



The future of anticoagulation management in atrial fibrillation in Europe

An assessment of today's challenges with recommendations for the future

Research report

Catherine Lichten, Sophie Castle-Clarke, Catriona Manville, Veronika Horvath, Enora Robin, Joachim Krapels, Sarah Parks, Megan Sim, Olga van Zijverden, Joanna Chataway



EUROPE

The Future of Anticoagulation Initiative
was funded by Daiichi Sankyo Europe

For more information on this publication, visit www.rand.org/t/rr1053

Published by the RAND Corporation, Santa Monica, Calif., and Cambridge, UK

© Copyright 2015 RAND Corporation

RAND® is a registered trademark.

Date of preparation: August 2015 | Job code: DSC/15/0023d

RAND Europe is a not-for-profit research institute whose mission is to help improve policy and decisionmaking through research and analysis. RAND's publications do not necessarily reflect the opinions of its research clients and sponsors.

Limited Print and Electronic Distribution Rights

This document and trademark(s) contained herein are protected by law. This representation of RAND intellectual property is provided for noncommercial use only. Unauthorized posting of this publication online is prohibited. Permission is given to duplicate this document for personal use only, as long as it is unaltered and complete. Permission is required from RAND to reproduce, or reuse in another form, any of its research documents for commercial use. For information on reprint and linking permissions, please visit www.rand.org/pubs/permissions.html.

Support RAND

Make a tax-deductible charitable contribution at

www.rand.org/giving/contribute

www.rand.org

www.randeurope.org

The future of anticoagulation management in atrial fibrillation in Europe

An assessment of today's challenges with recommendations for the future

Catherine Lichten, Sophie Castle-Clarke, Catriona Manville, Veronika Horvath, Enora Robin, Joachim Krapels, Sarah Parks, Megan Sim, Olga van Zijverden, Joanna Chataway

RR-1053-UKRF

Preface

The Future of Anticoagulation Initiative was funded by Daiichi Sankyo Europe. It was a project that aimed to investigate the current landscape and explore possible directions of future developments in atrial fibrillation management, with a particular focus on stroke prevention and the use of oral anticoagulants. There were six countries of focus: Belgium, France, Germany, Italy, Spain and the UK.

This report presents the key observations from the study, a series of short-term and longer-term recommendations, and a summary of the methods involved in the research. The full methodology is set out in the accompanying annexes. In addition to the methodology, the annexes document each part of the project. They comprise a report on findings from the rapid evidence assessment of literature and clinical guidelines, a report on findings from key informant interviews, a description of future scenarios discussed in the project's scenarios workshop, and a table summarising factors identified in the evidence assessment and interviews as relevant for the current and future management of anticoagulation in atrial fibrillation patients.

Also available are two research briefs on the study, AF-related stroke prevention: today and the future, aimed at readers from the healthcare professional and patient communities. The annexes and research briefs can be accessed online on the RAND Europe website.

RAND Europe is an independent not-for profit policy research organisation that aims to improve policy and decisionmaking in the public interest, through research and analysis. RAND Europe's clients include European governments, institutions, non-governmental bodies (NGOs) and firms with a need for rigorous, independent, multidisciplinary analysis. This report has been subject to RAND's quality assurance process, which consists of rigorous peer review.

For more information about RAND Europe or this document, please contact:

Joanna Chataway, RAND Europe
Westbrook Centre, Milton Road
Cambridge CB4 1YG
United Kingdom
Tel. +44 (1223) 353 329 | Email. chataway@rand.org

Foreword

As a medical student I was taught that atrial fibrillation was so common that it should be regarded as a variation of normal, seen particularly in the elderly. At that time it was not appreciated that this heart rhythm disturbance was associated with a high risk of stroke and heart failure, and that early diagnosis and treatment could greatly improve the lives of patients afflicted with the disorder. Progressively over the last five decades the true importance of atrial fibrillation has become apparent and we now know highly effective ways in which we can treat patients to restore the length and quality of their lives. However, the inactive legacy of the past persists and we need to refocus the attention of healthcare professionals on this cardiovascular condition, which is now reaching epidemic proportions.

Atrial fibrillation – the landscape

Over the last decade it has been appreciated that the population in the Western world is growing older. In 25 years, more than a quarter of the EU population will be at least 65 years of age. Diseases of the elderly will become much more common, and amongst these is atrial fibrillation, which is a disorder of the rhythm of the heart. The prevalence of this disease in the general population will practically double, rising from less than 2 per cent to more than 3 per cent between now and 2060. This heart rhythm disorder is not immediately dangerous to those in whom it occurs – it may remain undiscovered for months or years.

Changing demographics – the impact of ageing

The rhythm disturbance is a consequence of ageing itself and a wide variety of underlying comorbidities. Its eventual consequences are very damaging – five times the likelihood of stroke, double the risk of heart failure, dementia, sudden death and hospitalisation. The oncoming epidemic of atrial fibrillation represents

a challenge to almost every member of the population: to those who will be directly affected, to almost every member of the population who will be related to or know someone who suffers from the disease, and to society in general, which must set up and maintain methods of managing and coping with this increasingly prevalent heart problem.

Innovation brings promise – scientific solutions continue to evolve

Of course, it is not a coincidence that medical science has been drawn into this arena, and it is very fortunate that new diagnostic and therapeutic methods have been developed to address atrial fibrillation. Technological advances in medicine mean that it is now possible to sample the electrocardiograms of those at risk of sustaining a rhythm disorder, adjusting lifestyles that may promote the condition, managing underlying comorbidities that encourage atrial fibrillation and directly treating rhythm disorders to eliminate or delay their progress. In particular, the most impactful and upsetting aspect of this disorder – a much higher rate of stroke in those with atrial fibrillation – can be largely prevented. New, easily used and highly effective medications have now been developed. Scientific solutions are available and continue to rapidly improve.

Equity of care and access – a continuing priority

Some of these innovations have emerged in clinical practice, but many have not. Implementation has been inconsistent across Europe and most patients are deprived of the best solutions to their problems with atrial fibrillation. Of course, most patients are completely unaware of the inadequacy of their treatment. However, patient associations have evolved in many parts of Europe to try to inform and educate patients,

their relatives and carers, and importantly to assist healthcare professionals to deal better with the large numbers of those at risk from this disease. Additionally, ongoing efforts to foster an understanding of atrial fibrillation and its consequences with national and European parliamentarians continue. These efforts extend to the European Commission where dialogue has been and is occurring, regarding the need for equity of access to the highly effective treatments that are available for this heart rhythm disorder.

Engagement and motivation – the key to success

The first part of any solution to this often insidious condition is well in hand, but there exist many barriers and blocks to the practical implementation of new developments. The Future of Anticoagulation Initiative sets out to inform and encourage healthcare professionals, and those who are able to influence the policy and practical engagement of healthcare systems. This report considers the issues that exist today and those that will potentially engulf us tomorrow. The means to successfully tackle this dangerous disease are already available and will continue to improve – all we need is the motivation to move ahead and work together to ensure that every effort is made to rid society of the potential impact and consequences of atrial fibrillation.

Professor John Camm, Chair of the Future of Anticoagulation Steering Committee, Professor of Clinical Cardiology, St. George's, University of London and Professor of Cardiology, Imperial College London, United Kingdom

Future of Anticoagulation Initiative Steering Committee



**Professor John Camm,
Chair of the Future of
Anticoagulation Steering
Committee**

Professor of Clinical Cardiology, St. George's, University of London and Professor of Cardiology, Imperial College London, United Kingdom



Professor Andreas Goette

St. Vincenz-Hospital Paderborn and University Hospital Magdeburg, Germany



**Professor Josep Brugada
Terradellas**

Cardiologist, Hospital Clínic de Barcelona, University of Barcelona. Chief of Arrhythmias of the Pediatric Hospital Sant Joan de Déu. Professor of Cardiology, University of Barcelona, Spain



Professor Reinhold Kreutz

Professor of Clinical Pharmacology and Hypertensiology, Head of the Department of Clinical Pharmacology and Toxicology, Charité – University Medicine Berlin, Germany



Professeur Jean-Marc Davy

Département de Cardiologie et Maladies Vasculaires, Hôpital Arnaud de Villeneuve - CHU de Montpellier, France



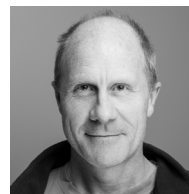
Trudie Lobban MBE

Founder & CEO - Arrhythmia Alliance / STARS / AF Association, United Kingdom



**Professor Raffaele de
Caterina**

Professor of Cardiology and Director of the University Cardiology Division, G. d'Annunzio, University, Chieti, Italy



Dr Jonathan Salter

General Practitioner and Director of SW Healthcare, a Federation of General Practices in South Worcestershire, United Kingdom



**Professor Hans-Christoph
Diener**

Professor of Neurology, Chairman of the Department of Neurology and Stroke Center, University of Duisburg-Essen, Germany

Dr Andrew Walker

Health Economist, Robertson Centre for Biostatistics, University of Glasgow, Scotland, United Kingdom

Abstract

Atrial fibrillation (AF) is the most common type of cardiac arrhythmia, affecting approximately 1–2 per cent of the population worldwide. Those who suffer from AF have a five times higher risk of stroke. AF prevalence increases with age and it affects roughly 18 per cent of the population over 85. Consequently, as populations age, AF is becoming an increasingly significant public health issue. Over recent years there have been developments in treatment and management options, both for treating the arrhythmia directly, and assessing and reducing the risk of AF-related stroke, but there is a need to ensure that available knowledge is applied optimally to benefit patients so that opportunities to prevent AF-related stroke are not missed. The aims of this project were to assess the current landscape and explore the direction of future developments in AF management in Europe, with a focus on the use of anticoagulants in the prevention of AF-related stroke. Through rapid evidence assessment, key informant interviews, PESTLE analysis and the development

and exploration of future scenarios, we have developed sets of shorter- and longer-term recommendations for improving AF-related patient outcomes. The short-term recommendations are: i) improve AF awareness among the public and policymakers; ii) support education about AF management for healthcare professionals and patients; and iii) maintain engagement in AF-related research across the health services.

The long-term recommendations focus on the following observations: i) a longer-term view in decisions on spending for AF awareness, education, care and management is important for improving health outcomes; ii) there is a need for continued improvement in patient stratification and personalisation of care; iii) increased interaction among primary, community, secondary and tertiary care would enable knowledge sharing and more whole-patient approaches to care; and iv) developments in devices and data should be monitored to maximise benefits for AF management.

Table of contents

Preface	iii
Foreword	v
Future of Anticoagulation Initiative Steering Committee	vii
Abstract	ix
Table of contents	xi
Table of figures and tables	xii
Executive summary	xiii
Acknowledgements	xix
Abbreviations	xxi
Chapter 1: Introduction	1
1.1. Study aims and methods in brief	2
Chapter 2: Current landscape of AF and AF-related stroke prevention	5
2.1. A growing public health challenge	5
2.2. Identification of patients with AF	5
2.3. AF awareness	8
2.4. Management of AF.....	8
2.5. Developments in AF management.....	13
2.6. Current challenges.....	15
Chapter 3: Looking to the future	17
3.1. Short-term recommendations.....	18
3.2. Longer-term recommendations	22
Chapter 4: Conclusion	27
References	29

Table of figures, tables and boxes

Figure E.1:	AF prevalence in the EU (projected), showing number of individuals (top) and percentage of total population (bottom) with AF	x
Figure E.2:	Summary of research approach.....	xi
Figure 1.1:	Summary of research approach.....	3
Figure 2.1:	AF prevalence in the EU (projected), showing number of individuals (top) and percentage of total population (bottom) with AF	6
Figure 2.2:	EU Population by age group. Source: Eurostat (2014)	7
Figure 2.3:	Growth in the relative frequency of research publication records in the database Medline containing 'atrial fibrillation' in the abstract or title over the period 1960–2012	13
Table 2.1:	Guidelines review – summary	12
Box 1.1:	AF basics.....	2
Box 2.1:	Stroke and bleed risk scoring systems.....	11

Executive summary

As populations age, the prevalence of atrial fibrillation (AF), the most common heart arrhythmia, is rising. Bringing a five-fold increase in stroke risk and affecting nearly one in five people over 85, AF constitutes a rapidly growing public health burden for Europe. AF prevalence is predicted to be at least 3.3 per cent by 2050.

The Future of Anticoagulation Initiative

To address this challenge, research organisation RAND Europe has conducted a qualitative analysis of current issues in AF management in Europe and how things could change in the coming 5–10 years, focusing on the use of oral anticoagulants in six European countries (Belgium, France, Germany, Italy, Spain and the UK).¹ The study is part of the Future of Anticoagulation Initiative, a set of activities aimed at improving anticoagulation care in AF patients.

The study was guided by a steering committee (see box) and involved:

- Reviewing research literature and clinical guidelines.
- 60 interviews with doctors, patient representatives and others from the six focus countries.
- Analysis of political, economic, social, technological, legal and environmental factors that impact AF management.
- Discussion of possible future scenarios for AF management.

The Future of Anticoagulation Initiative – International Steering Committee

Representing professional and patient perspectives, the committee guided research, consideration of future scenarios and shaping of recommendations to improve the outlook for AF.

Members:

- Prof John Camm (Chair), UK
- Prof Josep Brugada, Spain
- Prof Jean-Marc Davy, France
- Prof Raffaele De Caterina, Italy
- Prof Hans-Christoph Diener, Germany
- Prof Dr Andreas Goette, Germany
- Prof Reinhold Kreutz, Germany
- Trudie Lobban MBE, UK
- Dr Jonathan Salter, UK
- Dr Andrew Walker, UK

What is AF?

- AF is the most common type of irregular heart rhythm, or arrhythmia
- In AF, contractions of different parts of the heart, the atria and ventricles, become out of sync. Blood can pool in the atria, and blood clots can form. If the clots move to the brain, they may block blood flow and cause an AF-related stroke.
- AF can be symptomless, or it can cause:
 - Palpitations
 - Breathlessness
 - Chest pain
 - Light-headedness
 - Fatigue
 - Fainting

¹ The study was carried out following rigorous research methods, but does not constitute a systematic review of evidence. It should also be noted that the findings are based in part on the views of a set of 60 interviewees and the steering committee, and these groups do not constitute a representative sample from across the six countries of focus.

AF – a growing issue

Across Europe, AF prevalence is 2 per cent. As populations age and risk factors such as diabetes and obesity become more common, prevalence is rising.

