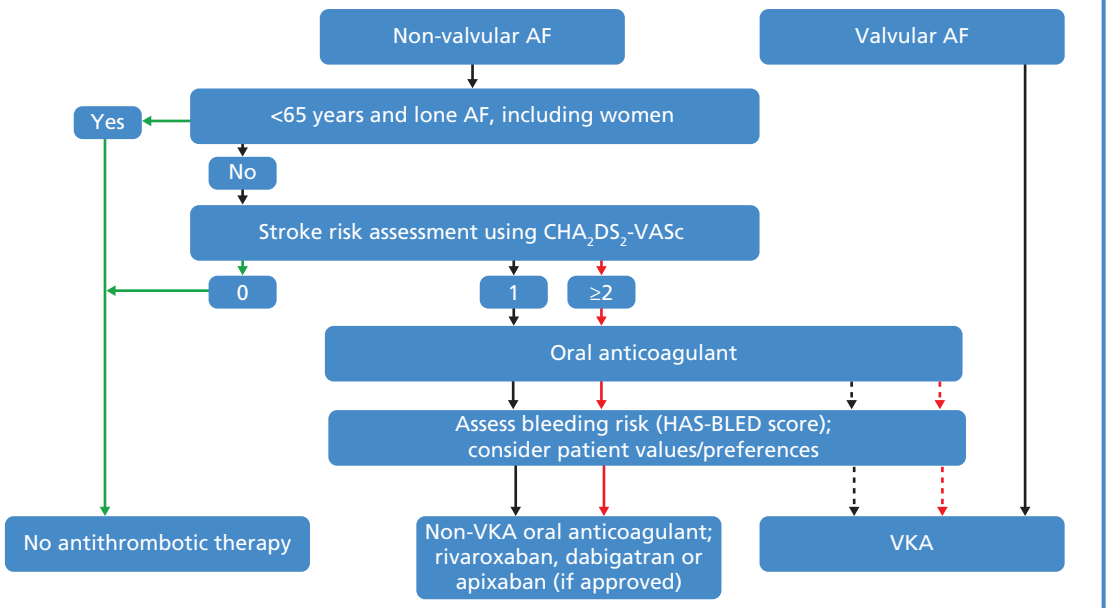
The ESC guidelines also incorporate the HAS-BLED bleeding risk score (Figure 14).[90] Patients with a HAS-BLED score of 3 or higher are considered to be at high risk of bleeding, requiring regular review during antithrombotic treatment. Several recent studies have demonstrated the HAS-BLED scheme to most accurately predict bleeding risk, including the risk for intracranial haemorrhage, compared with various other schema.[138,140,141] The ESC guidelines state that OAC therapy should not be withheld based on HAS-BLED score.[90] The score is also recommended for use in identifying modifiable bleeding risk factors (such as high blood pressure, labile international normalized ratio (INR), concomitant aspirin or of non-steroidal anti-inflammatory drug use in an anticoagulated patient) that can be addressed to reduce bleeding risk.[90]

Table 9. Summary of 2012 ESC guidelines for the prevention of AF-related stroke.[90]

Stroke risk	CHA_2DS_2-VASc = 0	CHA_2DS_2-VASc = 1	CHA_2DS_2-VASc ≥2
Recommendations	No antithrombotic therapy	An OAC should be considered, based on assessment of bleeding risk and patient preferences	An OAC is recommended
Details	Recommendation also applies to women aged <65 years with lone AF (CHA_2DS_2-VASc = 1 based on sex)	Non-VKA OACs are preferred over VKAs (INR 2–3) for most patients based on the net clinical benefit of these OACs. In particular, non-VKA OACs are preferred if VKAs cannot be used, there are difficulties in maintaining INR 2–3 or there is an inability to attend or carry out INR monitoring. None of the non-VKA OACs are recommended for use in patients with severe renal impairment (CrCl <30 ml/min) Rivaroxaban: 20 mg od is preferred; 15 mg od with: ♦ High bleeding risk (HAS-BLED ≥3) ♦ Moderate renal impairment: CrCl 30–49 ml/min Dabigatran: 150 mg bid is preferred; 110 mg bid with: ♦ Elderly patients ≥80 years ♦ Concomitant use of interacting drugs such as verapamil ♦ High bleeding risk (HAS-BLED ≥3) ♦ Moderate renal impairment: CrCl 30–49 ml/min Apixaban (if approved): no specific recommendations available yet – see section 'Recommendations for non-vitamin K antagonist oral anticoagulants'	

bid, twice daily; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, Stroke or transient ischaemic attack – Vascular disease, age 65–74 years, female sex; CrCl, creatinine clearance; HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalised ratio, Elderly, Drugs/alcohol concomitantly; INR, international normalized ratio; OAC, oral anticoagulant; od, once daily; VKA, vitamin K antagonist.

Figure 14. Clinical flow chart for the use of oral anticoagulation for the prevention of AF-related stroke.



Line colour indicate CHA_2DS_2-VASc score: green =0, blue =1. red ≥2.
Line style indicates preference: solid line = prefered, dashed line = alternative.
Adapted from Authors/Task Force Members, 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: An update of the 2010 ESC Guidelines for the management of atrial fibrillation * Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J* (published on behalf of the European Society of Cardiology) 2012;[Epub ahead of print] by permission of Oxford University Press.[90]
AF, atrial fibrillation; CHA_2DS_2-VASc, congestive heart failure, Hypertension, Age ≥75 years (2 points), Diabetes mellitus, Stroke or transient ischaemic attack (2 points), Vascular disease, Age 65–74, Sex category (female); HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly, Drugs/alcohol concomitantly; VKA, vitamin K antagonist.

Recommendations for non-vitamin K antagonist oral anticoagulants

Non-VKA OACs are now included in recommendations in the 2012 guidelines from the ESC and in some national country-specific guidelines.

Guidelines from the ESC

The guidelines place a preference on use of the non-VKA OACs over VKAs based on non-VKA OACs offering better efficacy, safety and convenience than VKAs (Table 9 and Figure 14).[90] Although not approved in Europe at the time of publication, apixaban is included because the authors of these guidelines expect approval in the near future. The guidelines conclude that there is insufficient evidence to recommend one non-VKA OAC over another. They note that differences in cost, patient characteristics, tolerability and drug compliance may be considered when choosing between the agents.

Despite this, there is a suggestion that if a patient experiences an ischaemic stroke during therapy with rivaroxaban or apixaban, they could be switched to dabigatran 150 mg twice daily (if the patient is eligible for this dose based on age and co-morbidities).[90] This suggestion is based on the fact that dabigatran 150 mg twice daily was the only non-VKA OAC to significantly reduce the risk of both ischaemic and haemorrhagic stroke compared with warfarin.[90,217,218,223]

2012 guidelines from the ESC recommend the use of non-VKA OACs rather than VKAs in all patients with AF who are at risk of stroke and for whom oral anticoagulation is recommended

The non-VKA OACs are not recommended for use in patients with severe renal impairment (creatinine clearance [CrCl] <30 ml/min) (Table 9),[90] although the European label for rivaroxaban states that the drug can be used with caution in patients with a CrCl of 15–29 ml/min.[252] There is also a recommendation that renal function should be tested before initiation and during therapy with a non-VKA OAC, particularly for patients taking dabigatran. Renal function should be tested at least annually if a patient has normal renal function (CrCl ≥80 ml/min) and more often (2–3 times a year) in patients with moderate impairment (CrCl 30–49 ml/min). Dose adjustment recommendations for rivaroxaban and dabigatran, based on renal function, age and HAS-BLED score, are outlined in Table 9. Specific recommendations

for dose adjustment of apixaban may become available once the drug is approved (Table 9).

Individual national guidelines

Country-specific guidelines for prevention of AF-related stroke exist for several countries in Europe, including the UK,[88] Italy,[274] France[275] and Spain (a Spanish summary[276] of the guidelines from the ESC by Camm *et al.* 2010 is available[49]). No specific guidelines exist in Germany, but the German Cardiology Society asked some of the German authors of the 2010 ESC guidelines to provide commentary on these guidelines.[49,277] The commentary concluded that these guidelines present an easily applicable foundation for the modern, evidence-based management of AF in most patients.[277]

Additional real-world efficacy and safety data for the non-VKA OACs are required

Considering that the non-VKA OACs rivaroxaban and dabigatran are available and have reimbursement approval in several countries in Europe, some countries have issued Health Technology Assessments relating to use of these drugs. The National Institute for Health and Clinical Excellence (NICE) recommends rivaroxaban and dabigatran as options for patients with AF with one or more stroke risk factor.[255,265] For patients already taking warfarin, NICE suggests the risks and benefits of switching therapies should be considered in light of the level of INR control achieved with warfarin. In their assessment of dabigatran, NICE noted that, with the associated risks, it may not be reasonable to expect newly diagnosed patients to try warfarin first.[265] Healthcare Improvement Scotland issued a statement on prevention of stroke and systemic embolism in adult patients with non-valvular AF.[278] In this statement, it is recommended that warfarin should be the anticoagulant choice for patients with good INR control (and CHA_2DS_2-VASc score of 2 or more), but that physicians should consider dabigatran or rivaroxaban for patients who are complying with warfarin but have poor INR control, or for patients with an allergy to or who experience intolerable side-effects with warfarin.[278] This caution is owing to the fact that there is, as yet, limited experience with the non-VKA OACs outside of the clinical trial setting. In 2012, the French National Authority for Health's Commission for Transparency issued an opinion on rivaroxaban and dabigatran.[279, 280] The Commission expressed a favourable opinion for the use of both rivaroxaban and dabigatran as an option for patients with AF and at least one risk factor for stroke as a first or second option (in patients with poor INR control with warfarin). An evaluation of the two anticoagulants was thought to be difficult on the basis of the results of the RE-LY and ROCKET studies given their designs; however, without taking this bias into account, it appears that rivaroxaban is less effective for stroke prevention, but causes fewer severe gastrointestinal bleeding events, than dabigatran.[280] In addition, the increased risk of myocardial infraction with dabigatran does not seem to be associated with rivaroxaban.

Dabigatran and rivaroxaban are recommended as options for patients with poor INR control with warfarin

Drug reviews have also been issued for rivaroxaban and dabigatran by the Canadian Agency for Drugs and Technologies.[281,282] The Agency recommends dabigatran for patients for whom warfarin is indicated but who have inadequate INR control or for patients with a prior serious hypersensitive reaction to warfarin.[281] Rivaroxaban is recommended for patients with a $CHADS_2$ score of 2 or more who are unable to achieve adequate anticoagulation with warfarin.[282] These reviews do not distinguish between patients already in receipt of OAC therapy and newly diagnosed or 'VKA-naïve' patients.

With the recommendation to use the CHA_2DS_2-VASc scheme to assess stroke risk and guide stroke prevention therapy, more patients who are at risk of AF-related stroke are now recommended to receive OACs according to 2012 ESC guidelines. All patients at risk of stroke (CHA_2DS_2-VASc score ≥1) are now recommended to receive OAC therapy. In these guidelines, antiplatelet therapy is not a preferred option for any patient group. Non-VKA OACs are now recommended for use over VKA therapy in the 2012 ESC guidelines. The improved efficacy, safety and convenience offered by non-VKA OACs compared with VKAs may also improve adherence to guidelines and compliance with therapy. The next chapter discusses how well guideline recommendations are incorporated into practice and possible reasons as to why guidelines are not always followed.

Chapter 11
Guidelines: theory versus practice

Key points

- **Although several sets of guidelines exist for preventing AF-related stroke, 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 standard therapies, and a lack of physician and patient education on the positive balance of benefits versus risks for most treated patients, may contribute to inadequate prevention of AF-related stroke**

Underuse of anticoagulation

Despite the existence of several sets of international, European and country-specific guidelines for the prevention of AF-related stroke, their application varies greatly, and vitamin K antagonist (VKA) therapy is often underused.[283] A recent German study evaluated VKA use in over 180 000 patients with AF.[47] In 2008, there was definite VKA underuse for 41% of patient-days in patients with a $CHADS_2$ score of 1 or more and no clinical risks associated with anticoagulant therapy. If days with potential underuse are included, this figure rises to 58%.[47]

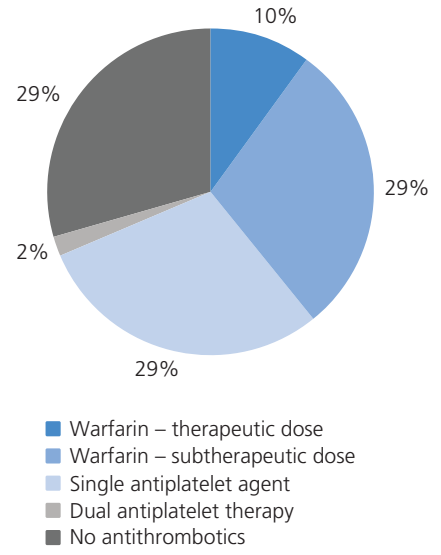
In some cases, patients eligible for VKA therapy may receive therapy with aspirin (an antiplatelet agent) instead, or the dose of VKA may be outside the recommended range (Figure 15).[18] Of patients newly diagnosed with AF in Italian primary care between 2001 and 2004, antiplatelet use but not anticoagulant use increased with stroke risk.[46] Only about one-quarter of patients with a $CHADS_2$ score of 2 received anticoagulant therapy and about one-third of these high-risk patients received no antithrombotic therapy at all. Similarly, in a Spanish AF study, only 57% of patients with a $CHADS_2$ score of 2 or above were receiving anticoagulant therapy and 19% of patients with a $CHADS_2$ score of 2 or above were receiving antiplatelet therapy.[45] All these studies highlight the discrepancy between the guideline recommendations and what is happening in much of routine clinical practice. The failure to provide appropriate prophylaxis to so many patients results in thousands of avoidable strokes, with all the clinical, economic and human burden that entails.

A review of the literature between 1997 and 2008 found anticoagulation treatment levels ranged from 19% to 81% in patients with AF and a prior stroke, with 21 of 29 studies reporting treatment levels below 60%.[244] A study of stroke in the UK from 1999 to 2008 found that, for patients with AF at the time of a first stroke, anticoagulant use was 29% and 22% for men and women, respectively.[284] Furthermore, these figures only rose to 48% and 35%, respectively, after the stroke. This study found that stroke incidence in the UK had decreased by one-third between 1999 and 2008, because prescriptions for cardiovascular risk management, e.g. for blood pressure and lipid regulation, had increased dramatically. Despite this improvement, the authors identified risk stratification for prevention of AF-related stroke as not yet being optimal, with prescriptions for anticoagulants to patients with AF before stroke only increasing slightly between 1999 and 2008.

It is worth noting that prescription of oral anticoagulation does not mean that the patient will subsequently be able to continue therapy. In the Italian study of patients newly diagnosed with AF, persistence with VKA

Discrepancies between guideline recommendations and usual clinical practice result in thousands of avoidable AF-related strokes

Figure 15. Medications received before admission to hospital by patients with known atrial fibrillation who suffered an acute ischaemic stroke.



Only 10% of patients received warfarin at a therapeutic dose. Adapted with permission from Gladstone *et al.* Potentially preventable strokes in high-risk patients with atrial fibrillation who are not adequately anticoagulated. *Stroke* 2009;40:235–240.[18]

therapy was less than 50% after 1 year and about 25% after 2 years.[46] A similar study in California of patients with AF starting on warfarin showed discontinuation rates of 26% within 1 year.[285] Therefore, patients starting warfarin and subsequently discontinuing are likely to make a considerable contribution to anticoagulation underuse. An alternative therapy is, therefore, needed for those patients who decide to discontinue therapy with VKAs.

Adherence to guidelines varies greatly, and VKA therapy is often underused, resulting in suboptimal outcomes

As well as underuse of anticoagulation in patients at high risk of AF-related stroke, anticoagulants can be inappropriately used in patients at very low risk of stroke, in whom the benefits of therapy may not outweigh its risks, e.g. the risk of bleeding. In an initial cohort of more than 10 000 patients with AF in an ongoing global anticoagulant registry (Global Anticoagulant Registry in the FIELD; GARFIELD), 35% of patients with a CHA_2DS_2-VASc score of 0 were prescribed anticoagulant therapy and a further 35% of these patients were prescribed aspirin therapy.[286] Conversely, in this cohort, only half of the patients with a CHA_2DS_2-VASc score of 2 or more were receiving anticoagulant therapy.

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 with AF and a high risk of stroke was associated with a significantly greater risk of thromboembolism during the 1-year study period, whereas inappropriate treatment (where treatment was not recommended by current guidelines) was not associated with a significantly higher risk of bleeding.[48]

Reasons for poor adherence to guidelines

Adherence to guidelines for the prevention of AF-related stroke may be low for several reasons. These include difficulties in maintaining the international normalized ratio (INR) within the therapeutic range (see section on 'Strategies for preventing formation of blood clots', Chapter 8, page 49)[21] and physicians' concerns, often misplaced, about bleeding risk, particularly in the elderly.[41]

Difficulties in maintaining dose of VKA 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).[287] In the International Study of Anticoagulation Management (ISAM), the mean time spent within therapeutic INR range varied significantly by country.[205] The proportion of INR tests within range was 69.5% for Italy, 64.9% for Spain and 59.3% for France. 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 range for a smaller proportion of time than patients who were monitored frequently, according to strict protocols.[288] 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 bleeding. Furthermore, a therapeutic INR at stroke onset is also

associated with greater early functional improvement and improved long-term survival.[289] Conversely, VKAs are associated with a significant number of adverse events. For example, over a 2-week period in 1998, VKA-associated haemorrhages accounted for 13% of hospitalizations due to drug-related adverse events in France.[290]

Physicians' concerns about bleeding risk

Some physicians may overestimate the risk of bleeding associated with the use of VKAs and underestimate their benefits in preventing thromboembolism and stroke; conversely, they may underestimate the bleeding risk of aspirin therapy and overestimate its benefits.[41,43,291] As a result, some eligible patients are not receiving optimal therapy that could prevent AF-related strokes.[18] 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, because elderly patients may be prone to falls, there is a concern among physicians that elderly patients who fall may suffer a severe haemorrhage if they are taking VKA therapy.[292–294] However, evidence has shown that, in patients with AF who are receiving anticoagulants, the risk of a cerebral bleed from falling is so small that the benefits of treatment outweigh the risks.[295] Furthermore, the incidence of stroke among patients aged 75 years or older with AF is lower in those who are receiving VKA therapy than in those taking aspirin, with no associated increase in the risk of haemorrhage.[188]

Bleeding risk during VKA therapy in patients with AF is not homogeneous and a number of clinical factors that are associated with increased bleeding risk have been identified, including high blood pressure, older age and history of bleeding.[135,138] A number of bleeding risk stratification schemes exist, including a new, simple major bleeding risk score known as HAS-BLED,[135] which is used to predict bleeding risk in the 2012 European Society of Cardiology (ESC) guidelines.[90] The HAS-BLED score is described in more detail in the section on 'Approaches to risk stratification' (Chapter 6, page 35). Several recent studies have demonstrated that HAS-BLED predicts bleeding risk more accurately than various other schema.[138,140,141]

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 had treated a patient who had suffered a bleeding event. These physicians also treated other patients with AF up to 90 days before and 90 days after the bleeding event in question.[296] 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. 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.[296] 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.

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 compared with perceptions among physicians. For both groups, the aim was to identify how big the reduction in risk of stroke should be to justify antithrombotic 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.[297] For VKA therapy to be justified, physicians considered that it needed to prevent a significantly higher number of strokes than the number that patients thought acceptable (Table 10). The number of strokes that needed to be prevented to justify aspirin therapy did not differ significantly between patients and physicians.[297]

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

When perceptions of bleeding risk were evaluated, the maximum number of bleeding events associated with warfarin or aspirin that patients found acceptable was significantly

Table 10. Thresholds for the justification of therapy reported by patients with atrial fibrillation at high risk of stroke versus those reported by physicians.

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 bleeding events 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

Table compares reduction in risk of stroke regarded as necessary and how much risk of excess bleeding is acceptable over 2 years of antithrombotic treatment by patients and physicians. Data from Devereaux *et al.* 2001.[297]
NS, not significant; SD, standard deviation.

Compared with physicians, patients place more value on stroke avoidance and less value on avoidance of bleeding

higher than that considered acceptable by physicians (Table 10). Moreover, the results suggest that physicians perceive the risk of bleeding to be higher with VKAs than with aspirin. This perception is at variance with the findings by Mant *et al.* that, compared with aspirin, well-managed warfarin decreases stroke risk without increasing the risk of bleeding.[188]

These results indicate that patients place more value than physicians do on the avoidance of stroke, and less value on the avoidance of bleeding.[297]

Reasons for poor patient adherence and compliance with vitamin K antagonist therapy

The views of the individual patient must be considered when deciding whether to use anticoagulant therapy, even if the physician is risk averse

The literature review described on page 72 also found that with more frequent monitoring, more time within the therapeutic INR range was achieved in an organized care setting, including specialist anticoagulation clinics.[288] The frequent monitoring and necessary dose adjustments associated with VKAs are inconvenient and time consuming. Recently, AntiCoagulation Europe (UK) and the AF Association carried out a survey of patients with AF in the UK who were taking warfarin.[298] Monitoring took between half an hour and an hour for 39% of patients, and over an hour for 19%. One in six of the patients relied on someone else to drive them to their appointment. In particular, elderly patients may be unwell, become confused or forgetful, or have difficulty with transport, resulting in missed appointments. This can be especially true for patients living in more remote areas. Patients with a prior stroke may have suffered cognitive impairment and, as such, be dependent on carers for attendance at clinics. Other challenges associated with VKA therapy include drug–drug interactions, imposed lifestyle restrictions, variable dose responses, the lack of adequate anticoagulation monitoring facilities in rural areas and the fear of bleeding within the brain. Half of the patients in the survey felt that warfarin had a high or fairly high impact on their quality of life, and almost one-third strongly agreed with the statement, 'I feel my whole life is controlled by warfarin'.

Patient education could play an important role in compliance and adherence with VKA therapy. It has been shown that greater patient knowledge of warfarin is associated with better INR control.[299] Furthermore, poor INR control is associated with discontinuation of warfarin therapy.[285] Poor INR control may reflect poor adherence, which might lead to discontinuation, or may raise concerns about the safety of continuing warfarin therapy.

To summarize, adherence to guidelines for the prevention of AF-related stroke 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 further education of both physicians and patients, and for improvements in guideline adherence across Europe. Because the non-VKA oral anticoagulants (OACs) are at least as effective as VKAs with a superior

safety profile, physicians may be more likely to prescribe them in practice (see Chapter 9, 'Non-vitamin K antagonist oral anticoagulants for prevention of atrial fibrillation-related stroke', page 57). The recent inclusion of the non-VKA OACs into 2012 European guidelines could, therefore, improve guideline adherence and increase the number of eligible patients receiving therapy to prevent AF-related stroke (see Chapter 10, 'Guidelines for prevention of atrial fibrillation-related stroke', page 67). Because the non-VKA OACs do not require frequent, routine monitoring and dose adjustment, more patients may be encouraged to take OAC therapy.

Chapter 12
Current challenges for the prevention of atrial fibrillation-related stroke

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
- Promote adherence to guidelines for the management of AF
- 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, especially those with the potential to expand the use of prophylaxis and to improve outcomes
- Improve knowledge and awareness among physicians involved in AF management
- Optimize integrated management and the continuum of care for all patients with AF
- Provide equity of access to AF therapy and information for all patients across the EU

Recent studies suggest at least 90% of patients with AF have a CHA_2DS_2-VASc score of 1 or more and, therefore, require anticoagulation therapy.[69,70,90,286,300] Studies estimate that only half of these patients receive anticoagulant therapy[286] and that, among this group, only 56% are within the therapeutic range.[287] It follows, therefore, that only approximately 25% of patients with AF are in receipt of appropriate and adequate treatment for stroke prevention. In addition, it is estimated that one-third of patients with AF are undiagnosed,[28,29] meaning that only approximately 17% of patients with AF receive appropriate treatment to prevent AF-related stroke.

Although AF-related stroke is preventable, it is clear that significant improvements are required in the detection and treatment of AF and in adherence to guidelines on the use of existing antithrombotic therapies to prevent AF-related stroke. The current challenges in the prevention of AF-related stroke are discussed in more detail in this chapter.

Improved detection and diagnosis of atrial fibrillation

Unfortunately, AF often remains undetected until an individual suffers a stroke. In a population of 478 patients with ischaemic stroke in Germany, 11% of the patients had AF that was undiagnosed prior to their stroke.[91] Awareness of the early signs of AF and common coexisting conditions is required to maximize the opportunity for stroke prevention in patients at risk. Clear strategies are needed that will lead to improved detection and diagnosis of AF by physicians. In part, this involves fostering an increased awareness among the general public that signs such as an irregular pulse and abnormal heart rhythm should be investigated. To this end, Arrhythmia Alliance, The Heart Rhythm Charity launched the 'Know Your Pulse' campaign in 2009.[39] The campaign aims to promote public awareness of the importance of pulse checking. Arrhythmia Alliance was set up in the UK to promote improved understanding,

diagnosis, treatment and quality of life for people with cardiac arrhythmias, and it is now established in many other European countries.[301]

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

There may be scope to introduce more widespread AF screening programmes in the wake of the positive results of the SAFE study, in which active screening identified 60% more AF cases than did routine care.[38,89] The 2012 guideline update from the European Society of Cardiology (ESC) recommends pulse checks for all patients aged 65 years and older followed by an electrocardiogram (ECG) in those with an irregular pulse.[90] 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 diagnosis and how best to support healthcare professionals in the interpretation of ECG results.[38] These recommendations need to be followed up and put into practice. The SEARCH-AF study has recently been initiated in Australia to evaluate screening by pulse check and a hand-held, single-lead ECG device for iPhones in community pharmacies.[302] As well as investigating the prevalence of newly diagnosed AF, the study will also assess the ability of pharmacists to interpret the ECG by comparison with a cardiologist's interpretation.

The recently initiated STROKESTOP study in Sweden will evaluate whether screening a population of 75-year-olds and 76-year-olds for silent AF, using ambulatory intermittent ECG recording, will cost-effectively reduce stroke in this population.[303] The study will include approximately 25 000 individuals who will be randomized to either screening or control groups. Participants will be followed for 5 years from the date of the first patient enrolled. An interim analysis is expected in 2015.

Europe-wide adherence to guidelines

Programmes aimed at improving the implementation of guidelines in clinical practice would be of benefit to European countries

The efficacy and tolerability of vitamin K antagonists (VKAs) in the prevention of AF-related stroke are well established,[10] but several drawbacks can lead to poor adherence to guidelines, as discussed previously.

Regular reviews, updates and endorsement of the guidelines will ensure that they remain relevant to current clinical practice and may thereby increase adherence.[41,304] Programmes aimed at improving the implementation of guidelines in clinical practice would also be of benefit to European countries. 'Get With The Guidelines-Stroke', carried out by the American Heart/Stroke Association, is an example of an initiative aimed at improving adherence to the latest scientific guidelines.[305] One of the roles of the ESC National Guidelines Coordinators is to be active in national implementation programmes of the ESC guidelines. These programmes include production and translation of educational materials and courses. In line with the core mission of the ESC National Guidelines Coordinators,[53] the EU can call for better alignment between Member States to identify key areas in which the guidance is being overlooked or in which agreement is required on divergent practices.

Increasing 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 is a registered charity committed to the prevention of thrombosis and the provision of information and support for people already receiving anticoagulant and antiplatelet therapy.[306] AntiCoagulation Europe conducted a survey as part of the 'It's About Time' campaign,[307] which aimed to provide insights into patients' experiences of their treatment with VKAs. The survey revealed 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 about 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.[307] The AF Association is a UK registered charity that focuses on raising awareness of AF by providing information and support materials for patients

and medical professionals involved in detecting, diagnosing and managing AF.[308] As well as producing a UK-specific AF report as a source of information for both policy-makers and healthcare professionals, AntiCoagulation Europe and the AF Association have created an online stroke risk calculator to enable patients to calculate their own personal stroke risk.[309] After using the calculator, patients receive a personal print-out of information, which can be discussed with their doctor when assessing the potential need for treatment to reduce the risk of AF-related stroke. StopAfib.org is an online patient-to-patient resource that provides information and support for individuals with AF.[310] StopAfib.org is a US-based organization but aims to support the global community of AF patients with information and discussion forums. The medical content of the site is overseen by a Medical Advisory Board that includes some of the world foremost cardiologists and researchers in the field, and provides information on the causes, consequences and management of AF so that patients can make informed choices about their care.

Recently, AntiCoagulation Europe (UK) and the AF Association carried out a small survey of 104 patients with AF taking warfarin in the UK.[298] Of the patients questioned, 56% were not aware that AF increases the risk of stroke and only 36% were aware that warfarin protects against stroke. 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.[311]

Likewise, the Stroke Association (UK), a member organization of the Stroke Alliance for Europe,[312] has initiated the ASK FIRST campaign to promote awareness of AF. This also included a survey in 2011 of over 1000 general practitioners concerning the main issues relating to proper diagnosis, management and treatment of AF.[313]

The AF AWARE group conducted an international quantitative survey in 11 countries, including the UK, France, Germany, Spain and Italy, to analyse understanding, perception and attitudes towards AF among physicians (cardiologists/electrophysiologists) and patients with AF.[87] Overall, 46% of physicians thought that their patient's ability to explain their condition was poor, and 1 in 4 patients surveyed felt unable to explain their condition to another person. Physicians thought that over 50% of their patients with AF had an important need for more and improved information about their condition. In terms of the quality and level of AF information provided to patients, only 35% of physicians considered it easy for patients to understand, although 57% of patients considered the information they had received to be easy to understand, and only 20% of physicians thought that enough information was provided. From a patient perspective, almost one-quarter (23%) did not know where to seek information, or who to contact to receive this additional information about AF. In the 'Living with Warfarin' survey carried out by AntiCoagulation Europe and the AF Association, fewer than one-third of patients said that they actively searched for information on warfarin.[298] Because information is increasingly internet based, patient access to the internet needs to be considered, especially for the elderly and carers for the cognitively impaired. In an epidemiology study of AF carried out in Portugal, almost all individuals with AF who had heard of it said their source of information was the media.[76] This highlights the potential role of the media, as well as healthcare providers, in disseminating information. Considering the fact that many patients with AF are elderly, information targeted at younger relatives or carers could also be of value so that they can help to relay this information to the patient in a more easily comprehensible way. Results from another recent survey ('Speak about AF') involving over 3700 patients and physicians in 12 countries worldwide, including Belgium, France, Germany, Greece, Italy and Spain, found that people with AF were likely to turn to family and friends (29%), pharmacists (26%) and websites (18%) for information about their condition.[314] The worry felt by patients with AF decreased as they became more informed over time.

Many patients do not understand the critically important role of anticoagulants in the prevention of blood clots and stroke

Better adherence to therapy

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

According to AntiCoagulation Europe, adherence to therapy is reliant on patients' understanding of their condition. Although some patients fully appreciate the need to stay within the therapeutic range – but fail to do so for reasons outside of 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 survey found that, although just below three-quarters of patients knew their target international normalized ratio (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 past 5–10 monitoring sessions, and 7% had not been in their target INR range in any of their past 5–10 sessions.[307] Furthermore, in a review of patient records from 15 general practices in the UK, warfarin was associated with 16.4% of monitoring errors.[315] One example of a severe monitoring error involved a 93-year-old patient taking warfarin whose last recorded INR was more than a year old; although the patient had missed three consecutive appointments, warfarin prescription was continued.

Healthcare professionals need to communicate with each other in order to provide consistent information and advice for patients

Greater patient 'empowerment'

Patient 'empowerment' can be associated with improved clinical outcomes

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 can lead to improved clinical outcomes.[316] For example, patient education and involvement in the management of VKA therapy has been shown to reduce the risk of major bleeding.[317] 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 understandable at different levels of literacy. However, inconsistencies in the level of education, socioeconomic and cultural factors, individual patient characteristics, and local/national provision of services in European countries, as well as other factors such as age and cognitive problems, may lead to inequalities in the uptake of patient information outputs.

Improved knowledge and awareness among healthcare professionals

Benefits of current treatments to prevent stroke

Poor adherence to guidelines on the part of physicians 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 oral anticoagulants (OACs) in the prevention of AF-related stroke. Physicians also need to be reassured that the risk of bleeding is usually small compared with the great benefits that therapy can bring.

Healthcare professionals should be convinced of the importance of communicating the benefits and risks of potential therapy to patients. There is often a significant amount of information for patients to absorb in a consultation with the physician. Therefore, information needs to be provided in an easy-to-understand format (written or interactive), with critical facts and advice repeated and patients' understanding confirmed. In addition, communication between different healthcare professionals who are interacting with the patient needs to be improved to ensure that consistent information and advice are provided. If patients are overwhelmed by too much information and/or contradictory recommendations, they are unlikely to understand and adhere to the prescribed treatment regimen.[318]

Such considerations underscore the need for the integrated management of patients, especially for those with multiple conditions.