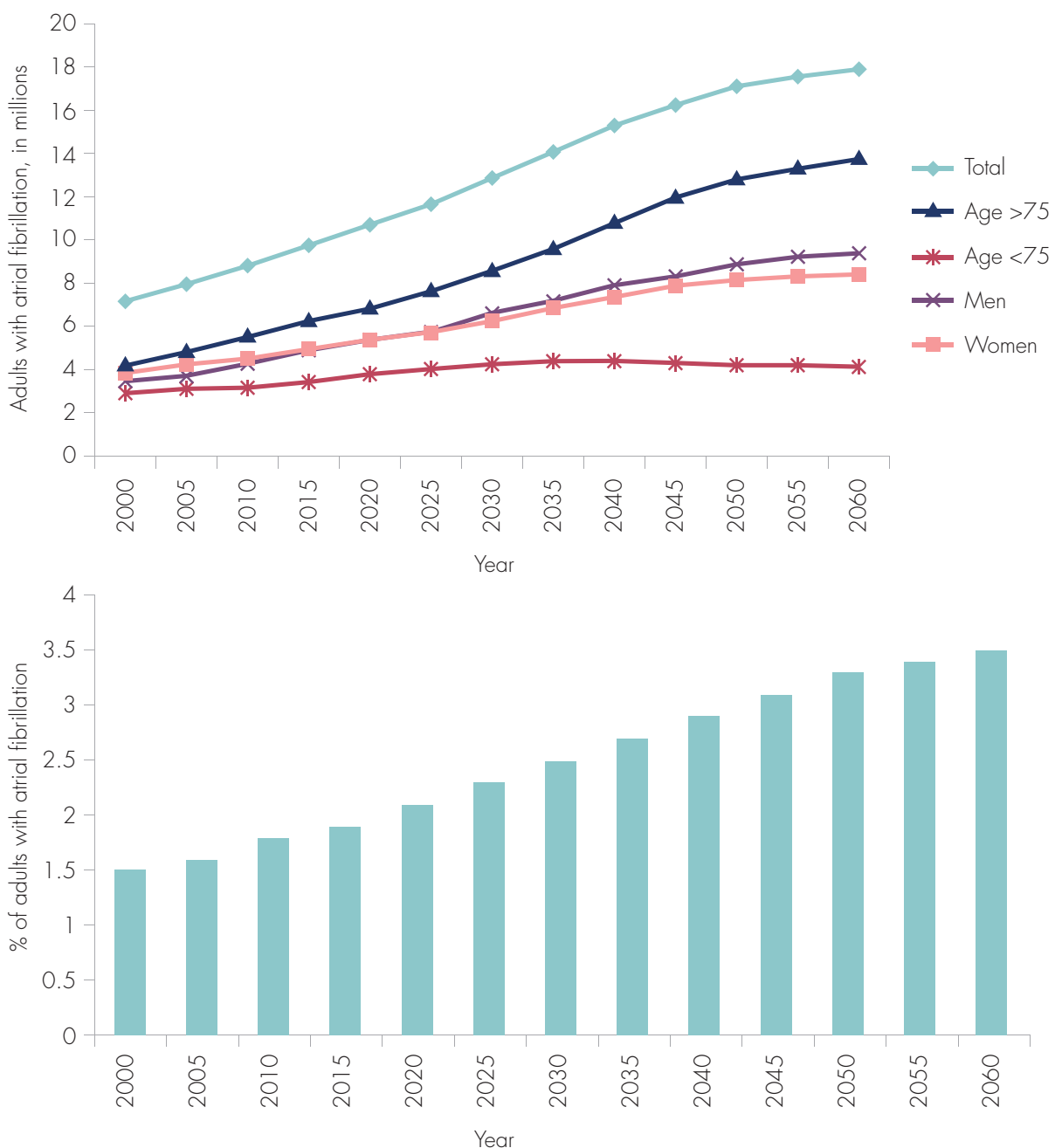
By 2050, prevalence is predicted to be more than 3 per cent.

The chance of having AF increases with age. Among people over 85, 18 per cent have AF.

AF and stroke:

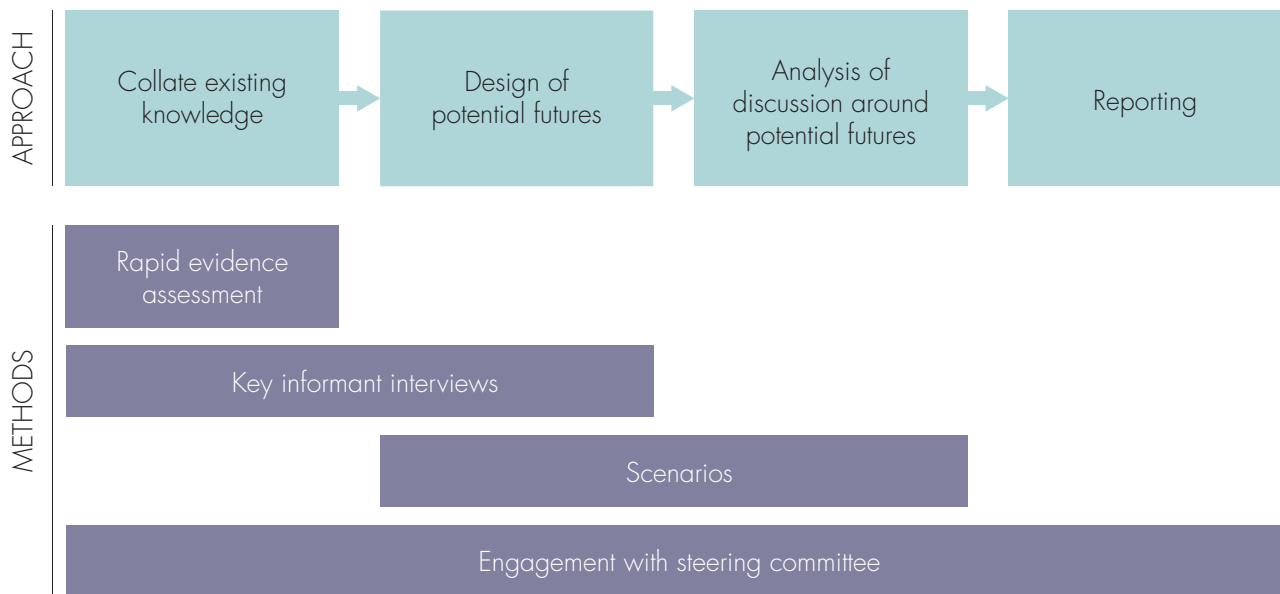
- Number of strokes linked to AF: 1 in 5
- Increase in stroke risk linked to AF: five-fold

Figure E.1: AF prevalence in the EU (projected), showing number of individuals (top) and percentage of total population (bottom) with AF



Source: Uses data from Krijthe et al. (2013) and Eurostat (2014). NB: The number of individuals under 75 years of age with AF is expected to decrease between 2040 and 2060 because the population in that age group is expected to decrease.

Figure E.2: Summary of research approach



Key findings

Detection

- The irregular heart rhythm in AF can be detected with a manual pulse check and verified with an electrocardiogram (ECG).
- AF is currently under-diagnosed. A significant proportion of AF patients are diagnosed by chance during health checks carried out for other reasons, or following the occurrence of a stroke.
- Reasons cited for under-diagnosis include the fact that AF can be asymptomatic and a lack of awareness about AF and its symptoms.
- To increase the chance of detection, the European Society of Cardiology (ESC) recommends that patients at higher risk of having AF be ‘opportunistically screened’ by receiving a pulse check when they visit their doctor.

Management

- In AF patients, therapies mainly aim to correct the irregular heart rhythm and/or reduce the risk of AF-related stroke (the latter has been the focus of this study).
- To reduce the risk of AF-related stroke, drugs that prevent blood clot formation, called oral anticoagulants (OACs), are often used.² Doctors assess whether AF patients should receive oral

anticoagulants based on their age, gender and other health and lifestyle factors.

- There are two classes of OACs now available: vitamin K antagonists (VKAs) such as warfarin, which have been the mainstay of oral anticoagulation therapy for many years, and newer non-VKA oral anticoagulants (NOACs). Uptake of NOACs varies across regions and healthcare settings for reasons including cost issues and concerns about bleed risk.
- Both the underuse and overuse of OACs relative to clinical guidelines are ongoing concerns. There is evidence that patients at high risk of stroke are often not prescribed OACs as well as evidence of over-use of OACs to patients at low risk of stroke.

Looking towards the future

As AF becomes more prevalent, it is becoming increasingly important to address the challenges that prevent optimal management of the condition. We developed a set of recommendations, based on our research assessing the current landscape, to enable the best possible outcomes to be achieved from existing knowledge about AF and technology available for AF management, and help create an environment that would support further development in AF knowledge as well as options for treatment and management, and their application. Issues that arose are broadly similar

² For patients that cannot receive oral anticoagulants, other options for AF-related stroke prevention may be antiplatelet therapy, and left atrial appendage occlusion, closure or excision (according to the latest guidance from the European Society of Cardiology).

across the six countries of focus, and so the recommendations are relevant to all.

The first set of recommendations are more immediate and relate directly to AF-specific developments, while the others relate to the implications of broader health-care trends on AF and may require consideration and action over a longer time-frame.

Immediate, AF-specific recommendations

1: Improve AF awareness among the public and policymakers

- AF awareness is low at present, among both the general public and policymakers.
- Awareness needs to focus on the concept that AF increases the risk of preventable, AF-related stroke.
- Improved awareness could eventually lead to earlier detection and intervention, resulting in prevention of AF-related strokes and lives saved.

People who have experienced atrial fibrillation (AF) sometimes describe it as frightening, taking away confidence and hard to understand and explain to others. That is why it is important for all of us to work together to help raise understanding of AF and AF-related stroke. There is information, education, support therapies and treatments available that can help patients with AF to live their lives to the full. We need the public and healthcare professionals to be AF aware and highlight the importance of knowing your pulse and discussing with your doctor. Together we can help people living with AF, as well as reduce the potential risk of AF-related stroke.

Trudie Lobban MBE, Founder & CEO of the AF Association, UK

2: Support education about AF management for HCPs and patients

- Improved education of healthcare providers (across the broad range of practitioners who are likely to encounter AF) can lead to better guideline adherence and more informed decisions about AF management.
- Improved patient education can result in better patient adherence and persistence, leading to better patient outcomes.³
- In AF, the increase in stroke risk associated with non-compliance with anticoagulation therapy is serious.

3: Maintain engagement in AF-related research across the health services

- Continued progress in AF management would benefit from a whole-system approach involving primary, secondary and tertiary care as well as policymakers.
- There is a need for research to monitor impacts of interventions in education and other aspects of AF-related healthcare delivery.
- The involvement of tertiary care is important for progress in research and technology.

Longer-term recommendations

1: A longer-term view in decisions on spending for AF awareness, education, care and management is important for improving health outcomes

- Improving management of AF-related stroke requires that decisions made across the health system that affect AF management align with current evidence on the effectiveness of therapies and other management interventions.
- Disconnected budgets within health systems can create obstacles for ensuring consistency in decisionmaking across the system. For example, up-front costs may be a more significant factor in decisions about therapies than longer-term benefits and associated cost savings.
- There is a particular need for prevention, early detection and whole-patient approaches.

2: There is a need for continued improvement in patient stratification and personalisation of care

- AF patients may present a diversity of preferences, social situations and comorbidities which can be factored in to ensure they receive appropriate AF management.
- Improved patient stratification based on biomarkers, genomic information and heart imaging can lead to more individualised care that results in more effective management and treatment of AF.

3: Increased interaction among primary, community, secondary and tertiary care would enable knowledge sharing and more whole-patient approaches to care

- Many AF patients have comorbidities, and so it

³ In addition to speaking to a doctor, patients may wish to make use of resources provided by a patient association. One example is Atrial Fibrillation Association International: www.afa-international.org

is important to support continuity of care for AF patients and not manage AF in isolation.

- In addition to GPs and specialist HCPs, a range of players can contribute to aspects of AF patient management, including pharmacies, care homes and carers, and specialist nurses.
- It is important to promote interaction and knowledge exchange across actors involved in patient care.

4: Monitor developments in devices and data to maximise benefits for AF management

- Devices are being developed that can be used in AF detection and therapy.
- Software and data sharing can facilitate collaboration among HCPs and support decisionmaking, and help to identify high-risk patients who should be screened for AF.
- Large patient datasets will be useful for research, especially into patient risk stratification and the assessment of the utility and safety of therapeutic interventions, enabling better care.

Acknowledgements

We would like to acknowledge the input of the many people who have contributed to this study. Marion Zibelli, James Snodgrass and staff from Bairds CMC coordinated and carried out interviews in France, Spain, Italy and Germany. The valuable involvement of the project Steering Committee, which provided an independent and expert perspective, helped to guide the research and helped the researchers identify important issues and areas for focus. The Committee provided critical input in refining and exploring the future scenarios, and looking at how current challenges can be addressed.

We would also like to thank the interview participants, whose contribution of expertise from a range of viewpoints formed a crucial part of this work. We are grateful to Dr Eleanor Winpenny and Dr David Kryl from

RAND Europe for their insightful suggestions and comments on drafts of this report and interim work during the quality assurance process, and we acknowledge the valuable support provided by Dr Céline Miani in defining literature search terms, as well as logistics, interview management and related assistance from Calum MacLure and Stefan Soesanto. We also thank Dr Tom Ling of RAND Europe, who attended and provided support for the first project workshop as well as providing valuable input for the preparation of the scenarios workshop. However, any errors or omissions remain the responsibility of the project team.

Finally, we wish to acknowledge the support of Ruder Finn UK, who coordinated the project and facilitated interactions between the research team, steering committee and sponsor.