Management of patients receiving VKAs

There is a clear need for a proper infrastructure for the delivery and monitoring of VKAs across all European countries, 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.[319] 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.[320] 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.[320]

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,[319] helping to increase the period 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.[205,321] 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 the patient, which could lead to disruption of care if communication breaks down.[319] Therefore, healthcare providers may need education and support to ensure a seamless transition between the different strands in the patient pathway. As management of patients receiving anticoagulants evolves and new therapies become available, anticoagulation clinics may adapt to provide specialist support for the management of these evolving therapies.[319]

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-management (when the patient is responsible for their own INR measurement and dose adjustment) to be an effective and acceptable alternative to management at an anticoagulation clinic.[322,323] A Cochrane analysis of 18 clinical trials highlighted the benefits of patient self-monitoring (when the patient is advised on dose adjustment by telephone) and self-management in improving the quality of their oral anticoagulation therapy compared with standard monitoring.[324] Data from a study in Germany have also shown self-management to be cost-effective.[325] However, this approach may not be appropriate for all patients; for example, in the Cochrane analysis, self-monitoring or self-management could not be used for up to half of the patients requiring oral anticoagulation therapy.[324] In another study, 76% of patients invited decided not to undertake self-management and, of those that did, 26% did not complete training.[326] Therefore, appropriately trained physicians will still be needed to support self-management.

Increased training and advice on the management of anticoagulation therapy could increase the willingness of physicians to prescribe OACs

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 to optimize care.[327,328] Healthcare professionals will, again, need specific training to implement these programs in practice.

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 inadequate use – of VKAs, presently the predominant form of anticoagulant therapy, have led to the search for new therapies and other strategies that can be used in the prevention of AF-related stroke. Non-VKA OACs, such as rivaroxaban and dabigatran, that are easier to use and more convenient than VKAs are now available, with more predictable effects and a better safety profile; these non-VKA OACs have the potential to increase adherence to therapy and

The advent of the non-VKA OACs should increase adherence to therapy and improve clinical outcomes

improve outcomes for patients. A large multinational survey found that 68% of patients with chronic AF would be interested in anticoagulation drugs that do not require routine monitoring.[327]

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

Awareness of treatment innovations

Non-VKA OACs may simplify the management of patients with AF. As with any chronic intervention, however, high-quality guidance and education for doctors, patients and carers will be essential. Increased resources for education and rapid dissemination of information will allow faster introduction and uptake of the non-VKA OACs, and physicians will need to be made aware of such resources. Healthcare professionals will need to identify and manage eligible patients, so practical guidance for the use of the non-VKA OACs will also be essential. The non-VKA OACs do not require routine coagulation monitoring; therefore, there could be a shift to primary care prescribing of anticoagulant therapy for the prevention of AF-related stroke with anticoagulant clinics maintaining an educational role for patients and healthcare professionals.

The introduction of the non-VKA OACs means that there is likely to be a change in how patients in receipt of anticoagulant therapy are managed. To ensure that a patient is complying with their therapy, and for continual patient education, general practitioners will need to be prompted to discuss anticoagulant therapy with patients during any routine visit. Primary care physicians will also need to be aware of any necessary dose adjustments – for example, patients in receipt of dabigatran need to be switched to the lower dose when they reach 80 years of age.[90] Patients in receipt of non-VKA OACs also require periodic assessments of kidney function, and dose adjustment is needed in patients with a creatinine clearance (CrCl) of 30–49 ml/min.[90,239,252] General practitioners may require additional education in order to take on these new roles. As for patients currently in receipt of VKAs, continual patient education will also be required to ensure adherence to the non-VKA OACs after the patient's prescription is changed.

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 a holistic consideration of patients' needs, preferences and concerns relating to overall health, rather than just to the specific condition in focus.[330] Although a patient-centred approach is widely advocated, it is not always implemented.[330] Instead, healthcare is typically centred on treating the disorder rather than considering patients' individual needs.[330,331] There is evidence that anticlotting therapy tailored to patients' preferences is more cost-effective in terms of quality-adjusted life-years (QALYs) than giving the same therapy to every patient.[332] 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.

An optimized continuum of care

Continuity of care, involving continuing communication between healthcare providers, is essential for high-quality care. Because the provision of healthcare often involves several different service providers, continuity of care is defined as 'coherent healthcare with a seamless transition over time between various providers in different settings'.[333]

Biem *et al.* have described seven characteristics (the seven Cs) of optimal continuity of care.[333]

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 to physicians 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. In a review of general practices in the UK, general practitioners were quoted as saying that they found warfarin-treated patients 'dreadfully hard' to keep track of.[315] Practitioners noted that poor communication between healthcare settings made management of warfarin-treated patients difficult. In addition, when patients are transferred to other healthcare providers or to different settings, such as during hospitalization or at discharge, critical information can be lost. Transferring patients at night-time and at weekends has been reported to increase death rates.[334,335] Comprehensive, timely and appropriate discharge information is essential – ideally in a portable format (paper or disc)[336] – so that both the patient and the primary care practice have all the information that is needed for appropriate follow-up care. Insufficient discharge information can contribute to hospital readmission.[337] 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.

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

The potential consequences of a breakdown in continuity of care are illustrated in the case study below.

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 rate control of AF) and was transferred to a regional care hospital.

In hospital, the patient was seen by a resident physician in the emergency room. 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 (an antibiotic), and instructed to remain on metformin (for diabetes), enalapril (for high blood pressure), digoxin (to manage the heart rate in AF) and warfarin (to prevent AF-related stroke). 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 the following 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 his 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 that left him with weakness down his right side and speech impairment.

Case study adapted from Biem *et al.*[333]

Equity of access to healthcare 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.[338]

Programmes aimed at improving the implementation of guidelines into clinical practice would be of benefit to European countries

According to the EPF, current healthcare systems can be unfair and divisive and can fail to put the patients' perspective first.[339] There are significant differences across EU Member States in how the provision of health information is perceived and prioritized.[340]

Equal access for all

In addition to variations in care among countries in the EU, people of different ethnic backgrounds may have different access to healthcare, or their perceptions of the healthcare they receive may differ. It has been demonstrated that cultural beliefs can influence individuals' ideas about illness.[341]

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 throughout the EU.[339]

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

The European Commission began tackling the issue of health inequalities in October 2009 by publishing a communication entitled 'Solidarity in Health: reducing health inequalities in the EU'.[342] The communication acknowledges the differences in health and access to care between people living in different parts of the EU and between the most advantaged and most disadvantaged segments of the population. The European Parliament also produced a report on this subject in February 2011, drafted by Edite Estrela (Member of the European Parliament's Environment, Public Health and Food Safety Committee. S&D, Portugal).[343] Among other things, the report calls on the Commission and Member States to press ahead with their efforts to tackle socioeconomic inequalities and to develop prevention and awareness campaigns that target the most vulnerable groups in society. It also stresses that preventive measures and rehabilitation therapies must be non-discriminatory and fully accessible to patients across Europe. Finally, it also calls on the Commission and Member States to ensure that information on health is available in a form and in languages that everyone can understand. However, according to the EPF, the Commission's Communication was not satisfactory, with no reference to the particular needs of patients or the importance of health literacy, and no focus on the importance of chronic disease management. The report by the European Parliament, however, does reflect these concerns. A progress report on efforts towards reducing health inequalities is due to be published by the Commission at the end of 2012.

Integrated actions for national governments, healthcare professionals, patient organizations and payers

In April 2012, the Global Atrial Fibrillation Patient Charter was launched.[344]. Developed by a steering committee including AntiCoagulation Europe, Arrhythmia Alliance, AF Association, Irish Heart Foundation, StopAfib.org and Stroke Alliance for Europe in collaboration with 39 patient organizations from 20 countries, the Charter is now endorsed by over 90 medical, patient and consumer organizations from around the world.

The Global Atrial Fibrillation Patient Charter has been designed to bring a worldwide, unified voice to improving the treatment and care of individuals living with AF, and those at risk of AF-related stroke. It contains recommendations

about critical actions that policy-makers, healthcare providers, payers and national governments can take to save lives and reduce the burden of disease and the huge associated medical costs. The Charter recommendations propose solutions for many of the challenges outlined in this chapter, including the need for increased awareness and earlier diagnosis of AF, the requirement for enhanced continuity of care, and the need for timely and equal access to innovative therapies that overcome current treatment limitations, such as the non-VKA OACs. The Charter also calls for greater prioritization by governments of the prevention and treatment of AF-related stroke in accordance with to recent evidence-based guidelines as well as for the creation of national stroke registries to record the incidence and prevalence of AF-related stroke and its outcomes.

The Charter calls on national governments, policy makers, payers and healthcare providers to take the following actions:

'Early detection saves lives. Early diagnosis, followed by appropriate medical management, can improve the outlook for people living with AF. It can also lead to savings for national governments and healthcare providers. Pulse checks are a quick, simple and extremely low-cost way to detect if someone may have AF.

- We call on national governments to implement public information campaigns that raise awareness of the early signs of AF, the risk factors of stroke, and the importance of pulse checks backed up with readily available AF education and information materials

Stroke prevention should be a greater priority for governments. Strokes, including AF-related strokes, are preventable; when they occur, appropriate management can greatly reduce the associated personal, social and economic burdens.

- We call on national governments to make stroke and AF-related stroke prevention and care a national healthcare priority. We recommend national stroke registries be put in place to systematically and accurately record the incidence, prevalence and outcomes for people with AF-related strokes

Improved diagnosis and treatment of people who live with AF can prevent AF-related strokes and offer better outcomes if stroke occurs. Implementing guidelines is one way that healthcare organizations can improve healthcare and reduce cost.

- We call on healthcare providers to implement widely accepted clinical guidelines on the treatment of AF and AF-related stroke such as those developed by prominent medical societies including the American College of Cardiology/American Heart Association, Canadian Cardiovascular Society, European Society of Cardiology and Heart Rhythm Society

Enhancing knowledge and practices in the healthcare workforce will improve prevention, detection and management of AF and AF-related strokes. Awareness of heart rhythm disorders among many health professionals needs to be improved to ensure that disorders are diagnosed and treated effectively.

- We call on medical colleges and healthcare providers to ensure continued professional education about the diagnosis, treatment and aftercare of people with AF is mandatory for general practitioners
- We call on health professionals to strengthen collaboration between primary and secondary providers to make sure patients receive appropriate treatment throughout the care pathway

Innovative technologies that improve prevention, diagnosis, and treatment of people with AF or at risk of AF-related stroke must be made appropriately available at the earliest opportunity. Advances that lead to reduction in hospitalization and strokes as well as improvements in quality of life and long-term cardiac health in AF patients are urgently needed.

- We call on national governments to increase access to immediate emergency care and specialist stroke units where the newest technologies are available
- We call on payers to consider evidence that combines robust clinical data with evidence

of the impact on people affected by AF to make healthcare decisions that reflect the needs of those people'

The Global Atrial Fibrillation Patient Charter's supporting campaign, 'Sign Against Stroke in Atrial Fibrillation', is calling for individuals around the world to sign their names on www.SignAgainstStroke.com to demonstrate their support for the Charter and ask national governments to implement its recommendations to prevent AF-related strokes.

The campaign is a collaboration between various patient groups (supported by Bayer HealthCare) to promote visibility and use of the Global Atrial Fibrillation Patient Charter. It unites patient and medical communities and supports them to foster change in their countries based on the Charter agenda.

Individual policy-makers around the world have joined medical, patient and consumer organizations, and thousands of people, in supporting the Global Atrial Fibrillation Patient Charter and calling for national governments and the World Health Organization to act to improve the prevention of AF-related strokes. For example, Members of the European Parliament have signed the Charter and noted that it is very important that national Ministries of Health throughout the 27 European Member States pay attention to the Global Atrial Fibrillation Patient Charter, because its recommendations could help governments achieve the aims of the European Heart Health Charter and the recently adopted United Nations target to reduce NCD mortality by 25% by the year 2025.

The ongoing efforts of patient organizations and increasing recognition of the huge burden of stroke in Europe are aligned with the outcomes from the first European 'Day of the Brain', an expert conference that took place during the 2011 EU Polish Presidency. One of the recommendations from the post-conference conclusion was for EU Member States 'to introduce – in cooperation with all interested parties – national plans, strategies and all other measures for improving the implementation of prophylactic programmes aimed especially at eliminating vascular risk factors, and establishing procedures for ensuring effective and adequate health and social care in order to improve the quality of life of elderly patients and to support their carers.'[345] Implementation of the strategies in the Global Atrial Fibrillation Patient Charter would be strongly aligned with this recommendation.

Summary of current challenges

In summary, numerous challenges remain in the prevention of AF-related stroke. In line with the conclusion from the first European 'Day of the Brain' described previously, policymakers from EU Member States need to provide greater support in the implementation of strategies to reduce AF-related stroke.[345] The level and quality of information on AF provided to physicians and patients needs to be improved. Increased detection of AF by physicians is vital, and improved education is needed among patients and healthcare professionals on the benefit–risk profile of aspirin, VKAs and the non-VKA OACs for the prevention of AF-related stroke, as well as on the options for effective clinical management of patients with AF itself. Healthcare professionals need to be well informed about the non-VKA OACs and other therapeutic strategies that are emerging, and also about advances in the treatment of AF. It is also important to encourage patient empowerment and patient-centred care, in addition to ensuring equity of access to healthcare for all. Finally, improved implementation of and adherence to guidelines and implementation of strategies to ensure effective communication between healthcare professionals should improve patient management, as will optimization of the continuum of care. All of these factors can contribute to reducing the overall burden of AF-related stroke.

Chapter 13
New developments for the management of atrial fibrillation and the prevention of atrial fibrillation-related stroke

Key points

- **Non-pharmacological methods for managing abnormal heart rhythm (arrhythmia) exist, and research is ongoing in this area**
- **New implantable devices are being tested to improve detection of silent, asymptomatic AF or paroxysmal AF by continuous monitoring**
- **Non-vitamin K antagonist (VKA) oral anticoagulants (OACs) for stroke prevention in AF are now available. Others are also in development**
- **Catheter and surgical procedures have been developed both to manage AF and to reduce the risk of clots reaching the brain**

The shortcomings of the VKAs and the lack of effectiveness of aspirin limit their use in the prevention of AF-related stroke (see Chapter 8, 'Prevention of atrial fibrillation-related stroke', page 47). These limitations have led to an ongoing search for alternative effective and convenient therapies. Non-VKA OACs, which have completed or are in the later stages of development, are discussed in Chapter 9, 'Non-vitamin K antagonist oral anticoagulants for prevention of atrial fibrillation-related stroke' (page 57). Other antithrombotic agents are also in earlier stages of development, and there have been developments in anti-arrhythmic strategies used to treat AF, devices to prevent AF-related stroke and in implantable monitoring devices used to detect AF. These developments are discussed in more detail in this chapter.

Management of arrhythmia

Developments in pharmacological management of arrhythmia

The new intravenous anti-arrhythmic drug vernakalant is now approved for use in Europe for pharmacological cardioversion of AF lasting 1 week, or up to 3 days after cardiac surgery.[90] Vernakalant is now included in the 2012 European Society of Cardiology (ESC) guidelines as an option for pharmacological cardioversion of recent-onset AF if there is no or minimal structural heart disease.[90]

Developments in non-pharmacological management of arrhythmia

There are numerous non-pharmacological methods available for the management of abnormal heart rhythm, including:

- Electrical cardioversion: a process by which an abnormal heart rhythm is terminated by the delivery of a therapeutic dose of electric current to the heart
- Catheter ablation: an invasive procedure used to remove faulty electrical pathways from the heart
- Surgical procedures: open heart surgery or minimally invasive procedures that also serve to remove the faulty electrical pathways from the heart

These procedures have been discussed in detail in Chapter 8, 'Prevention of atrial fibrillation-related stroke' (page 47).