Steering committee members:

Name	Professional role and affiliation
Professor John Camm (Chair)	Chair of the Future of Anticoagulation Steering Committee, Professor of Clinical Cardiology, St. George's, University of London and Professor of Cardiology, Imperial College London, UK
Professor Josep Brugada	Medical Director of the Hospital Clinic of Barcelona and Chief of Arrhythmias of the Pediatric Hospital Sant Joan de Déu, Spain
Professor Jean-Marc Davy	Professor and Chief of Cardiology Department, Montpellier University Hospital, France
Professor Raffaele De Caterina	Professor of Cardiology and Director, University Cardiology Division, G. D'Annunzio University, Italy
Professor Hans-Christoph Diener	Professor and Head of Neurology, Chair of the Department of Neurology, Director of University Hospital & Essen Headache Centre, Essen, Germany
Dr Andreas Goette	St Vincenz Hospital Paderborn and University Hospital Magdeburg, Germany and Chair of European Heart Rhythm Association Scientific Programme Committee
Professor Reinhold Kreutz	Head of Pharmacology, Institute of Clinical Pharmacology and Toxicology, Berlin, Germany
Trudie Lobban MBE	Founder and Chief Executive Officer of the AF Association, UK
Dr Jonathan Salter	General Practitioner, NHS South Worcestershire Clinical Commissioning Group, UK
Dr Andrew Walker	Health Economist, Institute of Health and Wellbeing, University of Glasgow, UK

Abbreviations

AF	Atrial fibrillation
AFA	AF Association
AFFIRM	Atrial Fibrillation Follow-up Investigation of Rhythm Management trial
AFNET	German competence network on atrial fibrillation
AkdÄ	Drug commission of the German Medical Association
ARISTOTLE	Apixaban for Reduction of Stroke and other Thromboembolic Events in atrial fibrillation trial
ATA-AF	AntiThrombotic Agents in Atrial Fibrillation study
BAFTA	Birmingham AF Treatment of the Aged study
BCFI	Belgian Centre for Pharmacotherapeutic Information (Belgisch Centrum voor Farmacotherapeutische Informatie)
BHF	British Heart Foundation
BMBF	German Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung)
CCG	Clinical commissioning group
CPRD	Clinical Practice Research Datalink
DGK	German Cardiac Society (Deutsche Gesellschaft für Kardiologie)
ECG	Electrocardiogram
ENGAGE AF-TIMI	Effective aNticoagulation with factor xA next GEneration in AF – Thrombolysis in Myocardial Infarction
ESC	European Society of Cardiology
EHRA	European Heart Rhythm Association
GARFIELD-AF	Global Anticoagulant Registry in the FIELD
GLORIA-AF	Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation
GP	General practitioner
GRASP-AF	Guidance on Risk Assessment and Stroke Prevention for Atrial Fibrillation
HAS	French National Authority for Health (Haute Autorité de Santé)
HCP	Healthcare professional

INR	International normalized ratio
KII	Key informant interview
LAA	Left atrial appendage
LAAO	Left atrial appendage occlusion
NICE	National Institute for Health and Care Excellence
NOAC	Non-VKA oral anticoagulant
OAC	Oral anticoagulant
ORBIT-AF	Outcomes Registry for Better Informed Treatment of Atrial Fibrillation
OTC	Over the counter
PESTLE	Political, economic, social, technological, legal and environmental
PREFER in AF	PREvention of thromboembolic events – European Registry in Atrial Fibrillation
QALY	Quality-adjusted life year
QOF	Quality Outcomes Framework
RACE	Rate Control versus Electrical cardioversion for persistent atrial fibrillation trial
REA	Rapid evidence assessment
RE-LY	Randomized Evaluation of Long-term anticoagulation therapy trial
ROCKET-AF	Rivaroxaban Once-daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in AF
SAFE	Stroke prevention in Atrial Fibrillation Expert study
VKA	Vitamin K antagonist

Chapter 1 Introduction

Atrial fibrillation (AF) is the most common type of cardiac arrhythmia, affecting approximately 1.5–2 per cent of the population worldwide (Camm et al. 2012). It is a significant public health issue, as having AF is associated with a five times higher risk of stroke, three times higher risk of heart failure and increased mortality (Wolf et al. 1991, Camm et al. 2012). Overall, an estimated one in five strokes can be attributed to AF, and the risk of death from stroke among patients with AF is nearly double the risk of death from stroke among patients who do not have AF (Camm et al. 2010). Prevalence increases with age, varying from less than 0.5 per cent in the population under 40, to 18 per cent in the population over 85 (Fumagalli et al. 2012). Given that the population of Europe is ageing, it is expected that the prevalence of AF will rise, possibly even doubling by 2060 (Krijthe et al. 2013).

Normally when the heart beats, electrical signals travel across the heart, causing it to contract and pump blood. When AF is present, these electrical signals travel in an abnormal way, preventing contraction of the atria and disrupting the coordination that should exist between contractions of the atria (the two upper chambers of the heart) and ventricles (the two lower chambers of the heart). As a result, blood pools in the atria. Because blood clots can form when the blood pools, AF increases the risk of ischaemic stroke, which is one of the two main types of stroke and occurs if an artery that supplies oxygen-rich blood to the brain is blocked. Strokes result from damage to brain cells.

AF symptoms include palpitations, breathlessness, chest pain, light-headedness, and fatigue, but AF can also be present without causing any of these symptoms. The cause of AF is not always known, but it can be due to

damage to the heart that occurs when an individual has high blood pressure or coronary heart disease. Other risk factors include heart failure, heart valve disease, hyperthyroidism, obstructed breathing whilst sleeping, obesity, diabetes, alcohol consumption and lung disease (NIH National Heart, Lung and Blood Institute 2015).

Clinical guidelines categorise AF into four types, depending on the frequency and duration of its occurrence (Zamani & Verdino 2014):

1. Paroxysmal atrial fibrillation is recurrent AF (two or more episodes) that terminates on its own within 7 days, usually within less than 48 hours.
2. Persistent atrial fibrillation is continuous AF lasting for more than 7 days. It stops only in response to treatment.
3. Long-standing persistent atrial fibrillation is persistent AF lasting more than one year.⁴
4. Permanent atrial fibrillation refers to AF in cases where a decision has been made to not restore normal rhythm.

AF can also be considered valvular or, more commonly, non-valvular. Valvular AF generally refers to cases where AF is related to rheumatic valvular disease (mainly mitral stenosis, the hardening and narrowing of the heart's mitral valve) or prosthetic heart valves. However, the ESC Guidelines note that there is not a uniform definition for these categories (Camm et al. 2012).

Knowledge of the risks of AF has increased over time as its prevalence has grown, and the link between AF and stroke has become clearer. There have also been developments in treatment and management options (discussed further in Chapter 2) for addressing the arrhythmia directly and assessing and reducing the risk

⁴ This third category was introduced in the 2010 European Society of Cardiologists guidelines to make it easier to identify cases where a rhythm control strategy may still be beneficial (although it may previously have been considered too late to use such an approach). However, Wasmer & Eckard (2011) have questioned the usefulness of this additional category.

Box 1.1: AF basics

What is atrial fibrillation?

AF is the most common type of heart arrhythmia (irregular heart beat). It occurs when the electrical signals that travel across the heart, causing it to contract and pump blood, do not travel normally. This prevents contraction of the atria, disrupting coordination between contractions of the atria and ventricles, resulting in blood collecting in the atria.

AF symptoms include palpitations, breathlessness, chest pain, fatigue and light-headedness, but AF can also be present without causing any of these symptoms.

AF and stroke

AF increases the risk of stroke five-fold. There are two main types of stroke, ischaemic and haemorrhagic. Ischaemic stroke, the more common type, occurs if an artery that supplies oxygen-rich blood to the brain is blocked.

The risk of stroke is higher in people who have AF because blood clots can form when blood pools in the atria, and these clots can travel to the brain, where they may block blood flow in an artery and cause a stroke.

Source: NIH National Heart, Lung and Blood Institute (2015)

of AF-related stroke. Looking towards the future, as the prevalence of AF is expected to increase dramatically, there is a need to increase awareness of the condition and enable earlier diagnosis and improve care. It is also important to ensure that available knowledge and management options are applied optimally to benefit patients across healthcare settings, so that opportunities to prevent AF-related stroke are not missed.

1.1. Study aims and methods in brief

This study aims to assess the current landscape and challenges for the management of atrial fibrillation in Europe, and explore how this landscape could develop in future. It focusses on the role of anticoagulation for the prevention of AF-related stroke in six key European countries (Belgium, France, Germany, Italy, Spain and the UK) and has two main goals:

1. Develop an evidence base on the current reality of AF-related anticoagulation management in the six focus countries.
2. Develop an understanding of actions that could be taken today to improve the future outlook for AF management.

A key outcome of this study has been the identification of areas where action can be taken to reduce the risk of AF-related stroke in AF patients, particularly through the use of anticoagulation.

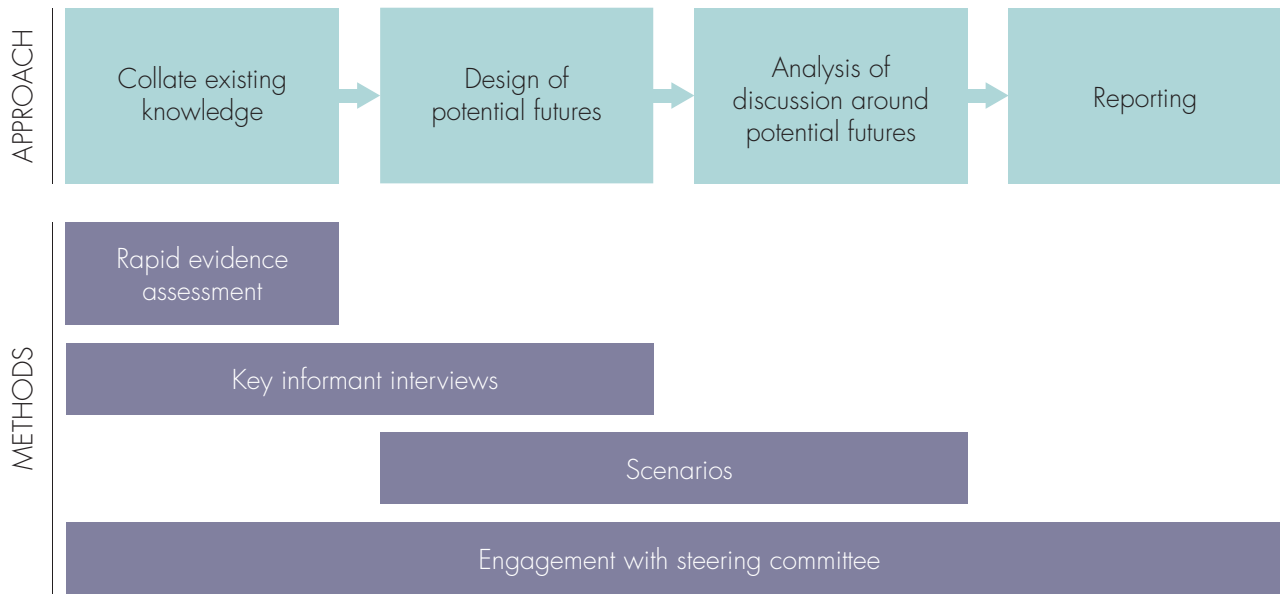
The study goals have been achieved by applying a multi-method approach to explore the current landscape and future scenarios of the management of atrial fibrillation in Europe, with a focus on anticoagulation (Figure 1.1). The study comprised an assessment of the

literature, 60 interviews with experts and the use of future scenarios as a tool for refining our understanding of the dynamics and issues that will impact the future landscape. All of these activities were carried out with feedback and input from a Steering Committee made up of 10 experts in cardiology and related areas from the six European focus countries. Findings from the desk-based tasks (the literature assessment and expert interviews) were analysed with a focus on political, economic, social, technological, legal and environmental (PESTLE) factors, in addition to population trends. This analysis was used to develop the scenarios, which were further refined in a workshop with the Steering Committee. The workshop also involved discussion of risks and opportunities associated with the scenarios under consideration, and this discussion served as the basis for developing recommendations.

While the study was carried out following rigorous research methods, it does not constitute a systematic review of evidence. Another limitation is that the findings are based in part on the views of a set of 60 interviewees and the steering committee, and these groups do not constitute a representative sample from across the six countries of focus.

The rest of this report is structured as follows: Chapter 2 provides an overview of the current landscape of the management of stroke prevention in AF patients, focusing on key issues and challenges; Chapter 3 looks to the future and presents two sets of recommendations for improving the management of AF-related stroke prevention, the first of which are more immediate and AF-specific and the second of which relate to broader and longer-term health trends; Chapter 4 presents concluding remarks. Additional detail is provided in the

Figure 1.1: Summary of research approach



report annexes, which consist of (A) a detailed description of methodology, (B) the full report from the rapid evidence assessment (REA), (C) findings from the key informant interviews (KIIs), (D) a description of the three future scenarios developed and refined in the workshop (including associated risks and opportunities), and (E) a summary table of findings from the REA and KIIs, organised by PESTLE area.

Chapter 2 Current landscape of AF and AF-related stroke prevention

2.1. A growing public health challenge

As the population ages, AF prevalence is expected to increase, with predictions indicating that it will nearly double by 2060 (Krijthe et al. 2013) (Figure 2.1). This trend will be seen across Europe, although the extent of the increase in each country will vary depending on the size of increase of the elderly population (Annex B). All of the six focus countries in this study are expecting a rise in their elderly population, with some (Germany and Spain) expecting that by 2050 nearly 40 per cent of the population may be over 60 (Figure 2.2). Meanwhile, the prevalence of AF increases with age, with the condition affecting 18 per cent of the population over 85 (Fumagalli et al. 2012). Because AF is associated with a five-fold increase in the risk of ischaemic stroke (Lotze et al. 2010), an increase in the prevalence of AF is likely to result in an increased occurrence of stroke.

The ageing population makes AF a problem for the healthcare system

Belgian cardiologist

The rise in AF prevalence may have significant economic implications. The annual cost of an average AF patient varies between countries, but has been estimated at €2,600–€3,000 (Occhetta et al. 2010). There are approximately 10 million patients with AF in the EU (see Figure 2.1), corresponding to a total cost of about €26–30bn. The primary driver for these costs is hospitalisation, which accounts for at least half of the overall cost, with other costs incurred from GP or specialist care and exams, drugs and loss of work (Occhetta et al. 2010). In terms of annual stroke costs, these range from €5,000–€30,000 per patient depending on severity and the amount of follow-up needed (Lucioni et al. 2010, Cotté et al. 2014). Fattore et al. (2012) found that AF increased the cost of hospitalisation for strokes,

but the difference was not statistically significant. An important factor in the economic burden of AF relates to detection of the condition. Currently AF is often only detected after a stroke; earlier AF detection and intervention to reduce stroke risk could reduce the occurrence of AF-related strokes and the associated economic burden.