Hybrid ablation

Hybrid ablation combines intracardiac catheter ablation by an electrophysiologist and

minimally invasive extracardiac surgical ablation by a cardiac surgeon, simultaneously in one procedure,[346] or sequentially.[347] The potential advantage of this method is that each technique reaches areas the other cannot reach, thereby ablating more faulty electrical pathways than either procedure alone. A recent European feasibility study followed 26 patients for 1 year after having a simultaneous hybrid procedure (7-day continuous Holter monitoring was carried out at 3, 6, 9 and 12 months).[346] Ten of the patients had persistent AF and one had longstanding persistent AF. Of 24 patients who reached 1-year follow-up, 96% underwent 7-day monitoring and 92% were in sinus rhythm (normal regular rhythm) without anti-arrhythmic drugs. Because two of the patients had undergone an additional catheter ablation for recurrent AF or atrial flutter, the single procedure 1-year success rate was 83%. Although all were discharged on a VKA, only 21% of the patients in sinus rhythm were taking VKA at 1 year.

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

Devices to improve detection of atrial fibrillation

AF can be both paroxysmal and asymptomatic, making diagnosis difficult, with up to one-third of patients with AF having so-called silent undiagnosed AF.[28,29] In one study of patients who had undergone cardioversion of AF, daily monitoring found 70% of recurrent episodes to be asymptomatic.[27] Furthermore, up to 35% of patients who have an ischaemic stroke do not have a defined cause for the event;[348] some of these events could be due to undetected paroxysmal AF.

Continuous monitoring to detect AF has been evaluated in patients with implanted cardiac pacemakers or defibrillators using diagnostic features in these devices. In a recent study, 2580 patients aged 65 years or older with high blood pressure were monitored for 3 months after implantation of a pacemaker or defibrillator.[349] Subclinical atrial tachyarrhythmias were detected by the devices in 10% of the patients. Over a further 2.5 years of follow-up, patients with these arrhythmias were 2.5 times more likely to suffer an ischaemic stroke than patients without subclinical arrhythmia. Furthermore, the stroke rate associated with subclinical arrhythmia may have been underestimated because 18% of the patients with arrhythmias received VKA therapy during follow-up. Sixteen per cent of the patients with a subclinical arrhythmia received a clinical diagnosis of AF during follow-up. Over the full 2.5 years of follow-up, subclinical atrial tachyarrhythmias were detected in 35% of the patients.

Recently, a new method of continuous monitoring for AF has been developed using implantable subcutaneous electrocardiogram (ECG) monitors.[28] These devices are currently used in Europe in patients with recurrent syncope (fainting) of uncertain origin, which is commonly caused by AF.[350] They may be useful for detecting silent paroxysmal AF in cryptogenic stroke patients or other patients at high risk of developing AF, such as elderly patients with high blood pressure or individuals with previous heart disease.[28] The CRYSTAL-AF trial of a subcutaneous ECG monitor used to continuously monitor cryptogenic stroke patients for at least 12 months is currently underway.[351] If these devices can be more widely used to improve AF diagnosis, then more patients with AF can be treated with anticoagulants to help reduce the burden of AF-related stroke.

Prevention of atrial fibrillation-related stroke

Developments in pharmacological prevention of AF-related stroke

There are still non-VKA OACs in development for the prevention of AF-related stroke. The direct Factor Xa inhibitor (see Figure 10, page 50) betrixaban has been studied in phase II trials.[352] As mentioned in Chapter 9, 'Non-vitamin K antagonist oral anticoagulants for prevention of atrial fibrillation-related stroke' (page 57), a phase III study (ENGAGE AF-TIMI 48) is also ongoing to evaluate the safety and efficacy profile of two doses of edoxaban versus warfarin.[221] Results are expected in 2013.[222]

Developments in non-pharmacological prevention of AF-related stroke

Non-pharmacological interventions for prevention of AF-related stroke concentrate on stopping potentially harmful blood clots reaching the brain. In patients with non-valvular AF, more than 90% of blood clots form in the left atrial appendage (LAA; part of the left atrium).[118] Closing or occluding the LAA may, therefore, be an effective way to reduce the risk of blood clots and stroke.

Catheter-based LAA occlusion

Several new devices have been developed that allow the LAA to be blocked off. Such devices are designed to be placed permanently just behind or at the opening of the LAA. Once in place, they should prevent any blood clots of a harmful size from entering the bloodstream and causing a stroke.

The Watchman device, a filter designed to occlude the LAA from inside the heart and trap thrombi inside the appendage, has marketing approval in Europe.[353,354] Intracardiac placement of the Watchman device is catheter based.[354] In the PROTECT AF randomized controlled trial of 707 patients with AF and a $CHADS_2$ score of 1 or more, occlusion of the LAA with the Watchman device was non-inferior to warfarin therapy for the prevention of stroke, cardiovascular death and systemic embolism (primary efficacy endpoint [3.0% vs 4.9% per year; more than 99.9% probability of non-inferiority]). Despite this, there was a higher rate of primary safety events (major bleeding, pericardial effusion and device embolization) in the intervention group compared with the warfarin group.[355] More recent data from continued follow-up of patients enrolled in this trial, and from a non-randomized registry of patients undergoing device implantation, suggest that safety events are primarily procedure-related and decrease both over time and with greater operator experience.[354] Although patients in receipt of the Watchman device routinely receive warfarin for at least 6 weeks until closure of the LAA is confirmed,[355] a recent study suggested the device may be effective in patients with AF who were unable to take warfarin.[356] Instead, these patients received aspirin and clopidogrel for 6 months followed by aspirin alone.[357] A further phase III study of the Watchman device, PREVAIL, was initiated in 2010 and is ongoing.[357,358] The smaller EVOLVE trial of a new-generation Watchman device is also ongoing.[359] Another intracardiac catheter-based device, the Amplatzer Cardiac Plug, is also available for clinical use in Europe.[353] This device has completed a feasibility and safety study in 143 patients with AF at 10 centres in Europe.[360] LAA occlusion was attempted in 137 of 143 patients and was successfully completed in 96% of these patients. Serious complications occurred in 7% of the patients, including two device embolizations. A phase I randomized trial of the Amplatzer Cardiac Plug compared with standard warfarin therapy is now underway.[353,361]

The LARIAT is a suture delivery system that uses an intra- and extracardiac (i.e. both inside and outside the heart) catheter-based approach to snare the LAA and ligate it closed.[353] Only a suture remains in the body after the procedure. The LARIAT system also has marketing approval in Europe.[353] A study of the device evaluated 119 patients with AF, of whom 87% had the correct LAA anatomy requirements for the device.[362] Complete LAA closure was achieved in 95% of the patients who underwent the procedure. A phase IV study of the LARIAT system was initiated in September 2012.[363] This study is in patients with AF at risk of thromboembolic events who are unable to take OAC therapy.

Guidelines from the ESC currently consider the evidence for the efficacy and safety of LAA closure to be insufficient, and percutaneous LAA closure is only recommended in patients with AF at high risk of stroke if long-term anticoagulation is contraindicated.[90]

Surgical LAA closure

The 2012 ESC guidelines suggest surgical excision of the LAA as a consideration for patients undergoing open heart surgery.[90] The AtriClip device is another new LAA closure option approved in Europe for use in patients undergoing cardiac surgery.[353,364] The system is used both in open heart and minimally invasive cardiac procedures. The device clips at the base of the LAA on the outside of the heart.

In the US-based, multicentre, phase II EXCLUDE trial, patients undergoing cardiac surgery with AF or with a $CHADS_2$ score greater than 2 were eligible for concomitant AtriClip placement.[365] Of 70 patients with successful placement of the clip, 96% had successful LAA occlusion after the procedure. Of patients who underwent imaging at 3 months, 98% had successful occlusion. A smaller, ongoing European study of 34 patients has reported early results.[366,367] Operative mortality occurred in 9% of patients, but these deaths were deemed unrelated to the device. After surgery, LAA occlusion was 100% and there were no strokes or transient ischaemic attacks (TIAs) at 3 months. Patients in this study also underwent concomitant surgical maze or ablation procedure. The authors of both studies conclude that further trials are needed to evaluate LAA occlusion for prevention of AF-related stroke.

Next steps

To summarize, several different approaches are in development for use in patients with AF. Further development of non-pharmacological approaches for the management of arrhythmia and surgical interventions to reduce thromboembolic risk continue apace.

Valuable insights into the impact of these new therapies on the prevention of AF-related stroke can be gained from real-life registries. A number of registries of patients with AF exist, most of which are country specific or focused on North America. New global registries of a different magnitude have now been established with a truly international reach. The ongoing GARFIELD registry will prospectively enroll and 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.[66] 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 non-VKA OACs, can contribute to the prevention of AF-related stroke.[66] As mentioned in Chapter 11, details of patient characteristics and the level of OAC use are now available from an initial cohort of approximately 10 000 patients enrolled in this registry.[65,286]

The Global Registry on Long-Term Oral Anti-thrombotic Treatment In Patients With Atrial Fibrillation (GLORIA-AF) was recently initiated with a planned enrolment of up to 56 000 patients with newly diagnosed AF across 2200 sites in 50 countries.[258] GLORIA-AF will compare the efficacy and safety of long-term treatment with different therapies for prevention of AF-related stroke, including VKAs, non-VKA OACs and aspirin. Another large registry has also been initiated in the US, which will enrol approximately 10 000 patients with AF. This Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) will also assess the impact of available antithrombotic therapies for prevention of AF-related stroke.[259]

The advent of the non-VKA OACs heralds a new era in prophylaxis of AF-related stroke. Over the coming months we can expect to see 'real-world' data on the routine use of these drugs as registries begin to report results. In addition, other pharmacological agents and devices are in development. As these become available, the options for providing patients with reliable, efficacious and safe methods of prophylaxis will continue to expand. It is hoped that the availability of new therapy options, together with a greater understanding of their impact on the burden of AF and AF-related stroke, will pave the way for better management of patients with AF and provide these patients with improved outcomes.

References

1. World Health Organization. Disease and injury regional estimates. Prevalence for WHO regions. Cause-specific mortality: regional estimates for 2008. 2008. http://www.who.int/gho/mortality_burden_disease/global_burden_disease_DTH6_2008.xls. Accessed October 2012
2. Truelsen T, Piechowski-Józwiak B, Bonita R *et al*. Stroke incidence and prevalence in Europe: a review of available data. *Eur J Neurol* 2006;13:581–98
3. Gustavsson A, Svensson M, Jacobi F *et al*. Cost of disorders of the brain in Europe 2010. *Eur Neuropsychopharmacol* 2011;21:718–79
4. Wolfe C, Rudd A. The Burden of Stroke White Paper: raising awareness of the global toll of stroke-related disability and death. 2007. http://www.safestroke.org/Portals/10/FINAL Burden of Stroke.pdf. Accessed October 2012
5. White CL, Poissant L, Coté-LeBlanc G *et al*. Long-term caregiving after stroke: the impact on caregivers' quality of life. *J Neurosci Nurs* 2006;38:354–60
6. Allender S, Scarborough P, Peto V *et al*. European Cardiovascular Disease Statistics: 2008 edition. Brussels: European Heart Network; 2008. http://www.ehnheart.org/component/downloads/downloads/683.html. Accessed October 2012
7. Stefansdottir H, Aspelund T, Gudnason V *et al*. Trends in the incidence and prevalence of atrial fibrillation in Iceland and future projections. *Europace* 2011;13:1110–17
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;36:1115–9
10. Fuster V, Ryden LE, Cannom DS *et al*. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2011;123:e269–367
11. 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
12. 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
13. European Heart Health Charter. 2012. http://www.heartcharter.org/read-charter/default.aspx. Accessed October 2012
14. Health-EU. 2012. http://ec.europa.eu/health-eu/health_problems/cardiovascular_diseases/index_en.htm. Accessed October 2012
15. World Health Organization. A comprehensive global monitoring framework, including indicators, and a set of voluntary global targets for the prevention and control of noncommunicable diseases. 2012. http://www.who.int/nmh/events/2012/discussion_paper3.pdf. Accessed October 2012
16. Lip GYH, Lim HS. Atrial fibrillation and stroke prevention. *Lancet Neurol* 2007;6:981–93
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. 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
19. 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
20. Hirsh J, Dalen J, Anderson DR *et al*. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. *Chest* 2001;119:8S–21S
21. Turpie AGG. Warfarin replacements: mechanisms underlying emerging agents. *Can J Cardiol* 2008;24 Suppl C:56C–60C
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. Palikhe NS, Kim SH, Park HS. What do we know about the genetics of aspirin intolerance? *J Clin Pharm Ther* 2008;33:465–72
24. Patel D, Moonis M. Clinical implications of aspirin resistance. *Expert Rev Cardiovasc Ther* 2007;5:969–75
25. US Preventive Services Task Force. Aspirin for the primary prevention of cardiovascular events: recommendation and rationale. *Ann Intern Med* 2002;136:157–60
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. Fetsch T, Bauer P, Engberding R *et al*. Prevention of atrial fibrillation after cardioversion: results of the PAFAC trial. *Eur Heart J* 2004;25:1385–94
28. Camm AJ, Corbucci G, Padeletti L. Usefulness of continuous electrocardiographic monitoring for atrial fibrillation. *Am J Cardiol* 2012;112:270–76
29. Collerton J, Davies K, Jagger C *et al*. Health and disease in 85 year olds: baseline findings from the Newcastle 85+ cohort study. *BMJ* 2009;339:b4904
30. 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

31. 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
32. 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
33. Council of the European Union. Conclusions on Innovation Union for Europe. 2010. http://www.consilium.europa.eu/uedocs/cms_data/docs/pressdata/en/intm/118028.pdf. Accessed October 2012
34. European Commission. About the European Innovation Partnership on active and healthy ageing. 2012. http://ec.europa.eu/research/innovation-union/index_en.cfm?section=active-healthy-ageing&pg=about. Accessed October 2012
35. European Parliament. EU position and commitment in advance of the UN high-level meeting on the prevention and control of non-communicable diseases. 2011. http://www.europarl.europa.eu/sides/getDoc.do?type=TA&reference=P7-TA-2011-0390&language=EN. Accessed October 2012
36. 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
37. 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
38. 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
39. Arrhythmia Alliance. 'Know Your Pulse' global campaign. 2010. http://www.atrialfibrillation-us.org/news-events/know-your-pulse. Accessed October 2012
40. 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;30:2969–80
41. Bungard TJ, Ghali WA, McAlister FA *et al*. Physicians' perceptions of the benefits and risks of warfarin for patients with nonvalvular atrial fibrillation. *Can Med Assoc J* 2001;165:301–2
42. 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
43. 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
44. Camm J. Antiarrhythmic drugs for the maintenance of sinus rhythm: risks and benefits. *Int J Cardiol* 2012;155:362–71
45. Barrios V, Calderon A, Escobar C *et al*. Patients with atrial fibrillation in a primary care setting: Val-FAAP study. *Rev Esp Cardiol* 2012;65:47–53
46. Mazzaglia G, Filippi A, Alacqua M *et al*. A national survey of the management of atrial fibrillation with antithrombotic drugs in Italian primary care. *Thromb Haemost* 2010;103:968–75
47. Wilke T, Groth A, Mueller S *et al*. Oral anticoagulation use by patients with atrial fibrillation in Germany. Adherence to guidelines, causes of anticoagulation under-use and its clinical outcomes, based on claims-data of 183,448 patients. *Thromb Haemost* 2012;107:1053–65
48. Nieuwlaat R, Olsson SB, Lip GYH *et al*. Guideline-adherent antithrombotic treatment is associated with improved outcomes compared with undertreatment in high-risk patients with atrial fibrillation. The Euro Heart Survey on Atrial Fibrillation. *Am Heart J* 2007;153:1006–12
49. Camm AJ, Kirchhof P, Lip GYH *et al*. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 2010;31:2369–429
50. 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. 2008. http://ec.europa.eu/health/ph_systems/docs/patient_com2008_en.pdf. Accessed October 2012
51. Commission of the European Communities. Proposal for a council recommendation on patient safety, including the prevention and control of healthcare associated infections. 2009. http://ec.europa.eu/health/ph_systems/docs/patient_rec2008_en.pdf. Accessed October 2012
52. Council to the European Union. Council recommendation of 9 June 2009 on patient safety, including the prevention and control of healthcare associated infections. 2009. http://ec.europa.eu/health/patient_safety/docs/council_2009_en.pdf. Accessed October 2012
53. European Society of Cardiology. National Guidelines Coordinators. 2012. http://www.escardio.org/guidelines-surveys/esc-guidelines/endorsements/Pages/National-Guidelines-Coordinators.aspx. Accessed October 2012
54. European Commission. Communication from the Commission to the European Parliament and the Council: taking forward the strategic implementation plan of the European Innovation Partnership on active and healthy ageing. 2012. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2012:0083:FIN:EN:PDF. Accessed October 2012
55. EUTRAF. The European Network for Translational Research in Atrial Fibrillation. 2012. http://www.eutraf.eu. Accessed October 2012
56. European Commission. Horizon 2020: the EU Framework Programme for Research and Innovation. 2012. http://ec.europa.eu/research/horizon2020/index_en.cfm?pg=h2020. Accessed October 2012

57. CORDIS. European Stroke Research Network. 2012. http://cordis.europa.eu/search/index.cfm?fuseaction=proj.document&PJ_RCN=10082605. Accessed October 2012
58. European Commission. EUSTROKE: European Stroke Research Network. 2012. http://ec.europa.eu/research/health/medical-research/cardiovascular-diseases/projects/eustroke_en.html. Accessed October 2012
59. 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
60. Falk RH. Atrial fibrillation. *N Engl J Med* 2001;344:1067–78
61. Fuster V, Rydén 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
62. Benjamin EJ, Levy D, Vaziri SM *et al*. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA* 1994;271:840–4
63. Benjamin EJ, Chen PS, Bild DE *et al*. Prevention of atrial fibrillation: report from a National Heart, Lung, and Blood Institute workshop. *Circulation* 2009;119:606–18
64. Huxley RR, Lopez FL, Folsom AR *et al*. Absolute and attributable risks of atrial fibrillation in relation to optimal and borderline risk factors: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation* 2011;123:1501–8
65. Kakkar AK, on behalf of the GARFIELD Registry Investigators. GARFIELD: multicentre international registry of patients newly diagnosed with atrial fibrillation at risk of stroke: the GARFIELD Registry. 2011. http://www.escardio.org/congresses/esc-2011/congress-reports/Pages/711-5-GARFIELD.aspx. Accessed October 2012
66. Kakkar AK, Mueller I, Bassand JP *et al*. International longitudinal registry of patients with atrial fibrillation at risk of stroke: Global Anticoagulant Registry in the FIELD (GARFIELD). *Am Heart J* 2012;163:13–9
67. Nieuwlaat R, Capucci A, Camm AJ *et al*. Atrial fibrillation management: a prospective survey in ESC member countries: the Euro Heart Survey on Atrial Fibrillation. *Eur Heart J* 2005;26:2422–34
68. Friberg L, Rosenqvist M, Lip GYH. Net clinical benefit of warfarin in patients with atrial fibrillation: a report from the Swedish atrial fibrillation cohort study. *Circulation* 2012;125:2298–307
69. Olesen JB, Lip GYH, Hansen ML *et al*. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. *BMJ* 2011;342:d124
70. van Staa TP, Setakis E, Di Tanna GL *et al*. A comparison of risk stratification schemes for stroke in 79,884 atrial fibrillation patients in general practice. *J Thromb Haemost* 2011;9:39–48
71. Gudbjartsson DF, Arnar DO, Helgadottir A *et al*. Variants conferring risk of atrial fibrillation on chromosome 4q25. *Nature* 2007;448:353–7
72. Schmutz M, Beer-Borst S, Meiltz A *et al*. Low prevalence of atrial fibrillation in asymptomatic adults in Geneva, Switzerland. *Europace* 2010;12:475–81
73. Heeringa J, van der Kuip DAM, Hofman A *et al*. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart J* 2006;27:949–53
74. Langenberg M, Hellemons BS, van Ree JW *et al*. Atrial fibrillation in elderly patients: prevalence and comorbidity in general practice. *BMJ* 1996;313:1534
75. Majeed A, Moser K, Carroll K. Trends in the prevalence and management of atrial fibrillation in general practice in England and Wales, 1994–1998: analysis of data from the general practice research database. *Heart* 2001;86:284–8
76. Bonhorst D, Mendes M, Adragao P *et al*. Prevalence of atrial fibrillation in the Portuguese population aged 40 and over: the FAMA study. *Rev Port Cardiol* 2010;29:331–50
77. Charlemagne A, Blacher J, Cohen A *et al*. Epidemiology of atrial fibrillation in France: extrapolation of international epidemiological data to France and analysis of French hospitalization data. *Arch Cardiovasc Dis* 2011;104:115–24
78. Lip GYH, Brechin CM, Lane DA. The global burden of atrial fibrillation and stroke: a systematic review of the epidemiology of atrial fibrillation in regions outside North America and Europe. *Chest* 2012; doi: 10.1378/chest.11-2888
79. Dewilde S, Carey IM, Emmas C *et al*. Trends in the prevalence of diagnosed atrial fibrillation, its treatment with anticoagulation and predictors of such treatment in UK primary care. *Heart* 2006;92:1064–70
80. 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
81. 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
82. 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
83. Seshadri S, Wolf PA. Lifetime risk of stroke and dementia: current concepts, and estimates from the Framingham Study. *Lancet Neurol* 2007;6:1106–14
84. Feuer EJ, Wun LM, Boring CC *et al*. The lifetime risk of developing breast cancer. *J Natl Cancer Inst* 1993;85:892–7

85. National Institute for Health and Clinical Excellence. Understanding NICE guidance: atrial fibrillation. 2006. http://www.nice.org.uk/nicemedia/pdf/CG036publicinfo.pdf. Accessed October 2012
86. Royal College of Physicians. Atrial fibrillation. National clinical guideline for management in primary and secondary care. The National Collaborating Centre for Chronic Conditions. 2006. http://www.nice.org.uk/nicemedia/pdf/CG036fullguideline.pdf. Accessed October 2012
87. Aliot E, Breithardt G, Brugada J *et al*. An international survey of physician and patient understanding, perception, and attitudes to atrial fibrillation and its contribution to cardiovascular disease morbidity and mortality. *Europace* 2010;12:626–33
88. National Institute for Health and Clinical Excellence. Atrial fibrillation: the management of atrial fibrillation. NICE Clinical Guideline 36. London: NICE; 2006. http://www.nice.org.uk/nicemedia/pdf/CG036niceguideline.pdf. Accessed October 2012
89. Fitzmaurice DA, Hobbs FDR, Jowett S *et al*. Screening versus routine practice in detection of atrial fibrillation in patients aged 65 or over: cluster randomised controlled trial. *BMJ* 2007;335:383
90. Camm AJ, Lip GYH, De Caterina R *et al*. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J* 2012;14:1385–413
91. Rizos T, Wagner A, Jenetzky E *et al*. Paroxysmal atrial fibrillation is more prevalent than persistent atrial fibrillation in acute stroke and transient ischemic attack patients. *Cerebrovasc Dis* 2011;32:276–82
92. 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
93. Friberg L, Hammar N, Rosenqvist M. Stroke in paroxysmal atrial fibrillation: report from the Stockholm Cohort of Atrial Fibrillation. *Eur Heart J* 2010;31:967–75
94. You JJ, Singer DE, Howard PA *et al*. Antithrombotic therapy for atrial fibrillation: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012;141:531S–75S
95. 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
96. 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. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. *Stroke* 2009;40:2276–93
97. 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
98. Bevan H, Sharma K, Bradley W. Stroke in young adults. *Stroke* 1990;21:382–6
99. Buchow H, Cayotte E, Agafitei L. Circulatory diseases - Main causes of death for persons aged 65 and more in Europe, 2009. 2012. http://epp.eurostat.ec.europa.eu/cache/ITY_OFFPUB/KS-SF-12-007/EN/KS-SF-12-007-EN.PDF. Accessed October 2012
100. 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
101. Mayo NE, Wood-Dauphinee S, Ahmed S *et al*. Disablement following stroke. *Disabil Rehabil* 1999;21:258–68
102. The European Stroke Organisation (ESO) Executive Committee, ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis* 2008;25:457–507
103. Kjellström T, Norrving B, Shatchkute A. Helsingborg Declaration 2006 on European stroke strategies. *Cerebrovasc Dis* 2007;23:231–41
104. World Health Organization. The atlas of heart disease and stroke. 2004. http://www.who.int/cardiovascular_diseases/resources/atlas/en. Accessed October 2012
105. O'Donnell MJ, Xavier D, Liu L *et al*. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet* 2010;376:112–23
106. Hart RG, Pearce LA. Current status of stroke risk stratification in patients with atrial fibrillation. *Stroke* 2009;40:2607–10
107. Andersen KK, Olsen TS, Dehlendorff C *et al*. Hemorrhagic and ischemic strokes compared: stroke severity, mortality, and risk factors. *Stroke* 2009;40:2068–72
108. 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
109. Stroke Risk in Atrial Fibrillation Working Group. Independent predictors of stroke in patients with atrial fibrillation: a systematic review. *Neurology* 2007;69:546–54
110. Asplund K, Markè L-Å, Terént A *et al*. Costs and gains in stroke prevention: European perspective. *Cerebrovasc Dis* 1993;3 Suppl 1:34–42
111. Lightowlers S, McGuire A. Cost-effectiveness of anticoagulation in nonrheumatic atrial fibrillation in the primary prevention of ischemic stroke. *Stroke* 1998;29:1827–32
112. Jørgensen HS, Nakayama H, Reith J *et al*. Acute stroke with atrial fibrillation. The Copenhagen Stroke Study. *Stroke* 1996;27:1765–9
113. Arboix A, Alio J. Cardioembolic stroke: clinical features, specific cardiac disorders and prognosis. *Curr Cardiol Rev* 2010;6:150–61

114. Winter Y, Wolfram C, Schaeg M *et al*. Evaluation of costs and outcome in cardioembolic stroke or TIA. *J Neurol* 2009;256:954–63
115. Ferro JM. Cardioembolic stroke: an update. *Lancet Neurol* 2003;2:177–88
116. Schneck M, Lei X. Cardioembolic stroke. eMedicine Neurology 2008. 2008. http://emedicine.medscape.com/article/1160370-overview. Accessed October 2012
117. 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
118. Iqbal MB, Taneja AK, Lip GYH *et al*. Recent developments in atrial fibrillation. *BMJ* 2005;330:238–43
119. Kwok CS, Loke YK, Hale R *et al*. Atrial fibrillation and incidence of dementia: a systematic review and meta-analysis. *Neurology* 2011;76:914–22
120. Lip GYH, Nieuwlaat R, Pisters R *et al*. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor based approach: the Euro Heart Survey on Atrial Fibrillation. *Chest* 2010;137:263–72
121. Hughes M, Lip GYH. 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
122. Friberg L, Benson L, Rosenqvist M *et al*. Assessment of female sex as a risk factor in atrial fibrillation in Sweden: nationwide retrospective cohort study. *BMJ* 2012;344:e3522
123. Lin LY, Lee CH, Yu CC *et al*. Risk factors and incidence of ischemic stroke in Taiwanese with nonvalvular atrial fibrillation – a nation wide database analysis. *Atherosclerosis* 2011;217:292–5
124. Olesen JB, Lip GYH, Lane DA *et al*. Vascular disease and stroke risk in atrial fibrillation: a nationwide cohort study. *Am J Med* 2012;125:e13–23
125. Olesen JB, Fauchier L, Lane DA *et al*. Risk factors for stroke and thromboembolism in relation to age among patients with atrial fibrillation: the Loire Valley Atrial Fibrillation Project. *Chest* 2012;141:147–53
126. Rietbrock S, Heeley E, Plumb J *et al*. Chronic atrial fibrillation: incidence, prevalence, and prediction of stroke using the Congestive heart failure, Hypertension, Age >75, Diabetes mellitus, and prior Stroke or transient ischemic attack ($CHADS_2$) risk stratification scheme. *Am Heart J* 2008;156:57–64
127. Wang TJ, Massaro JM, Levy D *et al*. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. *JAMA* 2003;290:1049–56
128. Hobbs FD, Roalfe AK, Lip GY *et al*. Performance of stroke risk scores in older people with atrial fibrillation not taking warfarin: comparative cohort study from BAFTA trial. *BMJ* 2011;342:d3653
129. Gage BF, van Walraven C, Pearce L *et al*. Selecting patients with atrial fibrillation for anticoagulation: stroke risk stratification in patients taking aspirin. *Circulation* 2004;110:2287–92
130. Hohnloser SH, Connolly SJ. Atrial fibrillation, moderate chronic kidney disease, and stroke prevention: new anticoagulants, new hope. *Eur Heart J* 2011;32:2347–9
131. Olesen JB, Lip GYH, Kamper AL *et al*. Stroke and bleeding in atrial fibrillation with chronic kidney disease. *N Engl J Med* 2012;367:625–35
132. Marinigh R, Lane DA, Lip GYH. Severe renal impairment and stroke prevention in atrial fibrillation: implications for thromboprophylaxis and bleeding risk. *J Am Coll Cardiol* 2011;57:1339–48
133. Olesen JB, Torp-Pedersen C, Hansen ML *et al*. The value of the CHA_2DS_2-VASc score for refining stroke risk stratification in patients with atrial fibrillation with a $CHADS_2$ score 0–1: a nationwide cohort study. *Thromb Haemost* 2012;107:1172–9
134. Potpara TS, Polovina MM, Licina MM *et al*. Reliable identification of "truly low" thromboembolic risk in patients initially diagnosed with "lone" atrial fibrillation: the Belgrade Atrial Fibrillation Study. *Circ Arrhythm Electrophysiol* 2012;5:319–26
135. Pisters R, Lane DA, Nieuwlaat R *et al*. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010;138:1093–100
136. Gage BF, Yan Y, Milligan PE *et al*. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). *Am Heart J* 2006;151:713–9
137. Fang MC, Go AS, Chang Y *et al*. A new risk scheme to predict warfarin-associated hemorrhage: the ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study. *J Am Coll Cardiol* 2011;58:395–401
138. Lip GYH, Frison L, Halperin JL *et al*. Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: the HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) score. *J Am Coll Cardiol* 2011;57:173–80
139. Gallego P, Roldán V, Torregrosa JM *et al*. Relation of the HAS-BLED bleeding risk score to major bleeding, cardiovascular events and mortality in anticoagulated patients with atrial fibrillation. *Circ Arrhythm Electrophysiol* 2012;5:312–8
140. Apostolakis S, Lane DA, Guo Y *et al*. Performance of the HEMORR(2)HAGES, ATRIA, and HAS-BLED bleeding risk-prediction scores in patients with atrial fibrillation undergoing anticoagulation: the AMADEUS (Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation) Study. *J Am Coll Cardiol* 2012;60:861–7
141. Roldán V, Marín F, Fernández H *et al*. Predictive value of the HAS-BLED and ATRIA bleeding scores for the risk of serious bleeding in a 'real world' anticoagulated atrial fibrillation population. *Chest* 2012; doi:10.1378/chest.12-0608
142. Olesen JB, Lip GYH, Lindhardsen J *et al*. Risks of thromboembolism and bleeding with thromboprophylaxis in patients with atrial fibrillation: a net clinical benefit analysis using a 'real world' nationwide cohort study. *Thromb Haemost* 2011;106:739–49