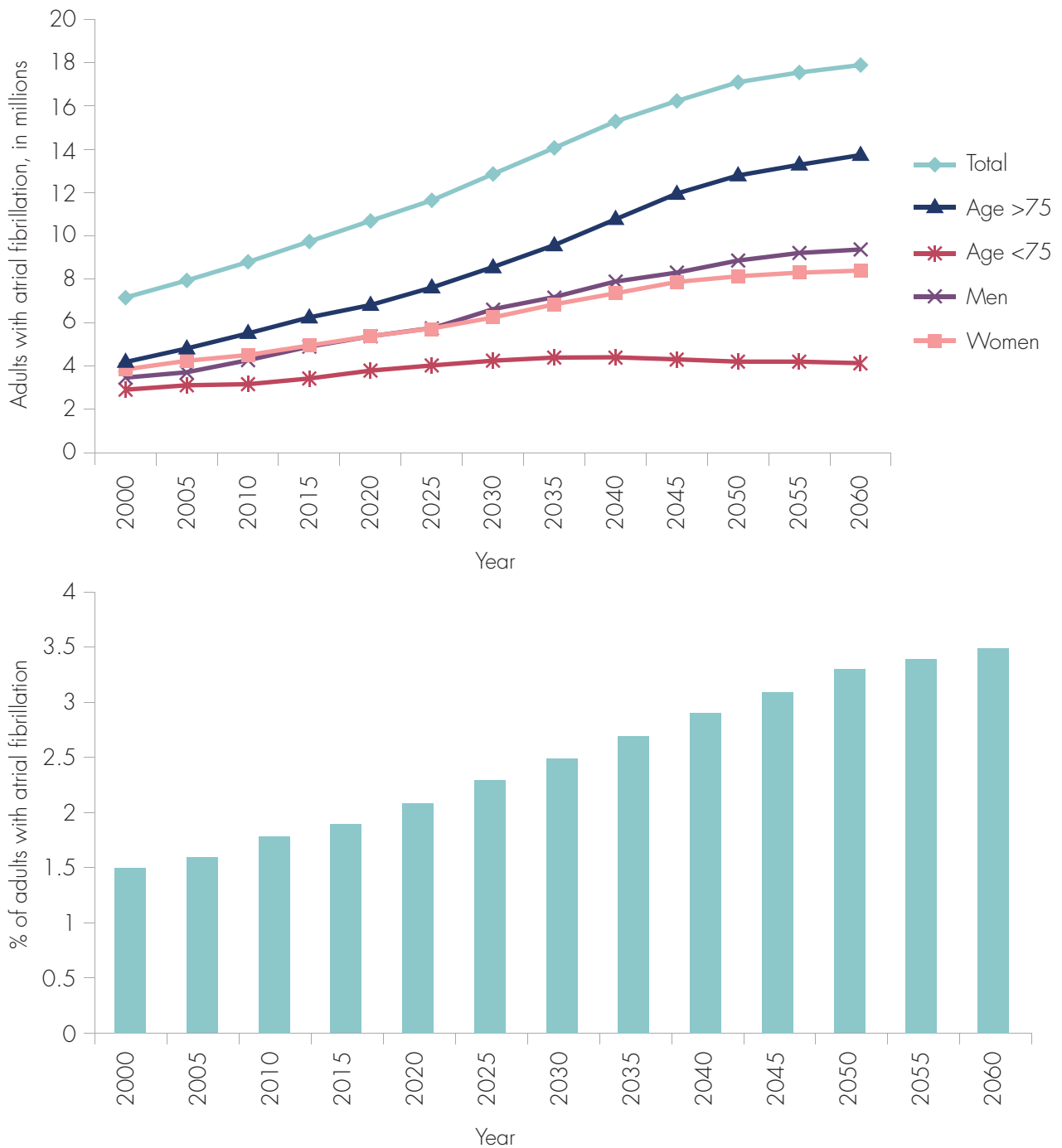
Despite these challenges, interviewees from across countries and stakeholder types reported that policy-maker awareness of AF is low, and that AF is viewed as a medical issue rather than a public health issue. While some interviewees (particularly from the UK and Belgium) said there is improvement occurring in political awareness of AF, interviewees overall felt that AF should be higher up the political agenda than it is. The main way suggested to increase political buy-in was to illustrate the economic consequences of AF and the potential to make important gains through straightforward approaches such as awareness raising, earlier detection and improved application of existing clinical guidelines. There was general hope that the growing evidence of the economic burden of AF would help focus attention on the need for consistently effective management of the condition (Wodchis et al. 2012, Stewart 2004, as cited in Wodchis et al. 2012).

Interviewees reported that, due to the current economic climate, health systems were under pressure and there were worries about how this pressure could be impacting on quality of care. For example, in Spain, Italy, Germany and the UK there were reports that treatment choices were strongly affected by available budgets and the cost of treatment; in Spain not all drugs are available in all areas, resulting in patients travelling to other regions for treatment.

2.2. Identification of patients with AF

AF is an under-diagnosed condition (Fitzmaurice et al. 2007, as cited in Snowcroft & Cowrie 2014) and

Figure 2.1: AF prevalence in the EU (projected), showing number of individuals (top) and percentage of total population (bottom) with AF

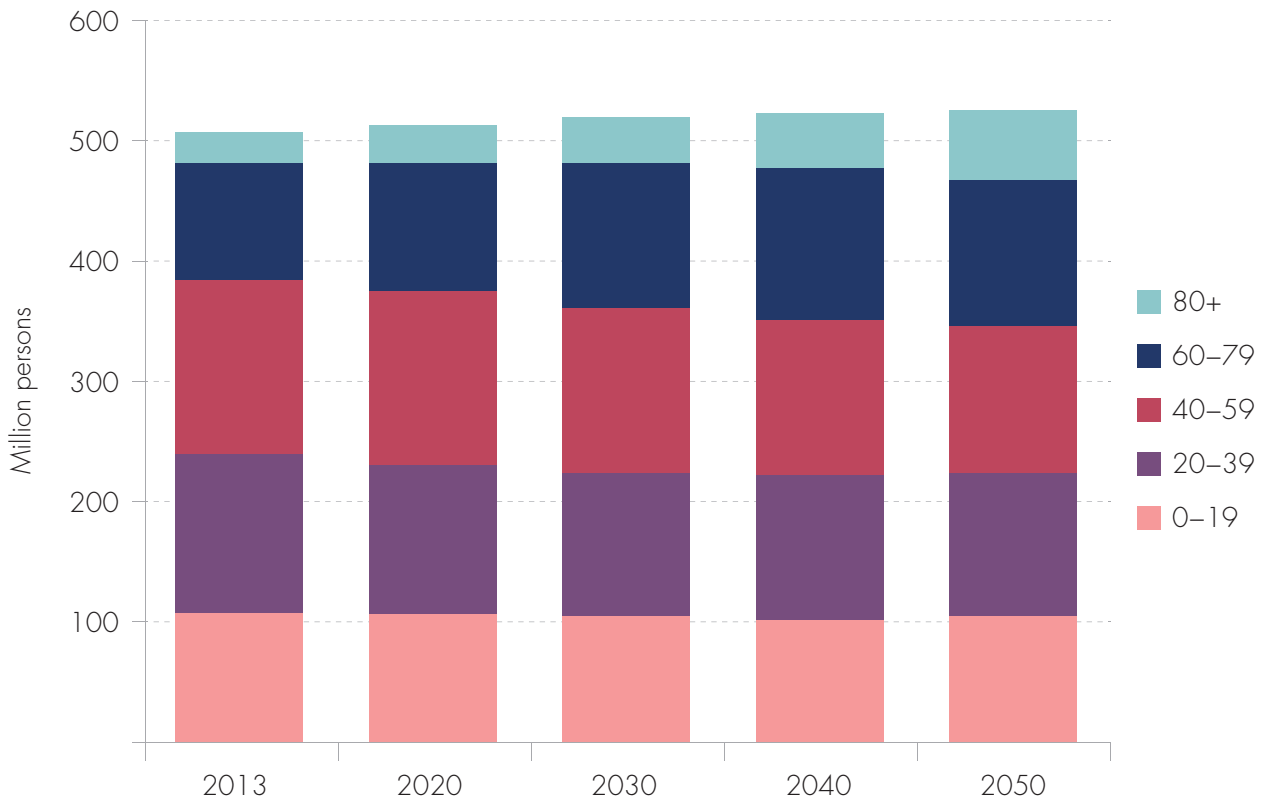


Source: Uses data from Krijthe et al. (2013) and Eurostat (2014)

a significant proportion of people with AF are diagnosed by chance during health assessments carried out for other reasons, or due to having a stroke (Sankaranarayanan et al. 2013). There may be multiple reasons for under-diagnosis, including the fact that AF can be asymptomatic and a lack of awareness about the condition and its symptoms.

AF patients can experience symptoms such as palpitations, shortness of breath, dizziness and chest pain. However, up to 40 per cent of elderly hospital patients have been found not to have any symptoms at all (Sankaranarayanan et al. 2013). These asymptomatic patients commonly do not know that they are suffering from AF, and those who do are often only diagnosed

Figure 2.2: EU Population by age group



Source: Eurostat (2014)

by chance (Sankaranarayanan et al. 2013). AF can be detected through a simple, manual pulse check followed up by heart monitoring with an electrocardiogram for verification (Camm et al. 2012).

Opportunistic screening, where patients are checked for AF when they visit doctors for other reasons, is widely supported as a means to achieve higher rates of detection to enable early intervention. Opportunistic screening for those over 65 has been recommended by the European Society of Cardiology (Camm et al. 2012) and in the UK by the Royal College of Physicians in Edinburgh (Stott et al. 2010, as cited in Lowres et al. 2013). Currently, routine mass screenings are not carried out in any countries at a national level. Interviewees in the present study generally agreed that screening should be targeted towards at-risk groups or done opportunistically. Opportunistic screening was tested against routine screening by the SAFE study, which found that opportunistic screening improved on routine practice, whereas routine screening did not (Hobbs et al. 2005). Consistent with this view, a local screening and outreach campaign in Spain was found to have had little effect on diagnosis of previously undetected AF and it was concluded that opportunistic screening is thus

a better strategy for early detection (Sanmartín et al. 2013). Interviewees emphasised that pulse checks, either done at home by the patients themselves, or in GP surgeries or pharmacies, are a simple and effective way of checking for AF and should be used more. In an initiative in Italy, 3,000 pharmacies have participated in providing free pulse checks during the week of World Stroke Day (29 October) (Camm et al. 2014b). An Australian study, SEARCH-AF, has also shown that screening in pharmacies using iPhone ECG can be both feasible and cost-effective (Lowres et al. 2014).

It would be great if facilities were available to do diagnosis in pharmacies

Italian policy influencer

Apps which allow screening for AF may make a huge impact

German cardiologist

While countries have not implemented widespread screening campaigns, there is some focus on interventions to increase diagnosis rates. In Italy, as well as self-administered pulse checks being encouraged, it is recommended that GPs carry out pulse checks, possibly

when measuring blood pressure (Battigelli et al. 2013). Some parts of the UK also promote GP pulse checks (AFA 2015b) and in France increased GP training has been introduced to improve diagnosis rates (Haute Autorité de Santé 2008).

2.3. AF awareness

A key barrier to early diagnosis is a general lack of awareness of AF among the general public. A 2014 survey found that 87 per cent of people surveyed in France didn't know what AF is; this lack of public knowledge was raised as a key problem by interviewees (Ifop/Bayer 2014). One approach highlighted by multiple interviewees as a way to increase general awareness utilises public campaigns focussing on what AF is, the risks and why treatment is needed. Campaigns of this type have been launched with support from pharmaceutical companies and charities. The French Stroke Association (AVC), in collaboration with a pharmaceutical industry sponsor, have launched an awareness campaign in France; in the UK the AF Association and Arrhythmia Alliance have run the 'Know Your Pulse' campaign since 2009⁵; and in 2014 the Italian association for the fight against AF (ALFA) has started a campaign on the importance of self-performed pulse checks.

*Awareness campaigns could be important...
Physicians generally know the risks of AF but the
population does not know what it is, nor the risks*

French cardiologist

*We absolutely need more visibility for AF and more
education on symptoms and risks*

German policy influencer

A big national public campaign is missing

UK patient representative

However, the idea that greater awareness of the importance of stroke prevention in AF, more screening and the increased availability of oral anticoagulants (used in preventing AF-related stroke and discussed below) are sufficient for reducing the incidence of AF-related stroke has been questioned by Yiin et al. (2012). This study showed that over the past two decades in a UK region, despite the introduction of these measures, the number of AF-related strokes increased substantially. It

raised the issue that improved prevention and care is required in addition to early diagnosis.

2.4. Management of AF

Approaches for caring for patients with AF consist of two main strategies: treatment of AF itself and prevention of AF-related stroke. Treatment options can be pharmacological or non-pharmacological and can focus on relieving the symptoms of AF and/or correcting the heart arrhythmia, while approaches for stroke prevention aim to reduce the risk of a patient developing stroke as a consequence of AF.

2.4.1. Treatment of AF

AF can be treated through rhythm or rate control strategies, which aim to directly address the irregular rhythm of the heartbeat in AF and/or alleviate AF symptoms. The objective of rate control is to slow heart rates that are excessively fast and reduce stress on the cardiovascular system. Rhythm control aims to restore and maintain a normal heart rhythm. Rate control strategies include AV-node blocking drugs such as digoxin, beta-blockers and calcium channel blockers, and AV node catheter ablation plus pacemaker treatment. On the other hand, rhythm control strategies include anti-arrhythmic drugs, such as amiodarone, flecainide, propafenone, and sotalol, as well as interventions such as electrical cardioversion and left atrial ablation. Anti-arrhythmic drugs generally act by interfering with the activity of ion channels, thereby disrupting the transmission of electrical signals in the heart (Zamani & Verdino 2014). Electrical cardioversion consists of mild electric shocks intended to trigger the heart to return to its normal rhythm. Studies using anti-arrhythmics and cardioversion have found a lack of benefit of rhythm control relative to rate control in the general AF population, although there may be less evidence available on impacts in younger and highly symptomatic patients (Van Gelder et al. 2002, Zamani & Verdino 2014).

Left atrial catheter ablation involves inserting soft wire electrodes through veins into the atria and isolating the area that triggers atrial fibrillation using radio-frequency (heat) or cryo (cold) energy (Marcus et al. 2013). There is limited evidence regarding the benefits of catheter ablation in terms of mortality or stroke prevention and most trials have included only patients under the age of

⁵ See the Know Your Pulse website (as of 19 March 2015): <http://www.knowyourpulse.org/>

65 (Sankaranarayanan et al. 2013). While further trials assessing catheter ablation are underway,⁶ one recent study has evaluated the safety and efficacy of catheter ablation in elderly patients (age >74) for maintaining normal sinus rhythm. It concluded that the treatment is safe and effective, reduced stroke risk and mortality, and enabled warfarin treatment to be safely stopped (Nademanee et al. 2014). Another analysis found that patients over the age of 80 received cardioversion and catheter ablation less frequently than younger patients, and the authors stressed that elderly patients should not be denied these interventions (Fumagalli et al. 2012).