143. AF Association. Living with AF. 2012. http://www.atrialfibrillation.org.uk/case-studies/living-with-af.html. Accessed October 2012
144. Thrall G, Lip GYH, Carroll D *et al*. Depression, anxiety, and quality of life in patients with atrial fibrillation. *Chest* 2007;132:1259–64
145. 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
146. 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
147. van Swieten JC, Koudstaal PJ, Visser MC *et al*. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988;19:604–7
148. Dulli DA, Stanko H, Levine RL. Atrial fibrillation is associated with severe acute ischemic stroke. *Neuroepidemiology* 2003;22:118–23
149. 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
150. 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
151. Evers SM, Struijs JN, Ament AJ *et al*. International comparison of stroke cost studies. *Stroke* 2004;35:1209–15
152. Spieler JF, Lanoe JL, Amarenco P. Socioeconomic aspects of postacute care for patients with brain infarction in France. *Cerebrovasc Dis* 2002;13:132–41
153. 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
154. 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
155. Camm AJ, Savelieva I. Atrial fibrillation: the rate versus rhythm management controversy. *J R Coll Physicians Edinb* 2012;42 Suppl 18:23–34
156. Roy D, Talajic M, Nattel S *et al*. Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med* 2008;358:2667–77
157. Van Gelder IC, Hagens VE, Bosker HA *et al*. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med* 2002;347:1834–40
158. Wyse DG, Waldo AL, DiMarco JP *et al*. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002;347:1825–33
159. Hohnloser SH. Benefit-risk assessment of current antiarrhythmic drug therapy of atrial fibrillation. *Clin Cardiol* 2012;35 Suppl 1:28–32
160. 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
161. 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
162. Kober L, Torp-Pedersen C, McMurray JJ *et al*. Increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med* 2008;358:2678–87
163. Connolly SJ, Camm AJ, Halperin JL *et al*. Dronedarone in high-risk permanent atrial fibrillation. *N Engl J Med* 2011;365:2268–76
164. Freemantle N, Lafuente-Lafuente C, Mitchell S *et al*. Mixed treatment comparison of dronedarone, amiodarone, sotalol, flecainide, and propafenone, for the management of atrial fibrillation. *Europace* 2011;13:329–45
165. Stopafib.org. Using electrical cardioversion for atrial fibrillation. 2012. http://www.stopafib.org/electrical.cfm. Accessed October 2012
166. StopAfib.org. Can atrial fibrillation be cured? 2012. http://www.stopafib.org/cured.cfm. Accessed October 2012
167. Medi C, Sparks PB, Morton JB *et al*. Pulmonary vein antral isolation for paroxysmal atrial fibrillation: results from long-term follow-up. *J Cardiovasc Electrophysiol* 2011;22:137–41
168. Scherr D, Sharma K, Dalal D *et al*. Incidence and predictors of periprocedural cerebrovascular accident in patients undergoing catheter ablation of atrial fibrillation. *J Cardiovasc Electrophysiol* 2009;20:1357–63
169. Boersma LV, Castella M, van Boven W *et al*. Atrial fibrillation catheter ablation versus surgical ablation treatment (FAST): a 2-center randomized clinical trial. *Circulation* 2012;125:23–30
170. Mackman N. Triggers, targets and treatments for thrombosis. *Nature* 2008;451:914–18
171. Perzborn E, Roehrig S, Straub A *et al*. The discovery and development of rivaroxaban, an oral, direct Factor Xa inhibitor. *Nat Rev Drug Discov* 2011;10:61–75
172. 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
173. Ansell J, Hirsh J, Hylek E *et al*. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008;133:160S–98S
174. 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
175. Amouyel P, Mismetti P, Langkilde LK *et al*. INR variability in atrial fibrillation: a risk model for cerebrovascular events. *Eur J Intern Med* 2009;20:63–9

176. 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
177. Petersen P, Boysen G. Prevention of stroke in atrial fibrillation. *N Engl J Med* 1990;323:482
178. 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
179. Connolly SJ, Laupacis A, Gent M *et al*. Canadian Atrial Fibrillation Anticoagulation (CAFA) Study. *J Am Coll Cardiol* 1991;18:349–55
180. EAFT (European Atrial Fibrillation Trial) Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. *Lancet* 1993;342:1255–62
181. 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
182. 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
183. Stroke Prevention in Atrial Fibrillation Investigators. Stroke Prevention in Atrial Fibrillation Study. Final results. *Circulation* 1991;84:527–39
184. 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
185. 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
186. Patrono C, Baigent C, Hirsh J *et al*. Antiplatelet drugs: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008;133:199S–233S
187. Catella-Lawson F. Vascular biology of thrombosis: platelet-vessel wall interactions and aspirin effects. *Neurology* 2001;57:S5–7
188. Mant J, Hobbs FDR, 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
189. van Walraven C, Hart RG, Singer DE *et al*. Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation: an individual patient meta-analysis. *JAMA* 2002;288:2441–48
190. Gullov AL, Koefoed BG, Petersen P *et al*. Fixed minidose warfarin and aspirin alone and in combination vs adjusted-dose warfarin for stroke prevention in atrial fibrillation: second Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation Study. *Arch Intern Med* 1998;158:1513–21
191. Hellemons BS, Langenberg M, Lodder J *et al*. Primary prevention of arterial thromboembolism in non-rheumatic atrial fibrillation in primary care: randomised controlled trial comparing two intensities of coumarin with aspirin. *BMJ* 1999;319:958–64
192. Hu DY, Zhang HP, Sun YH *et al*. [The randomized study of efficiency and safety of antithrombotic therapy in nonvalvular atrial fibrillation: warfarin compared with aspirin]. *Zhonghua Xin Xue Guan Bing Za Zhi* 2006;34:295–8
193. Rash A, Downes T, Portner R *et al*. A randomised controlled trial of warfarin versus aspirin for stroke prevention in octogenarians with atrial fibrillation (WASPO). *Age Ageing* 2007;36:151–6
194. Stroke Prevention in Atrial Fibrillation Investigators. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II Study. *Lancet* 1994;343:687–91
195. Vemmos KN, Tsivgoulis G, Spengos K *et al*. Primary prevention of arterial thromboembolism in the oldest old with atrial fibrillation—a randomized pilot trial comparing adjusted-dose and fixed low-dose coumadin with aspirin. *Eur J Intern Med* 2006;17:48–52
196. US Preventive Services Task Force. Aspirin for the prevention of cardiovascular disease: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2009;150:396–404
197. 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
198. 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
199. The ACTIVE Investigators. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med* 2009;360:2066–78
200. ACTIVE Writing Group of the ACTIVE Investigators. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet* 2006;367:1903–12
201. Hylek EM. Contra: 'Warfarin should be the drug of choice for thromboprophylaxis in elderly patients with atrial fibrillation'. Caveats regarding use of oral anticoagulant therapy among elderly patients with atrial fibrillation. *Thromb Haemost* 2008;100:16–7
202. 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
203. 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

204. 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
205. 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
206. 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
207. 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
208. Szucs TD, Bramkamp M. Pharmacoeconomics of anticoagulation therapy for stroke prevention in atrial fibrillation: a review. *J Thromb Haemost* 2006;4:1180–5
209. 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
210. Appleby J, Devlin N, Parkin D. NICE's cost effectiveness threshold. *BMJ* 2007;335:358–9
211. 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
212. Lip GYH, Frison L, Grind M *et al*. Effect of hypertension on anticoagulated patients with atrial fibrillation. *Eur Heart J* 2007;28:752–9
213. 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
214. Turpie AGG. New oral anticoagulants in atrial fibrillation. *Eur Heart J* 2008;29:155–65
215. Moia M, Mantovani LG, Carpenedo M *et al*. Patient preferences and willingness to pay for different options of anticoagulant therapy. *Intern Emerg Med* 2012; doi: 10.1007/s11739-012-0844-3
216. Turpie AGG. Oral, direct Factor Xa inhibitors in development for the prevention and treatment of thromboembolic diseases. *Arterioscler Thromb Vasc Biol* 2007;27:1238–47
217. Patel MR, Mahaffey KW, Garg J *et al*. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365:883–91
218. Granger CB, Alexander JH, McMurray JJ *et al*. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365:981–92
219. Connolly SJ, Eikelboom J, Joyner C *et al*. Apixaban in patients with atrial fibrillation. *N Engl J Med* 2011;364:806–17
220. Weitz JI, Connolly SJ, Patel I *et al*. Randomised, parallel-group, multicentre, multinational phase 2 study comparing edoxaban, an oral factor Xa inhibitor, with warfarin for stroke prevention in patients with atrial fibrillation. *Thromb Haemost* 2010;104:633–41
221. Ruff CT, Giugliano RP, Antman EM *et al*. Evaluation of the novel factor Xa inhibitor edoxaban compared with warfarin in patients with atrial fibrillation: design and rationale for the Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation-Thrombolysis In Myocardial Infarction study 48 (ENGAGE AF-TIMI 48). *Am Heart J* 2010;160:635–41
222. Daiichi Sankyo Inc. Global study to assess the safety and effectiveness of DU-176b vs standard practice of dosing with warfarin in patients with atrial fibrillation (EngageAFTIMI48). 2012. http://www.clinicaltrials.gov/ct2/show/NCT00781391. Accessed October 2012
223. Connolly SJ, Ezekowitz MD, Yusuf S *et al*. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139–51
224. Connolly SJ, Ezekowitz MD, Yusuf S *et al*. Newly identified events in the RE-LY trial. *N Engl J Med* 2010;363:1875–6
225. Uchino K, Hernandez AV. Dabigatran association with higher risk of acute coronary events: meta-analysis of noninferiority randomized controlled trials. *Arch Intern Med* 2012;172:397–402
226. Hankey GJ, Stevens S, Piccini JP *et al*. Predictors of intracranial hemorrhage among anticoagulated patients with atrial fibrillation: insights from the rivaroxaban once-daily oral direct Factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation (ROCKET AF). *Stroke* 2012;43:A152
227. Nutescu EA, Shapiro NL, Ibrahim S *et al*. Warfarin and its interactions with foods, herbs and other dietary supplements. *Expert Opin Drug Saf* 2006;5:433–51
228. Baker RI, Coughlin PB, Gallus AS *et al*. Warfarin reversal: consensus guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis. *Med J Aust* 2004;181:492–7
229. Blech S, Ebner T, Ludwig-Schwellinger E *et al*. The metabolism and disposition of the oral direct thrombin inhibitor, dabigatran, in humans. *Drug Metab Dispos* 2008;36:386–99
230. Bristol-Myers Squibb, Pfizer EEIG. Eliquis (apixaban) Summary of Product Characteristics. 2011. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002148/WC500107728.pdf. Accessed October 2012
231. Wong PC, Pinto DJ, Zhang D. Preclinical discovery of apixaban, a direct and orally bioavailable factor Xa inhibitor. *J Thromb Thrombolysis* 2011;31:478–92
232. Raghavan N, Frost CE, Yu Z *et al*. Apixaban metabolism and pharmacokinetics after oral administration to humans. *Drug Metab Dispos* 2009;37:74–81
233. Fox KAA, Piccini JP, Wojdyla D *et al*. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. *Eur Heart J* 2011;32:2387–94

234. Hohnloser SH, Hijazi Z, Thomas L *et al*. Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial. *Eur Heart J* 2012; doi: 10.1093/eurheartj/ehs274
235. Eikelboom JW, Wallentin L, Connolly SJ *et al*. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. *Circulation* 2011;123:2363–72
236. Legrand M, Mateo J, Aribaud A *et al*. The use of dabigatran in elderly patients. *Arch Intern Med* 2011;171:1285–6
237. Go AS, Fang MC, Udaltsova N *et al*. Impact of proteinuria and glomerular filtration rate on risk of thromboembolism in atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. *Circulation* 2009;119:1363–9
238. Eikelboom JW, Connolly SJ, Gao P *et al*. Stroke risk and efficacy of apixaban in atrial fibrillation patients with moderate chronic kidney disease. *J Stroke Cerebrovasc Dis* 2012;21:429–35
239. Boehringer Ingelheim International GmbH. Pradaxa (dabigatran etexilate) Summary of Product Characteristics. 2012. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/05/WC500127777.pdf. Accessed October 2012
240. Jorgensen HS, Nakayama H, Reith J *et al*. Stroke recurrence: predictors, severity, and prognosis. The Copenhagen Stroke Study. *Neurology* 1997;48:891–5
241. Hankey GJ, Patel MR, Stevens SR *et al*. Rivaroxaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of ROCKET AF. *Lancet Neurol* 2012;11:315–22
242. Easton JD, Lopes RD, Bahit MC *et al*. Apixaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of the ARISTOTLE trial. *Lancet Neurol* 2012;11:503–11
243. Diener HC, Connolly SJ, Ezekowitz MD *et al*. Dabigatran compared with warfarin in patients with atrial fibrillation and previous transient ischaemic attack or stroke: a subgroup analysis of the RE-LY trial. *Lancet Neurol* 2010;9:1157–63
244. Ogilvie IM, Newton N, Welner SA *et al*. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. *Am J Med* 2010;123:638–45
245. Deplanque D, Leys D, Parnetti L *et al*. Secondary prevention of stroke in patients with atrial fibrillation: factors influencing the prescription of oral anticoagulation at discharge. *Cerebrovasc Dis* 2006;21:372–9
246. Oldgren J, Alings M, Darius H *et al*. Risks for stroke, bleeding, and death in patients with atrial fibrillation receiving dabigatran or warfarin in relation to the $CHADS_2$ score: a subgroup analysis of the RE-LY trial. *Ann Intern Med* 2011;155:660–7
247. Halperin JL, Wojdyla D, Piccini JP *et al*. Efficacy and safety of rivaroxaban compared with warfarin among elderly patients with nonvalvular atrial fibrillation in the ROCKET-AF trial. *Stroke* 2012;43:A148
248. Connolly S, Pogue J, Hart R *et al*. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet* 2006;367:1903–12
249. Hylek EM, Frison L, Henault LE *et al*. Disparate stroke rates on warfarin among contemporaneous cohorts with atrial fibrillation: potential insights into risk from a comparative analysis of SPORTIF III versus SPORTIF V. *Stroke* 2008;39:3009–14
250. Ezekowitz MD, Wallentin L, Connolly SJ *et al*. Dabigatran and warfarin in vitamin K antagonist-naive and -experienced cohorts with atrial fibrillation. *Circulation* 2010;122:2246–53
251. Mahaffey KW, Wojdyla D, Hankey GJ *et al*. Outcomes in vitamin K antagonist-naïve and -experienced patients: results from ROCKET AF. *Eurostroke*. Lisbon, Portugal, 22 May–25 May 2012; Abstract OAID65
252. Bayer Pharma AG. Xarelto (rivaroxaban) Summary of Product Characteristics. 2012. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000944/WC500057108.pdf. Accessed October 2012
253. Canadian Agency for Drugs and Technologies in Health. Therapeutic review: safety, effectiveness, and cost-effectiveness of new oral anticoagulants compared with warfarin in preventing stroke and other cardiovascular events in patients with atrial fibrillation. 2012. http://www.cadth.ca/media/pdf/NOAC_Therapeutic_Review_final_report.pdf. Accessed October 2012
254. Lip GYH, Larsen TB, Skjøth F *et al*. Indirect comparisons of new oral anticoagulant drugs for efficacy and safety when used for stroke prevention in atrial fibrillation. *J Am Coll Cardiol* 2012;60:738–46
255. National Institute for Health and Clinical Excellence. Rivaroxaban for the prevention of stroke and systemic embolism in atrial fibrillation; Technology appraisal TA256. 2012. http://www.nice.org.uk/ta256. Accessed October 2012
256. Wisler JW, Becker RC. A guidance pathway for the selection of novel anticoagulants in the treatment of atrial fibrillation. *Crit Pathw Cardiol* 2012;11:55–61
257. Eriksson BI, Quinlan DJ, Eikelboom JW. Novel oral Factor Xa and thrombin inhibitors in the management of thromboembolism. *Annu Rev Med* 2011;62:41–57
258. Boehringer Ingelheim. GLORIA ™-AF registry Program investigating use of antithrombotic therapy in 56,000 patients with atrial fibrillation at risk of stroke announced. 2012. http://www.boehringer-ingelheim.com/news/news_releases/press_releases/2012/20_april_2012_dabigatranetexilate.html. Accessed October 2012
259. Piccini JP, Fraulo ES, Ansell JE *et al*. Outcomes registry for better informed treatment of atrial fibrillation: rationale and design of ORBIT-AF. *Am Heart J* 2011;162:606–12