Currently it is hard to tell whether ablation can impact OAC uptake

Italian cardiologist

There are not enough ablation skills in the UK... but robotics being developed could make catheter ablation easier

UK cardiologist

2.4.2. Stroke prevention

In addition to AF treatment approaches, there are strategies that cut the risk of AF-related stroke by reducing the potential for blood clots to form. These include non-pharmacological approaches such as left atrial appendage occlusion (LAAO), and pharmacological approaches consisting of anticoagulant therapy (the focus of the present study) or antiplatelet therapy.

LAAO closes off the left atrial appendage, a key site for blood clot formation in the presence of AF. However, up to one quarter of thromboembolic events take place from outside this site, so patients can still be at risk of stroke after LAA closure (Han et al. 2012). Antiplatelet therapy is relatively uncommon – some European guidelines do advise dual antiplatelet therapy (as discussed below), although this is generally only for patients who refuse anticoagulants, or for whom anticoagulants are contraindicated.

Pharmacological approaches to anticoagulation have for decades relied on vitamin K antagonists (VKAs) such as warfarin (used in the UK, Italy and Belgium), fluindione (France), phenprocoumon (Germany)

and acenocoumarol (Spain) (Kirchhof et al. 2014). However, there are drawbacks to this type of oral anticoagulant, such as increased risk of bleeding complications, the potential for drug–drug and drug–food interaction, the need for routine blood coagulation monitoring (through international normalised ratio (INR) measurement of clotting time) and the drugs' narrow therapeutic window (Han et al. 2012).

In light of the challenge of keeping VKAs within an acceptable treatment range, Cotté et al. (2014) looked at the length of time patients spend in the target range of VKAs in France, Germany, Italy and the UK. They found that more than half the patients evaluated in France (52 per cent), Germany (56 per cent) and Italy (54 per cent) had poorly controlled treatment (defined as spending less than 70 per cent of time within the target therapeutic range). In the UK this proportion was just 35 per cent, and this difference may be attributable to the use of specialised clinics for monitoring treatment, where patients were more closely followed and the dose of VKA was adapted in a more responsive manner than was the case in the other countries. Carefully controlling treatment was shown to be a significant issue; poorly controlled treatment was associated with a higher incidence of stroke. Among patients with well-controlled treatment, incidence was 0.5/100 person-years, but it was 1/100 for patients with poorly controlled treatment.

Over the past decade, a new class of oral anticoagulants, termed non-VKA oral anticoagulants (NOACs), have been introduced, and these have been shown to overcome a number of the problems listed above. In contrast to VKAs, NOACs offer 'rapid, predictable and stable anticoagulation with a fixed-dose regime, few clinically relevant drug interactions and no need for routine laboratory monitoring of anticoagulant intensity' (Kornej et al. 2013, 1). They overcome many of the problems related to VKAs, and may make long-term treatment more convenient. They are, however, contraindicated for patients with valvular AF. Three NOACs have been approved for use in Europe: apixaban and rivaroxaban (direct factor Xa inhibitors) and dabigatran (a direct thrombin inhibitor). A fourth NOAC, edoxaban (also a direct factor Xa inhibitor), has been approved in Switzerland and is currently undergoing regulatory review in the EU.

⁶ Three ongoing trials are the Catheter Ablation versus Anti-Arrhythmic Drug Therapy for AF (CABANA) Trial, Early treatment of Atrial fibrillation for Stroke prevention Trial (EAST), and the Catheter Ablation versus Standard conventional Treatment in patients with LEft ventricular dysfunction and Atrial Fibrillation (CASTLE-AF) trial (Zamani & Verdino 2014).

NOACs require fewer coagulation controls and are not affected by diet... Greater prescription of them in the future would be positive

Italian policy influencer

A number of studies have compared NOACs with VKAs and have found the former to be more effective for stroke prevention in the general population with AF. For instance, the ARISTOTLE (Apixaban for Reduction of Stroke and Other Thromboembolic Events in AF) trial randomly assigned AF patients who had at least one risk factor to apixaban or warfarin therapy. It found that apixaban was better than warfarin in terms of preventing stroke or systemic embolism, and it caused less bleeding (Granger et al. 2011). Total mortality was also reduced relative to warfarin, although there was no significant reduction in the incidence of ischaemic stroke (Dweck et al. 2012). The RE-LY (Randomized Evaluation of Long-term anticoagulation therapy) trial tested two twice-daily doses of dabigatran (150mg and 110mg) against warfarin, and the 150mg twice-daily dose was associated with a significant reduction in stroke or systemic embolism with no difference in major bleeding compared with warfarin (Connolly et al. 2009). The 110mg twice-daily dose was non-inferior to warfarin in terms of stroke and systemic embolism, and significantly reduced major bleeding rates (Dweck et al. 2012). Finally, rivaroxaban was tested against warfarin in a double-blind randomised trial, ROCKET-AF (Rivaroxaban Once-daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in AF). In comparison to ARISTOTLE and RE-LY, this trial involved patients at a higher risk of cerebro-vascular events. The ROCKET-AF trial found that rivaroxaban was non-inferior to warfarin in terms of the primary endpoint of stroke and systemic embolism. As a result of these trials, apixaban, rivaroxaban and dabigatran are recommended in updated European guidelines for AF (see below). Edoxaban was tested in the ENGAGE in AF-TIMI 48 (Effective aNticoaGulation with factor xA next GEneration in AF – Thrombolysis in Myocardial Infarction 48) trial and found to be both non-inferior to warfarin in terms of stroke and systemic embolism prevention, and associated with lower bleeding and death risks from cardiovascular causes (Giugliano et al. 2013).

However, there are still a number of issues raised in the literature regarding the use of anticoagulants and NOACs in particular. One concern is the fact that there is no established antidote for NOACs (Dweck et al. 2012, Sardar et al. 2014, Zarraga & Kron 2013). VKAs can be reversed with vitamin K (although this may take 24 hours or more), but no such direct antidote exists for NOACs – although a number are being investigated. While the lack of an antidote was raised as a concern by interviewees in this study, many felt that it was more of an excuse not to give NOACs. They mentioned that vitamin K is not an ideal antidote for VKAs due to the long time that may be required for it to reverse the anticoagulation effect of VKAs. Moreover, NOACs have shorter half-lives than VKAs, which means that missed doses of NOACs are more likely to result in clinical consequences than in the case of VKAs (Sardar et al. 2014, Zarraga & Kron 2013). On the other hand, shorter half-lives may have advantages in relation to elective surgery because they allow patients to stop treatment closer to the date of an operation (Dweck et al. 2012).

Another significant issue is that NOACs cost more than VKAs, but that higher cost may be offset by the savings made by not needing to do the frequent coagulation monitoring required with VKAs (Deedwania 2013). As discussed below in Chapter 3, it is difficult to obtain a clear picture of the perceived and real impacts of costs in choosing between VKAs and NOACs for oral anticoagulation.

2.4.3. Clinical guidelines

We reviewed clinical guidelines for AF management from the focus countries, focussing on prevention of AF-related stroke.⁷ Our review concentrated on recommendations for when and how to use stroke prevention therapies. The main points are presented in Table 2.1, covering the use of tools to assess stroke and bleeding risks, the use of antiplatelet therapy, the conditions for using VKAs and NOACs, and whether use of LAAO is recommended. The guidelines are broadly aligned in areas such as how to assess stroke and bleeding risk (two key risks that need to be taken into consideration in prescribing anticoagulation therapy), but key differences exist regarding the use of aspirin, oral anticoagulants and LAAO.

All guidelines suggest using either CHADS₂ or CHA₂DS₂-VASc to assess stroke risk, and HAS-BLED

⁷ France, Italy, Spain and the UK have national guidelines, while Germany mainly uses the European Society of Cardiology guidelines.

Box 2.1: Stroke and bleed risk scoring systems

CHA₂DS₂-VASc scores for risk stratification in atrial fibrillation	HAS-BLED scores for risk stratification in atrial fibrillation
Congestive heart failure (1 point)	<i>Hypertension (1 point)</i>
Hypertension (1 point)	<i>Abnormal liver or renal function (1 point each)</i>
Age ≥ 75 (2 points)	<i>Stroke (1 point)</i>
Diabetes (1 point)	<i>Bleeding (1 point)</i>
Stroke or transient ischaemic attack (2 points)	<i>Labile INR (1 point)</i>
Vascular disease (1 point)	<i>Elderly – greater than 65 years (1 point)</i>
Age 65–75 (1 point)	<i>Drugs or alcohol (1 point each)</i>
Sex category (1 point for female)	

to assess bleeding risk (Table 2.1). The CHADS₂ scoring system calculates stroke risk on the basis of five factors: congestive heart failure, hypertension, diabetes mellitus, stroke and age of 75 years or above; the CHA₂DS₂-VASc includes these factors as well as vascular disease, age 65–74 years, female sex and an increased weighting on age 75 years or above (Odum et al. 2012). The ESC guidelines, along with all of the country guidelines reviewed, recommend the use of the HAS-BLED system to assess bleeding risk. This calculates bleed risk on the basis of hypertension, abnormal liver or renal function, a history of stroke, bleeding or unstable INR, age (over 65 years) and drug or alcohol use.

The NOACs that have been approved for use in Europe are recommended over VKAs for non-valvular AF by the ESC, while guidelines in Italy and the UK recommend both VKAs or NOACs depending on patient needs. Guidelines from France and Spain recommend VKAs as the first choice for anticoagulation in non-valvular AF.⁸ Only the French health authority has ranked the NOACs by order of preference, with apixaban being the first, followed by rivaroxaban and then dabigatran. All guidelines reviewed recommend VKAs for patients with valvular AF and contraindications preventing the use of NOACs. Guidelines from the ESC and France recommend antiplatelet treatment, often given as aspirin or aspirin coupled with clopidogrel, for low-risk patients who refuse oral anticoagulants (i.e. VKAs or NOACs).

These guidelines have undergone recent updates to take into account regulatory body approvals of new drugs and new information becoming available through the publication of results from major clinical trials of NOACs: the RE-LY (dabigatran), ROCKET-AF (rivaroxaban), AVERROES (apixaban versus aspirin) and ARISTOTLE (apixaban) trials (Camm et al. 2012).

The ESC guidelines were updated in 2012, just two years after previously being issued (Camm et al. 2010), reflecting rapid changes in options for oral anticoagulation therapy as well as emerging evidence on the use of LAAO and anti-arrhythmic drugs. In the 2010 ESC guidelines, the recommendation was that the NOAC dabigatran could be considered as an alternative to VKA therapy (Camm et al. 2010). However, the 2012 guidelines state that NOACs are considered preferable to VKAs in most patients with non-valvular AF when used as tested in clinical trials. The 2012 ESC guidelines state: ‘The NOACs so far tested in clinical trials have all shown non-inferiority compared with VKAs, with better safety, consistently limiting the number of intracranial haemorrhages’ (p.2,726). They do issue this caution, however: ‘Since there is still limited experience with these agents, strict adherence to approved indications and careful post-marketing surveillance are strongly recommended’ (p.2,726). The 2012 guidelines also note that there is insufficient evidence to recommend one NOAC over another.

⁸ This situation reflects a recent change in French guidance based on a re-evaluation of data. France’s HAS had previously recommended NOACs as the first choice for anticoagulation in AF (HAS 2014a). It should be noted that, at time of writing, this change in position constituted a scientific opinion that had not yet come into force through a change in regulation.

Table 2.1: Guidelines review – summary

Recommended practice	ESC	France	Italy	Spain	UK
Use of CHA ₂ DS ₂ -VASc framework	Yes if patients have CHADS ₂ score 0–1	Yes	Yes	Yes	Yes
Use of HAS-BLED framework	Yes	Yes	Yes	Yes	Yes
Drug class recommended as first choice of treatment for non-valvular AF	NOACs	VKAs	NOACs or VKAs	VKAs	NOACs or VKAs
Drug class recommended as first choice for valvular AF	VKAs	VKAs	VKAs	VKAs	VKAs
Antiplatelet therapy offered for low-risk patients	Yes if OAC refused	Yes if OAC refused or contraindicated	No	Not referenced	No
Left atrial appendage occlusion recommended	Yes if OAC contraindicated	No	Yes if OAC contraindicated	No	Yes if OAC contraindicated

Guidelines adherence

Guidelines give a good indication of how to use new treatments, but they don't reflect practical cases properly

Spanish cardiologist

Guidelines are not well followed as they are long and dense and there are so many of them in primary care

UK cardiologist

Many interviewees noted that guidelines are not well followed in practice; this affects both whether anticoagulation is given at all, and whether NOACs or VKAs are prescribed. Focussing first on whether anticoagulants are prescribed appropriately, studies show that anticoagulation therapy tends to be under-prescribed (e.g. Lopes et al. 2010, Dores et al. 2011, Gorin et al. 2011, Diez-Manglano et al. 2014), although the degree of under-prescription is going down (Kirchhof et al. 2014). Studies have shown that as well as high-risk patients being under-prescribed anticoagulation, there is over-prescription of anticoagulation to low-risk patients (OSMED 2008, d'Angelo et al. 2013, Berrisso et al. 2014).

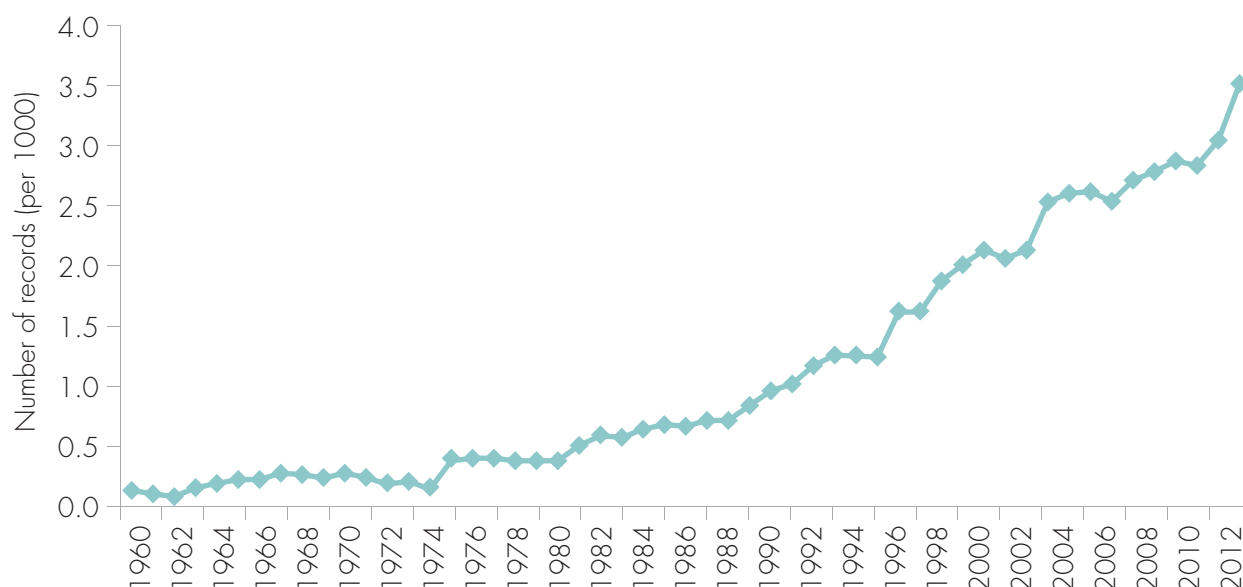
A number of causes have been suggested for the under-prescription of anticoagulants, including the narrow therapeutic range of VKAs and the inconvenience of monitoring, patient preference and compliance, a fear of bleeding and experience of bleeding events, and a large number of contraindications (Ogilvie et al. 2010). Interviewees felt that anticoagulants were

often not prescribed to high-risk patients due to conservatism. A study by O'Brien et al. (2014) supports this view. The authors found that anticoagulation decisions are more likely to be driven by perceived risks than by perceived benefits, and noted that one challenge is that risk factors for bleeding and stroke overlap.

Age has been related to reduced guideline adherence (Pugh 2011, Diez-Manglano 2014), and advanced age was mentioned by interviewees as a reason that GPs may be reluctant to provide anticoagulants, due to worries about increased bleeding risks and possible difficulty explaining the need for and ensuring compliance. Advanced age is often associated with polypharmacy, cognitive impairment and risk of falls, which may explain reduced guideline adherence (Pugh et al. 2011). Moreover, there is generally less evidence about AF treatment options for elderly or very frail patients as they may be underrepresented in clinical trials (Fumagalli et al. 2012).

A key reason for lack of adherence to guidelines may be that they do not necessarily capture complex, real-life situations. Related to this, patients outside of clinical trials tend to have a higher bleeding risk than those included in trials, which can reduce the applicability, or perceived applicability, of trial results (van Walraven et al. 2009). A number of strategies for making guidelines more useful were reported, including the EHRA Practical Guide on the use of NOACs (Heidbuchel et al. 2013), consensus documents in France that supplement guidelines with case studies, and A4 sheets detailing the salient guidelines in the UK.

Figure 2.3: Growth in the relative frequency of research publication records in the database Medline containing 'atrial fibrillation' in the abstract or title over the period 1960–2012



Source: NCBI (2015). Note that complete data were only available through 2012.

Interviewees also discussed whether NOACs were prescribed preferentially to VKAs in their countries, if that was what was suggested by the guidelines. It was suggested that the use of VKAs (or even aspirin) instead of NOACs was often related to cost; however, no interviewees felt that this was the only factor involved in the low uptake of NOACs. Other possible factors include the lack of real-life data on the use of NOACs, fear of bleeding risks, particularly as there is no antidote, lack of knowledge about AF and conservatism. While cost was seen as an important issue, it was not seen to directly affect the prescribing doctor in France and Belgium, as NOACs are fully reimbursed in these countries. In Spain, Italy, the UK and Germany the burden of cost is on GPs, and drug cost was seen as a factor in treatment decisions. In many countries the initial diagnosis and prescription is performed by a specialist, with follow-up treatment provided by GPs. There were reports in the UK and Germany of GPs changing the drugs from NOACs (prescribed by a specialist) to VKAs due to cost.

2.5. Developments in AF management

AF treatment and stroke prevention has developed rapidly in the last 10 years, and interviewees felt that it was likely that developments will continue. Within the medical research literature, there has been a substantial increase in the relative number of publications on atrial fibrillation over the past few decades, indicating an increase in research interest and activity in the topic (Figure 2.3). For every 1,000 records in the medical research database Medline in 2012, there are 3.5 with 'atrial fibrillation' in the abstract or title, compared with 2.2 in 2002 and 1.2 in 1992. The numbers of articles on AF are presented relative to the total number of records in Medline to account for increases in total numbers of publications over time. Among records referring to 'atrial fibrillation', there has also been an increase in the number referring to 'anticoagulation'. In 2014, a total of 15 per cent of 'atrial fibrillation' records refer to 'anticoagulation', up from 10 per cent in 2009 and 5 per cent or less prior to 1992.

In addition to research publications, around 55 clinical trials related to AF and anticoagulation are currently open and listed on the US National Institutes of Health clinical trials database, ClinicalTrials.gov.⁹ A number

⁹ Information accessed at ClinicalTrials.gov, using the general terms 'anticoagulation' and 'atrial fibrillation' as the condition search terms (accessed 15 March 2015).

of these focus on aspects of NOAC use and comparing NOACs with other drugs (VKAs and aspirin), while others explore the use of electronic devices for ECG monitoring or anticoagulation self-monitoring. Ongoing studies also focus on biomarkers and understanding variations in AF patients' symptoms and responses to therapies. Examples include a Swedish study of reasons for variations in quality of life and symptom burden for AF patients,¹⁰ a US study on genomic risk markers for AF following extended heart rhythm monitoring,¹¹ and a Dutch study on identifying a risk profile to guide AF therapy.¹²

Telemedicine will help in monitoring high risk patients with real-time ECG transmission

Belgian cardiologist

AF management may move towards more personalised approaches, using imaging techniques or genetic risk factors (Shenasa et al. 2012, Leong et al. 2012, Kirchhof et al. 2013, Helms et al. 2014), and which could focus more on prevention and early intervention (Shenasa et al. 2012, Woods and Olgin 2014). Approaches could also involve technological developments related to managing the condition, such as smartphone apps for self-monitoring INR. Shenasa et al. (2012) state that in future, AF management is likely to be more based on aetiology, with a particular focus on imaging techniques that will aid in prescription decisions for anticoagulation. Therefore, instead of relying on stroke and bleed risk frameworks, decisions could be based on clinical factors such as the emptying velocity of the left atrial appendage (Leong et al. 2012). This may lead to changes in the extent to which anticoagulation therapies are used. Similarly, personalised approaches may be developed through an understanding of genetic risk factors, although more needs to be done to understand these factors and how they could affect AF management (Helms et al. 2014).

Another way approaches to AF management might change is through a greater focus on AF prevention and early intervention. Shenasa et al. (2012) state that new trials should be designed to look at early intervention approaches, but they acknowledge that it may not be feasible or justified to put individuals on

pharmacological therapy at an early age. Woods & Olgin (2014) also note that more targeted approaches are needed to improve therapy of AF. The future may also hold developments in novel diagnostic techniques for AF. Biomarkers have the potential to identify underlying substrates of AF and predict AF progression, although there are currently no biomarkers to predict AF occurrence or guide treatment (Woods & Olgin 2014). AF prevention could also be achieved with management of risk factors through lifestyle changes such as alcohol avoidance and weight reduction.

Another possibility is that more effective interventions for reversing AF will be developed. One potentially promising candidate in this area is catheter ablation, currently an unusual treatment but one that is becoming more common in some areas. In Belgium, ablation is reimbursed for patients suffering from paroxysmal AF with minimal structural heart disease (and where it is judged that anti-arrhythmic and rate-control drugs have not controlled their symptoms sufficiently). The number of catheter ablation procedures performed there increased from 993 in 2008 to 2,064 in 2010; however, a comprehensive Health Technology Assessment (HTA) warned against possible over-use of the technique and noted that its cost-effectiveness was not clear (Van Brabant 2012a). A number of studies have tested cost-effectiveness of catheter ablation and found that it can be cost-effective for some segments of the population (Chan et al. 2006, McKenna et al. 2008, Reynolds et al. 2009, Reynolds et al. 2014). In the UK, NICE guidelines suggest ablation should be offered if drug treatment has failed to control symptoms for AF, or if drug treatment is unsuitable. Interviewees reported that ablation is usually reserved for younger patients experiencing severe symptoms and said it can be unclear which patients it is appropriate for, and whether anticoagulants are still needed after ablation. Some interviewees expressed hopes that, as the technology develops, it will become a cure for at least some segments of the AF population.

Development of NOACs and their antidotes continues, with a fourth NOAC expected to be introduced in the near future as well as antidotes. They have been shown to be cost-effective in comparison to VKAs (Harrington et al. 2013) and to be more appealing to patients

¹⁰ Official title: Observational Study of the Variation in Health-related Quality of Life and Symptom Burden in Patients Accepted for Catheter Ablation of Atrial Fibrillation in Relation to Biomarkers, Intracardiac Pressures and Echocardiography.

¹¹ Official title: THE GIRAFFE Study: Genomic Risk Markers for Atrial Fibrillation Following Extended Cardiac Rhythm Monitoring.

¹² Official title: Identification of a Risk Profile to Guide Atrial Fibrillation Therapy.

(Gonzalez-Quesada & Giuliano, 2014). However, as already discussed, some healthcare professionals remain hesitant about prescribing them. Interviewees expected that developments such as real-world data on safety and cost-effectiveness, an antidote, and options for using NOACs on patients with renal dysfunction or valvular AF would increase NOAC uptake.

There is a need for training and diagnosis in non-hospital facilities, with reporting via telemedicine
Italian cardiologist

Strategies for treating and managing AF have developed significantly over the last decade and HCPs are becoming increasingly aware of these developments. One key worry identified by interviewees in this study, and which was backed up by findings from Lotze et al. (2010), is that HCPs, and GPs in particular, need to be better informed about AF, particularly now that the range of options for stroke prevention has broadened with the introduction of NOACs. There was a general view that this situation is slowly improving. There are multiple examples of initiatives in place for improving HCP education, often with support from the pharmaceutical industry. For instance, interviewees in Belgium reported that cardiologists organise GP training and are developing an expertise centre where GPs can consult specialists. In France and Germany pharmaceutical companies are organising NOAC training for GPs and nurses (Davy 2014). It is expected that improved education will lead to better guideline adherence and improved treatment.

Improved patient education, given by more informed HCPs, was also desired by interviewees, particularly since it may improve compliance. Non-compliance is a general problem that is not specific to AF, but still highly relevant for AF given the need to prevent AF-related stroke. One factor affecting compliance for anticoagulants is the effect they have on quality of life (Ingelgard et al. 2006, as cited in Fay & Montana 2012). This effect is perceived as being greater for VKAs than NOACs as the former require frequent monitoring and clinic visits (Kneeland & Fang 2010). Other factors that may affect compliance are the inconvenience of taking medication, anxiety related to side-effects, anxiety about potential drug-interaction, the

impact on physical activities, and dietary and alcohol restriction (Kneeland & Fang 2010). While NOACs are a reduced burden on the patient, some interviewees expressed concern that monitoring of VKAs actually improves compliance, so compliance for NOACs may be lower. Although it was unclear whether NOACs or VKAs are better for compliance, interviewees agreed that if patients were better educated, and more effort was made to ensure they understand the reasons why they need to take their drugs, then compliance would improve. Improved patient education may also lead to patients being more empowered about their condition and care. Patient preference and empowerment was mentioned as a positive development by interviewees from the UK, Belgian, Spain, Germany and Belgium, provided that patients were well informed and doctors still held the final decisions. However, several interviewees from France expressed the view that treatment decisions were the role of doctors and that patients should have little influence on them.

2.6. Current challenges

In many respects, the challenges that arise in the context of AF are similar to those that arise for a range of chronic conditions. There is a need to promote general cardiovascular health and to increase awareness and education about the condition. In addition, as new therapies have become available (for example NOACs in the case of AF), there has been uneven adoption across different parts of the health system, due in part to a lack of familiarity with the therapies and their effects on different types of patients. Finally, many patients with AF are elderly and have a multiple health issues, which can create challenges for AF management.

There are also several key issues relevant to the AF context that set AF apart from some other chronic conditions. As many AF patients are asymptomatic, they do not know that they have the condition, which means that many go undiagnosed until they have a stroke or symptoms develop. In addition, the objective of therapy in asymptomatic patients with AF is to minimise stroke risk rather than to treat the condition itself or its symptoms. This means that anticoagulation drugs that patients are put on, such as VKAs or NOACs, do not make them feel better and, as a result, patients may be less likely to comply with drug regimes.

Chapter 3 Looking to the future

Through our research on the current landscape of AF management in Europe, with a particular focus on the role and use of anticoagulation, we have identified several challenges that prevent optimal outcomes from being achieved in terms of AF patient care and the general management of AF within health systems (as discussed in the previous chapter). Our findings also highlight the need for improvement in multiple aspects of AF management, from detection to care, and the need for better alignment of current practice with recommendations in clinical guidelines. These challenges relate to AF-specific awareness and education as well as wider trends in healthcare that will be relevant to the AF context. One theme that runs across multiple recommendations is the need to ensure that there is continued emphasis on cardiovascular health more generally. Another is the need for coordination and integrated care across health systems and stakeholders.

As we look to the future, addressing these challenges is particularly important given that, as European populations age, AF will become more prevalent, bringing an increased public health burden through AF-related stroke and other complications. To systematically explore the implications of developments in approaches to managing AF, focussing on the prevention of AF-related stroke, we used future scenarios as a tool. The scenarios, described in Annex D, build upon findings from interviews and literature about the current landscape and changes that could occur. They are logical and consistent pictures of the future that enable us to explore the implications of decisions made today.

The scenarios were presented in a workshop with the project Steering Committee, who discussed the key developments that would need to occur for a scenario to be reached, and the risks and opportunities associated with each scenario. On the basis of the output from this workshop as well as other findings,

we developed a set of recommendations for the more immediate future and the longer term (for detailed methods, see Annex A).

The aim of the recommendations is to focus attention on issues that are particularly important in relation to strategies for dealing with the challenges posed by AF. Actions aligned with these recommendations should enable the best possible outcomes to be achieved from existing knowledge about AF and existing technology available for AF management. These recommendations, which have relevance for and could involve actions from a range of stakeholders, should also help to create an environment that will support further development in AF knowledge, options for treatment and management, and the application of those further developments to benefit patients.