260. Holbrook A, Schulman S, Witt DM *et al*. Evidence-based management of anticoagulant therapy: antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians evidence-based clinical practice guidelines (9th edition). *Chest* 2012;141:e152S–84S
261. Eerenberg ES, Kamphuisen PW, Sijpkens MK *et al*. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. *Circulation* 2011;124:1573–9
262. Pragst I, Zeitler SH, Doerr B *et al*. Reversal of dabigatran anticoagulation by prothrombin complex concentrate (Beriplex P/N) in a rabbit model. *J Thromb Haemost* 2012;10:1841–8
263. van Ryn J, Litzenburger T, Waterman A *et al*. An antibody selective to dabigatran safely neutralizes both dabigatran-induced anticoagulant and bleeding activity in *in vitro* and *in vivo* models. *J Thromb Thrombolysis* 2011;9:110. Abstract P-MO-166
264. Rivaroxaban A Practical Guide V1.0. 2012. http://www.thrombosisguidelinesgroup.be/sites/default/files/Rivaroxaban Practical Guide V1 0_06-07-2012.pdf. Accessed October 2012
265. National Institute for Health and Clinical Excellence. Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation; Technology appraisal TA249. 2012. http://www.nice.org.uk/ta249. Accessed October 2012
266. Langkilde LK, Bergholdt Asmussen M, Overgaard M. Cost-effectiveness of dabigatran etexilate for stroke prevention in non-valvular atrial fibrillation. Applying RE-LY to clinical practice in Denmark. *J Med Econ* 2012;15:695–703
267. Lee S, Anglade M, Hagstrom K *et al*. Cost-effectiveness of apixaban compared to aspirin for stroke prevention in atrial fibrillation. *J Am Coll Cardiol*. 2012; 59 Suppl: E596
268. Shah SV, Gage BF. Cost-effectiveness of dabigatran for stroke prophylaxis in atrial fibrillation. *Circulation* 2011;123:2562–70
269. Lee S, Anglade MW, Meng J *et al*. Cost-effectiveness of apixaban compared with aspirin for stroke prevention in atrial fibrillation among patients unsuitable for warfarin. *Circ Cardiovasc Qual Outcomes* 2012;5:472–9
270. Deitelzweig S, Amin A, Jing Y *et al*. Medical cost reductions associated with the usage of novel oral anticoagulants vs. warfarin among atrial fibrillation patients, based on the RE-LY, ROCKET-AF and ARISTOTLE trials. *J Med Econ* 2012;15:776–85
271. Lip GYH, Kongnakorn T, Phatak H *et al*. Cost-effectiveness of apixaban against other novel oral anticoagulants (NOACs) for stroke prevention in atrial fibrillation patients. *Eur Heart J* 2012;32:54
272. Furie KL, Goldstein LB, Albers GW *et al*. Oral antithrombotic agents for the prevention of stroke in nonvalvular atrial fibrillation: a Science Advisory for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2012; doi: 10.1161/STR.0b013e318266722a
273. Skanes AC, Healey JS, Cairns JA *et al*. Focused 2012 update of the Canadian Cardiovascular Society atrial fibrillation guidelines: recommendations for stroke prevention and rate/rhythm control. *Can J Cardiol* 2012;28:125–36
274. Raviele A, Disertori M, Alboni P *et al*. [2010 AIAC guidelines for the management and treatment of atrial fibrillation]. *G Ital Cardiol (Rome)* 2011;12:7–69
275. Haute Autorité de Santé. HAS Guide for doctors - long term conditions atrial fibrillation. 2007. http://www.has-sante.fr/portail/upload/docs/application/pdf/ald_5_fibrillation_auriculaire.pdf. Accessed October 2012
276. Guías de práctica clínica para el manejo de la fibrilación auricular. 2011. http://www.revespcardiol.org/sites/default/files/elsevier/pdf/25/25v63n12a13188310pdf001.pdf. Accessed October 2012
277. Kirchhof P, Goette A, Gulba D *et al*. Kommentar zu den Leitlinien der ESC zum Vorhofflimmern. *Kardiologe* 2012;6:12–27
278. Healthcare Improvement Scotland. Prevention of stroke and systemic embolism in adult patients with atrial fibrillation. 2012. http://www.healthcareimprovementscotland.org/his/idoc.ashx?docid=05a9291c-f901-4a8e-85d0-de8699a31757&version=-1. Accessed October 2012
279. Haute Autorité de Santé. Commission de la Transparence: opinion on Pradaxa. 2012. http://www.has-sante.fr/portail/upload/docs/application/pdf/2012-03/pradaxa_15022012_avis_ct10749.pdf. Accessed October 2012
280. Haute Autorité de Santé. Commission de la Transparence: opinion on Xarelto. 2012. http://www.has-sante.fr/portail/upload/docs/application/pdf/2012-04/xarelto_avc_14032012_avis_ct11771.pdf. Accessed October 2012
281. Canadian Agency for Drugs and Technologies in Health. CDEC final recommendation: dabigatran etexilate [Pradax – Boehringer Ingelheim (Canada) Ltd]. New indication: atrial fibrillation, stroke prevention. 2011. http://www.cadth.ca/media/cdr/complete/cdr_complete_Pradax_June-27-11.pdf. Accessed October 2012
282. Canadian Agency for Drugs and Technologies in Health. CDEC final recommendation: rivaroxaban (Xarelto – Bayer Inc.). New indication: atrial fibrillation, Stroke Prevention. 2012. http://www.cadth.ca/media/cdr/complete/cdr_complete_Xarelto-SPAF_April-20-12.pdf. Accessed October 2012
283. Wittkowsky AK. Effective anticoagulation therapy: defining the gap between clinical studies and clinical practice. *Am J Manag Care* 2004;10:S297–306
284. Lee S, Shafe AC, Cowie MR. UK stroke incidence, mortality and cardiovascular risk management 1999–2008: time-trend analysis from the General Practice Research Database. *BMJ Open* 2011;1:e000269
285. Fang MC, Go AS, Chang Y *et al*. Warfarin discontinuation after starting warfarin for atrial fibrillation. *Circ Cardiovasc Qual Outcomes* 2010;3:624–31
286. Lip G, Bassand JP, Fitzmaurice D *et al*. Inappropriate utilization on anticoagulation in patients with atrial fibrillation: the Global Anticoagulant Registry in

the FIELD (GARFIELD) registry. *J Am Coll Cardiol* 2012;59:E670. Abstract 1236–167

287. 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
288. 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
289. Hannon N, Callaly E, Moore A *et al*. Improved late survival and disability after stroke with therapeutic anticoagulation for atrial fibrillation: a population study. *Stroke* 2011;42:2503–8
290. Pouyanne P, Haramburu F, Imbs JL *et al*. Admissions to hospital caused by adverse drug reactions: cross sectional incidence study. French Pharmacovigilance Centres. *BMJ* 2000;320:1036
291. Lip GY, Zarifis J, Watson RD *et al*. Physician variation in the management of patients with atrial fibrillation. *Heart* 1996;75:200–5
292. 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
293. Maeda K, Sakai T, Hira K *et al*. Physicians' attitudes toward anticoagulant therapy in patients with chronic atrial fibrillation. *Intern Med* 2004;43:553–60
294. 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
295. 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
296. 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
297. 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
298. AntiCoagulation Europe (UK), AF Association. Living with warfarin. 2012. http://www.anticoagulationeurope.org/files/files/booklets/LWW report.pdf. Accessed October 2012
299. Tang EO, Lai CS, Lee KK *et al*. Relationship between patients' warfarin knowledge and anticoagulation control. *Ann Pharmacother* 2003;37:34–9
300. Taillandier S, Olesen JB, Clémenty N *et al*. Prognosis in patients with atrial fibrillation and CHA(2)DS(2)-VASc score = 0 in a community-based cohort study. *J Cardiovasc Electrophysiol* 2012;23:708–13
301. Arrhythmia Alliance. International area. 2010. http://www.aa-international.org. Accessed October 2012
302. Lowres N, Freedman SB, Redfern J *et al*. Screening Education And Recognition in Community pHarmacies of Atrial Fibrillation to prevent stroke in an ambulant population aged >=65 years (SEARCH-AF stroke prevention study): a cross-sectional study protocol. *BMJ Open* 2012;2:e001355
303. Friberg L, Engdahl J, Frykman V *et al*. Population screening of 75- and 76-year-old men and women for silent atrial fibrillation (STROKESTOP). *Europace* 2012; doi: 10.1093/europace/eus217
304. Lip GY. Quality of service provision for anticoagulation in atrial fibrillation. Many patients are ineligible. BMJ 1996;312:51
305. American Heart Association. Get with guidelines - stroke overview. 2011. http://www.heart.org/HEARTORG/HealthcareResearch/GetWithTheGuidelinesHFStroke/GetWithTheGuidelinesStrokeHomePage/Get-With-The-Guidelines-Stroke-Overview_UCM_308021_Article.jsp. Accessed October 2012
306. AntiCoagulation Europe. Welcome to AntiCoagulation Europe. 2012. http://www.anticoagulationeurope.org. Accessed October 2012
307. AntiCoagulation Europe (UK). It's About Time campaign. 2005. http://www.bjpcn-cardiovascular.com/pdf/2028/Vol1_Num4_January_2005_p176–177.pdf?sid=683da8349028a619. Accessed October 2012
308. AF Association. AFA Aims. 2011. http://www.atrialfibrillation.org.uk/atrial-fibrillation-association/aims.html. Accessed October 2011
309. AF Association, AntiCoagulation Europe (UK). Atrial fibrillation: preventing a stroke crisis. 2011. http://www.preventaf-strokecrisis.org/. Accessed October 2012
310. StopAFib.org. 2012. http://www.stopafib.org/about.cfm. Accessed October 2012
311. Nadar S, Begum N, Kaur B *et al*. Patients' understanding of anticoagulant therapy in a multiethnic population. *J R Soc Med* 2003;96:175–9
312. Stroke Alliance for Europe. SAFE. 2012. http://www.safestroke.org/. Accessed October 2012
313. Stroke Association. Information for professionals. 2011. http://www.stroke.org.uk/involved/information-professionals. Accessed October 2012
314. SPEAKaboutAF. The SPEAK about AF survey. 2011. http://www.speakaf.com/_media/downloads/brochure.pdf. Accessed October 2012
315. Avery T, Barber N, Ghaleb M *et al*. Investigating the prevalence and causes of prescribing errors in general practice: the PRACtICe Study. 2012. http://www.gmc-uk.org/Investigating_the_prevalence_and_causes_of_prescribing_errors_in_general_practice___The_PRACtICe_study_Reoprt_May_2012_48605085.pdf. Accessed October 2012
316. Trummer UF, Mueller UO, 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
317. 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

318. Carpenter DM, DeVellis RF, Fisher EB *et al*. The effect of conflicting medication information and physician support on medication adherence for chronically ill patients. *Patient Educ Couns* 2010;81:169–76
319. Macik BG. The future of anticoagulation clinics. *J Thromb Thrombolysis* 2003;16:55–9
320. 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
321. 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
322. 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
323. Shojania KG, Duncan BW, McDonald KM *et al*. Making health care safer: a critical analysis of patient safety practices. *Evid Rep Technol Assess (Summ)* 2001:1–668
324. Garcia-Alamino JM, Ward AM, Alonso-Coello P *et al*. Self-monitoring and self-management of oral anticoagulation. *Cochrane Database Syst Rev* 2010:CD003839
325. Taborski U, Wittstamm FJ, Bernardo A. Cost-effectiveness of self-managed anticoagulant therapy in Germany. *Semin Thromb Hemost* 1999;25:103–7
326. 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
327. 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
328. Poller L, Keown M, Ibrahim S *et al*. An international multicenter randomized study of computer-assisted oral anticoagulant dosage vs. medical staff dosage. *J Thromb Haemost* 2008;6:935–43
329. Lip GYH, Agnelli G, Thach AA *et al*. Oral anticoagulation in atrial fibrillation: a pan-European patient survey. *Eur J Intern Med* 2007;18:202–8
330. Groene O, Lombarts MJ, 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 Suppl 1:i44–50
331. Ellis S. The patient-centred care model: holistic/multiprofessional/reflective. *Br J Nurs* 1999;8:296–301
332. Gage BF, Cardinalli AB, Owens DK. Cost-effectiveness of preference-based antithrombotic therapy for patients with nonvalvular atrial fibrillation. *Stroke* 1998;29:1083–91
333. 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
334. Bell CM, Redelmeier DA. Mortality among patients admitted to hospitals on weekends as compared with weekdays. *N Engl J Med* 2001;345:663–8
335. Goldfrad C, Rowan K. Consequences of discharges from intensive care at night. *Lancet* 2000;355:1138–42
336. 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
337. 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
338. European Patients' Forum. Declaration of the European Patients' Forum. 2003. http://www.eu-patient.eu/Documents/who we are/CoreDocuments/EPF_declaration.pdf. Accessed October 2012
339. European Patients' Forum. 150 Million reasons to act: EPF's Patients' Manifesto for the European Parliament and Commission 2009. 2009. http://www.eu-patient.eu/Documents/Events/Manifesto/epf_manifesto.pdf. Accessed October 2012
340. European Patients' Forum. European Patients' Forum Conference on Health Literacy. Brussels, 8-9 April, 2008. 2008. http://www.eu-patient.eu/Documents/Library/ConferenceSeminarReports/EPF_HealthLiteracyConference_2008_Report.pdf. Accessed October 2012
341. Hillier S. The health and health care of ethnic minority groups. In *Sociology As Applied to Medicine*. 4 edn. Scambler G (editor). Ballière Tindall; 1997. pp. 135–47
342. Commission of the European Communities. Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions - Solidarity in Health: reducing health inequalities in the EU. 2009. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2009:0567:FIN:EN:PDF. Accessed October 2012
343. European Parliament. Report on reducing health inequalities in the EU. 2011. http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//TEXT+REPORT+A7-2011-0032+0+DOC+XML+V0//EN&language=EN. Accessed October 2012
344. Global Atrial Fibrillation Patient Charter. 2012. http://www.signagainststroke.com/en/charter.html. Accessed October 2012
345. 1st European Day of the Brain. Ageing, Stroke, and Alzheimer's Disease - Finding Innovative Solutions Expert Conference during Polish Presidency of the European Union Council (Medical University of Warsaw). 2011. http://pl2011.eu/sites/default/files/users/shared/spotkania_i_wydarzenia/draft_post-conference_conclusion_18.11.11_0.pdf. Accessed October 2012
346. Pison L, La Meir M, van Opstal J *et al*. Hybrid thoracoscopic surgical and transvenous catheter ablation of atrial fibrillation. *J Am Coll Cardiol* 2012;60:54–61
347. AtriCure, Inc. Dual Epicardial Endocardial Persistent atrial fibrillation (AF) study (staged DEEP). 2012. http://www.clinicaltrials.gov/ct2/show/NCT011661205. Accessed October 2012
348. Kolominsky-Rabas PL, Weber M, Gefeller O *et al*. Epidemiology of ischemic stroke subtypes according to TOAST criteria: incidence, recurrence, and long-term survival in ischemic stroke subtypes: a population-based study. *Stroke* 2001;32:2735–40

349. Healey JS, Connolly SJ, Gold MR *et al*. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med* 2012;366:120–9
350. Moya A, Sutton R, Ammirati F *et al*. Guidelines for the diagnosis and management of syncope (version 2009). *Eur Heart J* 2009;30:2631–71
351. Sinha AM, Diener HC, Morillo CA *et al*. Cryptogenic stroke and underlying atrial fibrillation (CRYSTAL AF): design and rationale. *Am Heart J* 2010;160:36–41
352. Ahrens I, Peter K, Lip GY *et al*. Development and clinical applications of novel oral anticoagulants. Part II. Drugs under clinical investigation. *Discov Med* 2012;13:445–50
353. Luis SA, Roper D, Incani A *et al*. Non-pharmacological therapy for atrial fibrillation: managing the left atrial appendage. *Cardiol Res Pract* 2012;2012:304626
354. Reddy VY, Holmes D, Doshi SK *et al*. Safety of percutaneous left atrial appendage closure: results from the Watchman left atrial appendage system for embolic protection in patients with AF (PROTECT AF) clinical trial and the continued access registry. *Circulation* 2011;123:417–24
355. 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
356. Reddy VY, Neuzil P, Miller MA *et al*. First formal analysis of the "Asa Plavix Registry" (ASAP): Watchman left atrial appendage closure in atrial fibrillation patients with contraindication to oral anticoagulation. *Heart Rhythm* 2012;9:1580–1. Abstract LB02-2
357. Heartwire press release. Without warfarin, Watchman still prevents strokes, says registry. 2012. http://www.theheart.org/article/1398695.do. Accessed October 2012
358. Atritech. Evaluation of the WATCHMAN LAA closure device in patients with atrial fibrillation versus long term warfarin therapy (PREVAIL). 2012. http://www.clinicaltrials.gov/ct2/show/NCT01182441. Accessed October 2012
359. Atritech. Evaluation of the next generation WATCHMAN LAA closure technology in non-valvular AF patients (EVOLVE). 2012. http://www.clinicaltrials.gov/ct2/show/NCT01196897. Accessed October 2012
360. Park JW, Bethencourt A, Sievert H *et al*. Left atrial appendage closure with Amplatzer cardiac plug in atrial fibrillation: initial European experience. *Catheter Cardiovasc Interv* 2011;77:700–6
361. AGA Medical Corporation. AMPLATZER cardiac plug clinical trial. 2012. http://www.clinicaltrials.gov/ct2/show/NCT01118299. Accessed October 2012
362. Lee R, Barua K, Bednarek J *et al*. Percutaneous left atrial appendage exclusion using the Lariat in patients with atrial fibrillation: initial clinical experience and long-term results. *Heart Rhythm* 2012;9:1581.
363. University of California, San Francsico. Study of left atrial appendage closure in patients with atrial fibrillation - III (PLACE III). 2012. http://www.clinicaltrials.gov/ct2/show/NCT01680757. Accessed October 2012
364. Atricure. AtriCure announces European approval for its AtriClip(TM) system. 2009. http://ir.atricure.com/phoenix.zhtml?c=189981&p=irol-newsArticle&ID=1339133&highlight. Accessed October 2012
365. Ailawadi G, Gerdisch MW, Harvey RL *et al*. Exclusion of the left atrial appendage with a novel device: early results of a multicenter trial. *J Thorac Cardiovasc Surg* 2011;142:1002–9.e1
366. AtriCure, Inc. Safety and effectiveness of left atrial appendage occlusion. 2012. http://www.clinicaltrials.gov/ct2/show/NCT00567515. Accessed October 2012
367. Salzberg SP, Plass A, Emmert MY *et al*. Left atrial appendage clip occlusion: early clinical results. *J Thorac Cardiovasc Surg* 2010;139:1269–74