In the next two subsections, we present recommendations for the shorter and longer terms. The shorter-term set are more immediate and relate directly to AF-specific developments, while the longer-term set relate to the implications of broader healthcare trends on AF and may require consideration and action over a greater time-frame. Each recommendation is accompanied by an explanation of why it is important, potential implications or associated challenges, country-specific considerations (where relevant), and potential actions that can be taken to implement the recommendation. As the core focus of this research was the role of anticoagulation therapy for stroke prevention in AF, the recommendations focus primarily on issues related to the use of oral anticoagulants in AF patients.

3.1. Short-term recommendations

3.1.1. Short-term recommendation 1: Improve AF awareness among the public and policymakers

Key points

- AF awareness is low at present, among both the general public and policymakers.
- Awareness needs to focus on the concept that AF increases the risk of preventable, AF-related stroke.
- Improved awareness could eventually lead to earlier detection and intervention, resulting in prevention of AF-related strokes and lives saved.

Rationale

According to a range of stakeholders across all the countries of focus in this study, a fundamental barrier to progress in the management of AF, at the levels of both individual patients and the wider health system, is a lack of awareness about the condition. A recent survey in France found that only 13 per cent of people know what AF is and 60 per cent had never heard of it (Ifop/Bayer 2014). In contrast to AF, health conditions such as diabetes and cancer have a much higher public profile. In the case of AF, the lack of awareness was seen to be present among both policymakers and the general public, and it was generally accepted by interviewees and workshop participants that an increase in public awareness of AF would lead to an increase in awareness among policymakers.

It was also generally understood by study participants that increased awareness would be a key step for enabling change, with multiple benefits expected to arise. In particular, increased awareness could contribute to earlier detection of AF because patients and healthcare professionals would be more aware of AF symptoms and more alert to the possibility that AF can be present even in the absence of clear symptoms. Earlier detection could in turn enable earlier intervention and prevention of AF-related strokes, reducing the strain on health system resources that would be associated with caring for patients who suffer stroke. Increased awareness could also lead to increased knowledge of AF among patient families and carers, and increase their level of involvement with AF-related care.

Study participants stressed that there is a need for increased awareness focussing especially on the link

between AF and AF-related stroke: the fact that AF is both a marker of risk and a mechanism for AF-related stroke, and that these strokes are preventable. The link between AF and general cardiovascular health – conditions associated with AF include hypertension, congestive heart failure and coronary disease – was also seen as an area where greater awareness is needed.

Emphasising the link between AF and AF-related stroke was seen as a valuable approach because it would encourage interest from policymakers and the public while transmitting an important health message. For the policy context especially, workshop participants stressed that it is important to recognise the link between AF and the costs associated with AF-related stroke, as well as the idea that AF-related stroke is largely preventable. Investment in actions to reduce the risk of AF-related stroke can result in cost savings when fewer strokes occur, and a reduction in wider economic impacts such as lost working days due to AF-related stroke. To encourage policy change, quantitative evidence on factors influencing AF management decisions made by HCPs and the consequences of changing behaviours can also be effective.

Examples of existing figures that could be highlighted include the following:

- It has been estimated that around one in five strokes are attributed to AF overall, and one in three strokes in people over the age of 80 are attributed to AF (Wolf et al. 1991).
- Anticoagulants have been shown to reduce the risk of AF-related stroke. The VKA warfarin has been shown to reduce stroke by up to 64 per cent (Hart et al. 2007) and results from large-scale clinical trials of NOACs indicate that NOACs are not inferior to VKAs (Camm et al. 2012).

Challenges

Although increasing awareness of AF was generally seen as a desirable change that would be likely to result in benefits for AF patients and improvements in how AF is dealt with in the health system, it was also associated with potential challenges. For instance, workshop participants noted that there is a risk that increased awareness can lead to increased concern among patients. It may cause unnecessary anxiety among those who are healthy, leading to more primary care visits by the 'worried well'. In addition, more widespread detection of AF would increase the number of patients requiring management of their AF, increasing pressure on the health system. Finally, it may be more challenging to

ensure that the awareness message reaches AF patients who feel well and are thus unlikely to suspect they may have a chronic condition.

One practical challenge relates to securing funding to pay for awareness campaigns. In some countries it may be more appropriate to encourage engagement from government officials but in others insurance providers may have a greater interest in supporting actions for improving public health. While public spending may be under pressure, there is potential to build on support from pharmaceutical companies that are currently marketing NOACs and therefore have an interest in promoting awareness. However, it is also important to keep in mind that the success of a campaign can depend on the source of information, with public campaigns considered more likely to gain trust from patients, HCPs and the media than those sponsored by companies. Some study participants expressed the view that over-involvement from private companies may create suspicion about or resistance to a health message being put forward, while others suggested that alignment of public health interests with industry interests is an opportunity that should be leveraged to improve public health.

Implementing the recommendation

There are already some schemes aimed at raising awareness or providing general information about AF and its detection taking place in each of the six focus countries. These target a range of actors, from policymakers and the public to healthcare practitioners, and have been supported by various organisations, including patient associations and the pharmaceutical industry. For example, in France in 2014, the French Stroke Association (AVC) launched an AF Awareness campaign, ‘One danger can hide another’, in collaboration with other health organisations and a pharmaceutical industry sponsor.¹³ The campaign focusses on the message that AF results in a five-fold increase in the risk of stroke.

Other AF awareness campaigns have included a focus on pulse checks. In Belgium, the Belgian Heart Rhythm Association, with support from the pharmaceutical industry, organises an annual heart rhythm week that involves free screenings for AF and distribution of information about self-administered pulse checks. In the UK, two charities (Arrhythmia Alliance and the AF Association) have increased awareness of AF among

politicians by organising free pulse checks in the British Parliament as part of World Heart Rhythm Week, a campaign organised by the Arrhythmia Alliance. The campaign also provided pulse checks and information in pharmacies in the UK. While some study participants saw a need to run awareness campaigns focussed specifically on AF, another way to increase AF awareness is to include AF in existing campaigns, such as stroke awareness.

GPs can also play a role in both raising awareness and screening, although variability in the frequency of consultations with doctors across countries can impact on the effectiveness of this approach¹⁴ and it is important to ensure that people who do not tend to visit doctors can still be reached. Other actors that could be involved in awareness-raising and screening (e.g. pulse checks) include pharmacies, care homes and the media. One approach to awareness-raising and screening that has been highlighted in the UK is an initiative targeting emergency services. It increased awareness among ambulance clinicians about AF-related stroke risk and introduced AF screening in calls to emergency services, providing callers who are found to have AF with an information leaflet (AFA 2015b).

3.1.2. Short-term recommendation 2: Support education about AF management for HCPs and patients

Key points

- Improved education of healthcare providers (across the broad range of practitioners who are likely to encounter AF) can lead to better guidelines adherence and more informed decisions about AF management.
- Improved patient education can result in better patient compliance, leading to better patient outcomes.
- In AF, the increase in stroke risk associated with non-compliance with anticoagulation therapy is serious.

Rationale

Complementing the need for increased awareness of AF among the public and policymakers is the need for more education about AF for those directly affected by

¹³ ‘Un danger peut en cacher un autre’ at (as of 30 March 2015) <http://www.faattention.com>

¹⁴ For example, there are 9.7 annual doctor consultations per capita in Germany, compared with 5.0 in the UK (OECD 2013).

it (patients and HCPs). Education was seen by workshop participants to be distinct from awareness in that it would extend beyond awareness to cover specific information about what AF is, its associated risks and symptoms, and management options. It was perceived that significant and distinct benefits could result from improving education of both patients and healthcare providers. As with awareness, there is a need to connect AF to cardiovascular health more broadly and promote the idea that it is important to reduce the presence of risk factors that increase the likelihood of AF and AF-related stroke.

For healthcare providers, it was perceived that the need for education is highest in primary care, due to a current lack of education and because GPs play a key role in managing AF patients. The observation that current education of primary care HCPs should be improved is in line with other evidence that the use of oral anticoagulants varies depending on the setting where care is delivered (e.g. Gerber et al. 2012), with primary care physicians less likely to adhere to guidelines on the use of anticoagulants. The under-prescribing of anticoagulants relative to clinical guidelines is an issue that has been reported in multiple countries, including Belgium (De Bruecker et al. 2010, Denoël et al. 2014), Italy (Monte et al. 2006), Germany (Lotze et al. 2010, Ohlmeier et al. 2013), and Spain (Spanish Society of Cardiology 2013).

The need for education of HCPs is not limited to GPs. Study participants emphasised that, given the relatively high incidence of AF as well as its projected increase, a wide range of HCPs could expect to encounter AF patients, and so it is important that they be informed about AF management. Because they deal with a wide range of patients with a range of diseases and conditions, GPs face a particular challenge in staying up to date with current guidelines and approaches for assessing patients' risks of stroke and bleeding. However, given that GPs play a key role in AF patient management, it is important to ensure that they are well informed.

For patients, education is seen as being an important factor in patient outcomes because patients tend to be more compliant when they have a better understanding of their condition and the importance of the therapies they have been prescribed. Achieving this understanding is particularly important for the use of anticoagulation for stroke prevention in AF because patients generally do not feel any differently if they do not take their anticoagulation medication. Evidence from Italy has indicated that patient education may be an effective way to

improve compliance in the use of VKAs for stroke prevention in AF patients (Di Minno et al. 2004).

Another important aspect of education focusses on the need to ensure that patients have an accurate understanding of their condition and its associated treatment and management options. Some study participants stressed that it is important to avoid creating a false sense of security about the effectiveness of treatments, because doing so could reduce the perceived need for healthy behaviours aimed at reducing risk factors. Finally, providing improved information resources for patients can reduce patients' dependence on information obtained online, which may be unreliable or misleading. Study participants stressed that it is desirable to reduce patients' use of 'Dr Google'.

Challenges

Several challenges may arise in the course of taking action to improve education of AF patients. One barrier for patient education that was cited by study participants is the fact that in some countries, such as the UK, GPs have only very limited time to spend with patients. As a result, they lack the time to explain to patients the details of their condition and prescribed therapy. On the other hand, as is the case for awareness campaigns, it may be challenging to find sources of funding for separate education programmes. A challenge for improving HCP education is that it may be difficult to encourage some HCPs to participate in education programmes, as they may have limited interest or feel they do not need additional training.

Workshop participants felt that another challenge for patient education is that some HCPs, especially those in primary care, may dislike the concept of 'empowering' patients because they expect it will lead to patients wanting to say how they should be treated. As a result, these HCPs may resist supporting patient education initiatives. Findings from the analysis of interviews in this study suggest that there may be important differences across countries in attitudes to patient engagement. Responses indicated that there is a low expectation for patient engagement in France, for instance, with interviewees commenting that patients should assume that their doctor knows what is best and follow the doctor's instructions. By contrast, in the UK interviewees focussed more on the idea that patient preference is very important and should be taken into account in decisions about how to manage AF.

There is evidence that education may not be a sufficient to improve HCP's adherence to clinical guidelines. To

illustrate this, one reason that has been cited for the under- or inappropriate use of oral anticoagulants (VKAs or NOACs) in AF patients is that GPs tend to overestimate the risk of side-effects (and bleeding in particular) from using these drugs and to underestimate the risk of patients suffering an AF-related stroke (Gorin et al. 2011). However, while this is an issue that could be addressed in part through education, evidence indicates that knowledge of guidelines may not be enough to influence practice because environmental factors, resource availability, HCP attitudes and beliefs, and other factors can also be important (Fay & Montana 2012). There is also a risk that supplying a range of slightly different educational materials for physicians (which could come with NOACs as they arrive on the market, for example) could create confusion (Heidbuchel et al. 2013).

Indeed, pharmaceutical companies that are marketing NOACs have played a role in increasing awareness about AF among HCPs and supporting HCP education, and some study participants stressed that industry actors should be involved in awareness raising and have an important role to play in helping to link up patients, GPs and cardiologists. However, study participants also mentioned that it is important for companies playing this role to act in a coordinated way, and some interviewees raised concerns that the push from pharmaceutical companies in this area is contributing to resistance among some doctors to adopt NOACs. They also said there is a risk that companies will deliver mixed messages about specific NOAC products, instead of a single, valuable message about appropriate usage of NOACs as a class of drugs. It was acknowledged that encouraging collaboration between competing companies may be difficult; however, an information website for patients (discussed below) has been created with support from multiple companies.

Implementing the recommendation

A number of education initiatives are being run across the six countries of focus, targeting both patients and HCPs. Programmes for HCPs are supported in many cases by pharmaceutical companies, but professional societies and other organisations also play a role in this area. Key actors in patient education include nurses and patient groups. In addition to specific programmes, counselling from nurses and good communication between doctors and patients have been cited as ways to improve patient compliance (Di Minno et al. 2004).

The AF Association in the UK has also highlighted innovative practice in the management of AF, and it cites several examples of initiatives that include education for patients and HCPs and involve a range of actors in its *Healthcare Pioneers: Showcasing Innovative Practice in Atrial Fibrillation* (AFA 2015b). In addition to an initiative to increase awareness of AF-related stroke risk among emergency clinicians (cited in the recommendation on awareness), the document describes a cardiology service that assists primary care clinicians by offering expert advice on interpreting ECGs and managing patients, and providing training for GP practice nurses, among other services. Other initiatives have involved training for local pharmacists and patient education leaflets, as well as nurse-led arrhythmia clinics that provide education for patients and HCPs through in-person and telephone consultations for patients, technical support on ablation procedures and help for patients preparing for complex procedures (AFA 2015b).

I'd like to see more specialist nurses involved in diagnosis and management
UK nurse

Interviewees from Belgium, France and Germany highlighted examples of education programmes supported by pharmaceutical companies and professional associations. In Germany, for instance, a programme supported by industry provides training on the use of anticoagulation in AF patient management for both primary care nurses and patients, and one interviewee reported that it has provided training to around 800 nurses.

Another approach is to disseminate information for HCPs online and make available accurate, reliable online resources for patients. For example, for HCPs in the UK, a web resource established in 2013 provides healthcare professionals with information resources to enable them to improve the diagnosis, treatment and management of patients with AF. It is aimed at all healthcare professionals who engage with AF patients in different settings, and it also functions as a network and forum for exchange on good practice (AFA 2015a).

Among examples of online resources for patients, the EHRA and ESC have created a website, AFib Matters, that provides information on AF signs, symptoms and treatments and advice on living with AF, and is available in English, French and German, with other languages being implemented soon (EHRA 2015). The site acknowledges funding from several pharmaceutical industry sponsors.