Glossary

1 billion	1000 million
Ablation	In cardiovascular medicine, a procedure in which faulty electrical pathways in the heart are destroyed. Can be used to treat arrhythmias caused or maintained by these faulty pathways
Anticlotting agent	See antithrombotic therapy below
Anticoagulant	A type of drug that reduces the ability of the blood to clot by inhibiting any step in the coagulation pathway, thereby resulting in impaired formation of fibrin (the end result of the clotting pathway)
Antiplatelet agent	A type of drug that inhibits the formation of blood clots by inhibiting activation of blood platelets
Antithrombotic therapy	Any therapy that interferes with the formation of blood clots (thrombi), including both antiplatelet and anticoagulant drugs. Antithrombotic agents are also known as anticlotting agents or 'blood thinners'
Arrhythmia	A disorder of the heart rate (pulse) or heart rhythm
Aspirin	Acetylsalicylic acid, an antiplatelet agent that also has anti-inflammatory properties
Asymptomatic	Showing or causing no symptoms
Atenolol	A β-blocker drug. One of its uses is to control heart rate
Atherothrombotic event	An ischaemic event triggered by platelet activation after disruption of plaque or fatty deposits in the arteries
Atrial fibrillation (AF)	A heart rhythm abnormality, characterized by rapid, disorganized electrical signals, which cause the atria to contract very quickly, irregularly (known as fibrillation) and inefficiently
Atrial flutter	An arrhythmia characterized by rapid contractions of the atria; unlike the contractions seen with AF, however, atrial flutter has a consistent pattern
β-blockers	A class of drugs that prevent the stimulation of β-adrenergic receptors. They are used to treat a number of conditions, including arrhythmia and hypertension
Bradycardia	An abnormally slow heart rate
Cardioembolic or cardiogenic stroke	A stroke caused by a blood clot originating in the heart

Cardioversion	The process by which an abnormally fast heart rate or disturbance in heart rhythm is terminated by the delivery of an electric current to the heart at a specific moment in the heart cycle (electrical cardioversion) or injection of anti-arrhythmic agents (pharmacological cardioversion)
Coagulation	The process by which a blood clot is formed; essential for the arrest of bleeding
Coagulation pathway	The pathway of biochemical reactions that results in the formation of a blood clot
Digoxin	A cardiac glycoside extracted from the foxglove plant; used as a rate-control agent
Direct thrombin inhibitor	A class of anticoagulants that act by binding directly to thrombin and blocking interaction with its substrate fibrinogen, thus inhibiting the generation of fibrin and clot formation
Embolize	The process of forming an embolus (e.g. when a clot detaches from a vessel wall and is able to move freely in the circulation)
Embolus/embolism	A blood clot (thromboembolism), air bubble, piece of fatty deposit or other object is carried in the bloodstream and can lodge in a blood vessel and impede the circulation
Enzyme	A complex protein that is produced by living cells and that drives specific biochemical reactions
Epidemiology	The study of the occurrence and distribution of disease
Factor X	An enzyme that forms a key part of the coagulation cascade: in its activated form (Factor Xa), it cleaves the prothrombin enzyme (Factor II) to form thrombin (Factor IIa). Factor X is itself activated by Factor IX (and its cofactor VIII) and Factor VIIa (with its cofactor, Tissue Factor)
Factor Xa inhibitor	A class of anticoagulants that inhibit Factor Xa in the coagulation cascade either by binding directly to Factor Xa or indirectly through antithrombin. Inhibition of Factor Xa reduces the production of thrombin
Fibrinogen	A soluble plasma protein. In the final phase of the coagulation process, thrombin converts fibrinogen to insoluble fibrin, which polymerizes and forms the fibrous network base of a clot
Haemorrhagic stroke	A stroke caused by leakage from a blood vessel in the brain
Haemostasis	The stoppage of bleeding either by constriction of the blood vessels (vasoconstriction) and coagulation or by surgical means
Heart attack	An ischaemic event in a section of the heart after interruption of its blood supply (also known as myocardial infarction)
Holter monitor	A portable device for continuously monitoring the electrical activity of the heart
Incidence	The number of new cases of a disease or condition in a population over a given period of time

Infarction	The process of forming an infarct, or area of necrosis in a tissue or organ resulting from a loss of bloodflow to the area
International normalized ratio (INR)	Prothrombin time test results vary according to the activity of the thromboplastin reagent used. The INR conversion normalizes results for any thromboplastin preparation but is valid only with vitamin K antagonists
Ischaemic stroke	Stroke caused by a blood clot or embolus blocking a blood vessel in the brain
Morbidity	The state of having a disease; ill health
Phase III trial	A large-scale clinical trial, often involving several thousand patients, conducted to confirm the results of an earlier phase II trial or trials with smaller numbers of patients. Results from phase III trials often provide the basis for marketing approval by regulatory authorities
Platelet	A very small, disc-shaped component of the blood that forms a significant part of a blood clot, particularly in the arteries
Prevalence	The total number of cases of a disease or condition in a population at any given time
Prothrombin time	The prothrombin time measures clotting time in the presence of tissue factor (thromboplastin). It is used to assess the overall functioning of the extrinsic pathway (initiated by Factor VII and Tissue Factor) and the common pathway (beginning with Factor X); see Figure 10
Pulmonary vein isolation	A type of ablation procedure whereby the tissue surrounding the openings of the pulmonary veins to the left atrium (a common source of the aberrant electrical impulses responsible for AF) is electrically isolated. The scar tissue that forms prevents the impulses generated in this region from propagating, thus reducing or eliminating the stimulus that maintains the AF
Quality-adjusted life-year (QALY)	A measure that represents the composite of several outcomes affecting quality of life; 1 year in perfect health is considered to be equal to 1.0 QALY; 1 year in less than perfect health would have a QALY <1
Sotalol	A β-blocker drug used to treat arrhythmias
Stroke	A condition caused by disruption of the blood supply to part of the brain, or leaking of blood from a blood vessel into the brain, which may result in damage or death of brain cells
Subarachnoid haemorrhage	Bleeding between the protective membranes (meninges) covering the brain and spinal cord; specifically, bleeding between the pia mater (the innermost membrane) and the arachnoid mater (the 'middle' membrane covering the pia mater)
Subdural haemorrhage	Bleeding between the protective membranes (meninges) covering the brain and spinal cord; specifically, bleeding between the dura mater (the outermost membrane) and the arachnoid mater

Supraventricular tachycardia	A tachycardia that originates above the ventricles of the heart, as in the atria or the atrioventricular node
Syncope	Loss of consciousness resulting from insufficient blood flow to the brain (fainting)
Tachycardia	An abnormally fast heart rate
Therapeutic range	The interval between the lowest dose of a drug that is sufficient for clinical effectiveness and the higher dose at which adverse events or toxicity become unacceptable
Thrombin	Thrombin (Factor IIa) is the terminal enzyme of the coagulation cascade and converts fibrinogen into fibrin, which forms clot fibres. Thrombin also activates several other coagulation factors, in addition to protein C, which helps regulate the coagulation system
Thromboembolism	An embolism formed from a blood clot
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 class of compounds that inhibit the vitamin K-dependent formation of specific coagulation factors. This results in decreased levels of the affected coagulation factors, leading to anticoagulation
Warfarin	A vitamin K antagonist that is currently the most commonly used oral anticoagulant

Abbreviations

ACC	American College of Cardiology
ACCP	American College of Chest Physicians
AF	Atrial fibrillation
AHA	American Heart Association
ASP	Action for Stroke Prevention
ATRIA	Anticoagulation and Risk Factors in Atrial Fibrillation
$CHADS_2$	Congestive heart failure; Hypertension; Age ≥75 years; Diabetes; Stroke 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)
CHA_2DS_2-VASc	Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, Stroke or transient ischaemic attack – Vascular disease, age 65–74 years, female sex
CI	Confidence interval
CrCl	Creatinine clearance
DEEP AF	Dual Epicardial Endocardial Persistent AF
ECG	Electrocardiogram
EHN	European Health Network
EIP	European Innovation Partnership
EPF	European Patients' Forum
ERG	Evidence Review Group
ESC	European Society of Cardiology
ESN	European Stroke Network
EU	European Union
EUTRAF	European Network for Translational Research in Atrial Fibrillation
GARFIELD	Global Anticoagulant Registry in the FIELD
GLORIA-AF	Global Registry on Long-Term Oral Anti-thrombotic Treatment In Patients with Atrial Fibrillation
HAS-BLED	Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile International Normalized Ratio, Elderly, Drugs/alcohol concomitantly
HRS	Heart Rhythm Society
$HEMORR_2HAGES$	Hepatic or Renal Disease, Ethanol Abuse, Malignancy, Older Age (>75 years), Reduced Platelet Count or Function, Re-Bleeding, Hypertension, Anemia, Genetic Factors, Excessive Fall Risk and Stroke
IMI	Innovative Medicines Initiative
INR	International normalized ratio
ISAM	International Study Of Anticoagulation Management

LAA	Left atrial appendage
mRS	Modified Rankin Scale
NCD	Non-communicable disease
NICE	National Institute for Health and Clinical Excellence
OAC	Oral anticoagulant
ORBIT-AF	Outcomes Registry for Better Informed Treatment of Atrial Fibrillation
QALY	Quality-adjusted life-year
RRR	Relative risk reduction
SAFE	Screening for AF in the Elderly
SVT	Supraventricular tachycardia
TIA	Transient ischaemic attack
UN	United Nations
UK	United Kingdom
US	United States
VKA	Vitamin K antagonist
WHO	World Health Organization

Conflicts of Interest

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

Dr Álvaro Avezum
Research contract: Boehringer Ingelheim, GSK; ACTIVE-W, ACTIVE-A. Consultant: Boehringer Ingelheim, GSK, BMS, Pfizer, AstraZeneca. National Coordinator/Steering Committee member: ACTIVE W, ACTIVE A, RE-LY, ARISTOTLE, AVERROES, ROCKET AF

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

Professor John Camm
Advisor/speaker: AstraZeneca, ChanRX, Gilead, Merck, Menarini, Otsuka, Sanofi, Servier, Xention, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi, Pfizer, Boston Scientific, Biotronik, Medtronic, St. Jude Medical, Actelion, GlaxoSmithKline, InfoBionic, Incarda, Johnson & Johnson, Mitsubishi, Novartis, Takeda

Dr Carlos Cantú
Advisory board member: Bayer Co. Speaker: Ferrer, Bayer Co.

Professor László Csiba
None

Professor Antonio Dávalos
Consultant: Bayer, Boehringer Ingelheim

Dr Jorge Gonzalez-Zuelgaray
Speaker: Bayer, Medtronic

Professor Shinya Goto
Research grants: Sanofi-Aventis, Otsuka, Boehringer Ingelheim, Daiichi Sankyo, Honoraria: Sanofi-Aventis, AstraZeneca., Eisai, Otsuka, Bayer, Novartis, Astellas, Pfizer, Medtronics-Japan, Tanabe-Mitsubishi, Takeda, Daiichi Sankyo, Mochida, MSD

Professor Dr Werner Hacke
Consultant: Boehringer Ingelheim, Bayer. Speaker: Boehringer Ingelheim, Bayer. Research support: Boehringer Ingelheim, unrestricted grant for ECASS 4 (an IIT)

Professor Graeme J Hankey
Honoraria: Executive Committees – AMADEUS (Sanofi-Aventis), ROCKET AF (Johnson & Johnson), BOREALIS (Sanofi-Aventis); Steering Committee – TRA 20P TIMI 50; Stroke Outcome Adjudication Committees – RE-LY, AVERROES. Speaker/Consultant: Bayer, Boehringer Ingelheim, Pfizer Australia

Professor Michael G Hennerici
None

Mellanie True Hills
None

Professor Richard Hobbs
Speaker fees/sponsorship: AstraZeneca, Bayer, Boehringer Ingelheim, Medtronic, Merck, Novartis, Pfizer, Roche

Dr Torsten Hoppe-Tichy
None

Professor Dayi Hu
None

Professor Han-Hwa Hu
None

Professor Dr Paulus Kirchhof
Consulting fees/honoraria: 3M Medica, MEDA Pharma, AstraZeneca, Bayer Healthcare, Biosense Webster, Boehringer Ingelheim, Daiichi Sankyo, German Cardiac Society, MEDA Pharma, Medtronic, Merck, MSD, Otsuka Pharma, Pfizer/BMS, Sanofi, Servier, Siemens, TAKEDA. Research grants: 3M Medica/ MEDA Pharma, Cardiovascular Therapeutics, Medtronic, OMRON, Sanofi, St. Jude Medical, German Federal Ministry for Education and Research (BMBF), Fondation Leducq, German Research Foundation (DFG), European Union (EU). Travel support: ESC, EHRA, AFNET

Eve Knight
None

Joe Korner
None

Professor Dr Karl-Heinz Ladwig
None

Professor Antoine Leenhardt
Board member/conference speaker: Sanofi, Bayer, Daiichi Sankyo, Boehringer Ingelheim, Meda Pharma, Pfizer, MSD, St. Jude Medical, Boston, Servier

Dr Maddalena Lettino
Speaker: AstraZeneca, BMS, Boehringer, Eli Lilly, Daiichi Sankyo, Bayer, Pfizer, The Medicines Company. Advisory board member: Eli Lilly, The Medicines Company, BMS, Pfizer, MSD

Professor Gregory YH Lip
Consultant: Bayer, Astellas, Merck, Sanofi, BMS/Pfizer, Daiichi Sankyo, Biotronik, Portola, Boehringer Ingelheim. Speakers bureau: Bayer, BMS/Pfizer, Boehringer Ingelheim, Sanofi-Aventis

Trudie Lobban MBE
None

Professor Lorenzo Mantovani
Research grants: Bayer Research, Boehringer Ingelheim, Pfizer, Bristol-Myers Squibb. Consultant/Advisory Board member: Bayer

Dr Ayrton Massaro
None

Rod Mitchell
None disclosed

Professor Bo Norrving
Advisor/consultant: PhotoThera, SERVIER, SYGNIS Pharma AG. Speaker/member of a speakers bureau: Allergan, Bayer HealthCare Pharmaceuticals. Boehringer Ingelheim Pharmaceuticals

Dr David KL Quek
None

Dr Walter Reyes-Caorsi
Advisory Board member: Bayer Uruguay S.A. Speaker: Bayer Uruguay

Professor Dr Kui-Hian Sim
Ongoing clinical trial and Investigator fees: Sanofi, Roche, Eli Lily

Professor Norio Tanahashi
None

Professor Hung-Fat Tse
Advisor/consultant: Bayer Schering Pharma, Boehringer Ingelheim Pharmaceuticals, Sanofi-Aventis, St. Jude Medical, Cordis Corporation, Medtronic, GlaxoSmithKline, Merck Sharp & Dohme Corp

Professor Panos Vardas
Consultant/honoraria: Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Medtronic, Menarini, Servier

Dr Xavier Viñolas
Consultant: Bayer, Medtronic, St. Jude Medical, Boston Scientific

Professor Byung-Woo Yoon
None

Professor Shu Zhang
None disclosed

Atrial fibrillation (AF) – the most common sustained heart rhythm abnormality – affects approximately 10 million people in Europe. Individuals with AF are at a fivefold increased risk of stroke compared with the general population, and AF accounts for approximately 1 in 5 ischaemic strokes. With the prevalence of AF in Europe expected to rise dramatically to 25–30 million by 2050, prompt action is required to avoid a crisis.

About 1.3 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. 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 updated report aims to raise awareness of the need for better knowledge and management of AF, and that better prevention of AF-related stroke is both possible and achievable. However, greater investment is needed to prevent the thousands of avoidable AF-related strokes that occur each year. Coordinated action across the European Union is required urgently to achieve earlier diagnosis and better management of AF and to improve delivery of therapies to prevent AF-related stroke. Timely implementation of the recommendations detailed in this report, at European and national levels, will be crucial.