3.1.3. Short-term recommendation 3: Maintain engagement in AF-related research across the health services

Key points

- Continued progress in AF management would benefit from a whole-system approach involving primary, secondary and tertiary care as well as policymakers.
- There is a need for research to monitor impacts of interventions in education and other aspects of AF-related healthcare delivery.
- The involvement of tertiary care is particularly important for progress in research and technology.

Rationale

For continued progress in improving the care and management of AF patients, study participants highlighted the need to encourage and maintain engagement from across the health system, including HCPs in primary, secondary and tertiary care as well as policymakers. This engagement was seen as particularly important given that there is a wider shift taking place across Europe towards a larger role for primary and community care.

At the workshop, participants agreed that an ideal future for AF management would involve a major role for primary care together with increased awareness and knowledge about AF as well as improved detection. However, they believed that this shift towards primary care may carry the risk that some actors, particularly in secondary and tertiary care, become more excluded from involvement in patient care. They stressed that there is a need to maintain involvement from tertiary care to ensure that progress in research and technology continues, enabling gains beyond shorter-term administrative and organisation-based changes (which are also important to support). Maintaining industry interest is also important in order to promote innovation and research in diagnosis and therapy. Finally, improving healthcare delivery for AF requires research on health services related to AF care, including areas such as patient outcomes related to education, monitoring and other aspects of healthcare delivery.

Challenges

Multiple challenges exist for integrating research and healthcare. While not specific to AF, these include practical considerations related to making sure that clinicians have the time, resources and support they need

to carry out research, and to supporting interaction between clinicians and researchers. This is a particular challenge for primary care given the high burden faced by HCPs in this area, and can become increasingly difficult as that burden grows. In addition, while interest from industry has provided support for research related to new interventions, there will be a need for other sources of funding to support research that has less direct relevance for industry stakeholders.

Implementing the recommendation

In implementing this recommendation, it is important to support engagement and, subsequently, monitor the level of engagement over time. One way to encourage engagement from actors across the health system is to ensure a comprehensive approach to education, addressing the full range of medical practitioners who will encounter patients with AF. One approach for monitoring the extent of research engagement is to track the amount of funding going to support AF research, the number and scale of clinical trials being run, and the number of research articles on AF being published. Such monitoring can also focus within countries to assess the level of activity and identify whether there may be gaps in support or capacity for research within a country or more broadly.

3.2. Longer-term recommendations

3.2.1. Longer-term recommendation 1: A longer-term view in decisions on spending for AF awareness, education, care and management is important for improving health outcomes

Key points

- Improving management of AF-related stroke requires that decisions made across the health system that affect AF management align with current evidence on the effectiveness of therapies and other management interventions.
- Disconnected budgets within health systems can create obstacles for ensuring consistency in decisionmaking across the system. For example, up-front costs may be a more significant factor in decisions about therapies than longer-term benefits and associated cost savings.
- There is a particular need for prevention, early detection and whole-patient approaches.

Rationale

There is a general lack of clarity about the role of cost factors in therapy decisions within countries, with differences in health systems between countries contributing added complexity. However, interviewees generally felt that reduction in AF-related stroke could result from better alignment of decisions made across the health system with current evidence on how management options impact AF-related stroke risk. A few different areas were highlighted as needing increased focus but also as being challenging to support when decisions are made with less consideration for longer-term outcomes: prevention, early detection and whole-patient approaches. Time lags between spending and longer-term benefits, as well as disconnects between different parts of the healthcare system, can make it easier to base decisions more on up-front therapy costs.

This challenge can be illustrated by the case of decisions about whether to use VKAs or NOACs for anticoagulation therapy in AF patients. It was unclear to what extent the higher cost of NOACs as compared to VKAs could be offset by the reduced need for monitoring of patients, and interviewees mentioned that an added challenge is that different parts of the health system may bear the burden of drug and monitoring costs. However, there was general agreement among interviewees that having lower up-front costs for NOACs would increase their uptake, a view that is supported by evidence from the literature indicating that cost is a factor in decisions about NOAC use.

Long-term cost-effectiveness information may be available but not taken fully into account when there are immediate, short-term budget pressures. In Spain, an interviewee expressed frustration that NOACs remain unavailable in some regions despite evidence for their cost-effectiveness. In England, national guidelines based on information about long-term cost-effectiveness state that clinicians can choose whether to use VKAs or NOACs, based on the needs of the patient. However, decisions made at the local level (by Clinical Commissioning Groups) are influenced by strong incentives to balance annual budgets, and in the UK and Germany there were reports of GPs changing cardiologists' prescriptions to reduce costs.

Implementing the recommendation

Participants in the workshop stressed that addressing this situation is difficult in part because there is less political will for longer-term planning. In addition, technology and high-tech treatments may be more

attractive for policymakers and media than prevention and risk reduction.

Outcome-based reimbursement was discussed during the workshop as one approach for encouraging prevention, early detection and whole-patient approaches. With this approach, health outcomes would serve as a measure of adequate healthcare delivery. Options for implementing outcome-based reimbursement could include incentives for reducing stroke incidence in a given region. However, it was cautioned that incentives should not be created for using particular therapies because the emphasis should be on improving patient outcomes more holistically. Consistent with this concern is evidence that the UK's Quality Outcomes Framework (QOF), an incentive scheme for GPs to encourage and reward good practice that placed equal emphasis on the use of antiplatelet and oral anticoagulation medications for stroke prevention in AF patients, may have contributed to an over-reliance on antiplatelet medication (Cowan et al. 2013). However, UK interviewees felt that the QOF could be a useful tool for encouraging GPs to carry out routine pulse checks or use oral anticoagulants effectively, and interviewees from Spain and Italy (though not Belgium, France or Germany) said that a similar scheme could also be useful in their countries. Another approach that has been used in Germany to promote healthy behaviour among individuals and may have relevance for improving detection of AF is incentives (through lower insurance co-payments) for patients who attend regular check-ups or participate in health screening programmes (Schmidt et al. 2009).

3.2.2. Longer-term recommendation 2: There is a need for continued improvement in patient stratification and personalisation of care

Key points

- AF patients may present a diversity of preferences, social situations and comorbidities that can be factored in to ensure they receive appropriate AF management.
- Improved patient stratification based on biomarkers, genomic information and heart imaging can lead to more individualised care that results in more effective management and treatment of AF.

Rationale

There is potential for improvement in the extent to which AF management is tailored to the needs of individual

patients, in terms of both biomedical and social factors, by expanding and making use of the evidence base on biomarkers, genomic factors and outcomes for a range of patients and therapies. One area that could be further developed is stroke risk stratification, where our understanding of which patients should be prescribed anticoagulants for prevention of AF-related stroke could be further refined. A better understanding of that risk may make it possible to reduce the number of patients receiving anticoagulation in future.

In terms of social factors, there is also scope for patient preference to play a larger role in the future in decisions about which management options are most appropriate. Adapting management to patient needs and preferences can help improve compliance. For example, in terms of preferences for VKAs versus NOACs for anticoagulation, interviewees indicated that some patients may prefer the regular interaction they receive through monitoring when on VKAs. On the other hand, other patients, such as those who work full-time, may prefer the reduced burden associated with NOACs (the lack of a need for monitoring and fewer restrictions related to food and drug interactions).

Implementing the recommendation

Ongoing clinical trials are currently gathering evidence to enable a better understanding of biomarkers, risk factors and outcomes in patient groups that have been less well studied. In addition, patient registries have been and can be used to gather real-world data that provide information on patient characteristics and outcomes. Examples include the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) (O'Brien et al. 2014), PREFER-AF, the PREvention of thromboembolic events – European Registry in Atrial Fibrillation (Kirchhof et al. 2014), the registry activities of the German Competence Network (AFNET), GARFIELD-AF, the global anticoagulant registry in the field,¹⁵ and GLORIA-AF, the Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation.¹⁶ These registries could be used to monitor the impacts of interventions based on improving patient or HCP education, focussing on, for example, their effectiveness in reducing stroke. Another related initiative is NHS England's Clinical Practice Research Datalink (CPRD), an observational data and interventional research service that has improvement of

the use of patient data in research as one of its main objectives (CPRD 2015). The use of data is discussed further in longer-term recommendation 4.

3.2.3. Longer-term recommendation 3: Increased interaction between primary, community, secondary and tertiary care would enable knowledge sharing and more whole-patient approaches to care

Key points

- Many AF patients have comorbidities, so it is important to support continuity of care for AF patients and not manage AF in isolation.
- In addition to GPs and specialist HCPs, a range of players can contribute to aspects of AF patient management, including pharmacies, care homes and carers, and specialist nurses.
- It is important to promote interaction and knowledge exchange between all actors involved in patient care.

Rationale

There has been ongoing interest in Europe in strengthening systems for primary care, which are viewed as being important contributors to health outcomes and health equity, and being responsive to challenges such as demographic shifts and the rising prevalence of chronic diseases and multi-morbidity (EU EXPH 2014). Participants at the workshop agreed that the trend across Europe was towards a system where primary care plays a larger role. However, our research has indicated that primary care physicians are less likely than specialist doctors to adhere to clinical guidelines on the use of anticoagulants in AF patients, highlighting the importance of integrating specialist expertise into primary care.

Implementing the recommendation

A range of challenges prevent integration across different areas of healthcare systems. Challenges identified at the workshop include barriers to inter-professional exchange that may make collaboration more challenging, and HCPs lacking time for communication and interaction. Workshop participants stressed the need to incentivise positive action by HCPs to increase

¹⁵ <http://www.tri-london.ac.uk/garfield> (as of 7th April 2015)

¹⁶ <https://www.gloria-af.com/public/about.html> (as of 7th April 2015)

outreach between secondary and primary care HCPs. One approach for supporting primary care HCPs in the UK has been the establishment of nurse-led arrhythmia clinics, and rapid access arrhythmia clinics, that provide a range of support to those working in primary care and managing AF patients, including technical support on ablation as well as general education and training for both patients and HCPs. The UK is also developing GPs with a specialist interest in cardiology who are given cardiology training and support. This role has been welcomed, and has the potential to improve the quality of care for patients in the primary care setting (Pollard et al. 2014). Interviewees in Belgium highlighted a centre being developed that would make available cardiology specialists for consultation by GPs, reducing the need for patients themselves to visit specialists.

3.2.4. Longer-term recommendation 4: Monitor developments in devices and data to maximise benefits for AF management

Key points

- Digital devices are being developed that can be used in AF detection and therapy.
- Software and data sharing can facilitate collaboration among HCPs and support decisionmaking, and help to identify high-risk patients that should be screened for AF.
- Large patient datasets will be useful for research, especially into patient risk stratification, enabling better care.

Rationale

A range of technology developments can impact future AF management options and it is important that these are monitored so that opportunities for improving care can be captured and associated risks minimised. Some developments are AF-specific, such as the creation of devices and apps that can facilitate at-home INR or ECG monitoring. Others relate to wider developments. For example, developments in software for use by healthcare providers can support decisionmaking, help identify high-risk patients or enable easier collaboration between HCPs. One example of a tool for assisting with stroke risk stratification is the Guidance on Risk Assessment and Stroke Prevention for AF (GRASP-AF) software, which has been used in primary care settings in the UK to identify patients who would benefit from being prescribed anticoagulants (AFA 2015b).

Data is expected to play an increasingly significant role in healthcare research and delivery. Data from electronic health records and patient registries can provide valuable information for research, improving understanding of AF therapies, risk factors and associated outcomes, and enabling better care. In addition, real-time data on patient outcomes can be used to influence political decisions related to healthcare. Other emerging technologies include implantable heart monitoring devices, smart pills that link to mobile apps to monitor compliance, and therapeutic devices for use in surgical interventions such as left atrial appendage occlusion and ablation.

Data sharing is important; what the GP does needs to link to the nutritionist, endocrinologist, etc.

Health technology developer

Implementing the recommendation

At the workshop multiple practical considerations arose in discussions about devices, such as whether they would be available in pharmacies or through GPs and the importance of clarity on which devices to use if different options are available. In addition, devices will need assessment by government bodies. Particular risks to avoid would be devices giving false positives or negatives or a false sense of security. There is also a need to understand liability associated with their use.

It is important to note that while devices may assist with AF detection, they are not essential. Indeed, public campaigns encouraging pulse checks may continue to be a more effective way to reach a wide audience and increase detection. In addition, it is important to consider that attitudes to data and devices are likely to change as people who have grown up with more technology age, and as wider developments in data sharing continue. Concerns about data privacy may result in some patients being excluded from access to aspects of care.

Further risks in increasing the role of new technologies for use in AF management were also identified at the workshop. These included the potential for patients to feel they are being treated more by robots than by humans if HCPs increase their reliance on software and other digital tools. In addition, workshop participants expected that a general resistance to change from the public and/or HCPs may act as a barrier to technology adoption.

Chapter 4 Conclusion

Atrial fibrillation (AF) is a condition that becomes more prevalent as people age. As the European population ages and risk factors such as obesity and diabetes become more common, the prevalence of AF is expected to increase in the coming years. It affects roughly 1.9 per cent of the European population at present and roughly 18 per cent of the population over age 85. By 2050, it is expected to affect more than 17 million people in Europe, or 3.3 per cent of the population. In AF, the heart beats irregularly and blood collects in the atria of the heart, where clots can form. These clots can travel to the brain and cause a stroke, and AF increases the risk of stroke approximately five-fold. As a result, AF presents a significant burden both at a population level and for individuals who have the condition. However, there are interventions available to reduce the risk of AF-related stroke: therapies are mainly aimed at treating the arrhythmia itself through rhythm or rate control strategies, or at reducing the risk of stroke through the use of oral anticoagulation to prevent blood clot formation.

In the past few years, a new class of drugs for oral anticoagulation, non-VKA oral anticoagulants (NOACs), has come on the market. These drugs offer an alternative to vitamin K antagonists (VKAs) such as warfarin, which have been the mainstay of oral anticoagulation therapy for many years. While VKAs have drawbacks, including a need for regular monitoring of a patient's coagulation level, and interactions with other drugs and food, NOACs have been shown to offer similar benefits to VKAs in terms of stroke prevention with fewer drawbacks. Recently updated clinical guidelines from the European Society for Cardiology and national guidelines from France, Italy and the UK (but not Spain) now recommend the use of NOACs as the first choice of anticoagulation therapy for patients with non-valvular AF who are at risk of stroke. However, in practice, uptake of NOACs has been limited by issues related to cost, knowledge and education of clinicians (particularly those in primary

care), and concerns about bleed risk in the elderly or patients with comorbidities.

This study has explored the current landscape and future scenarios of the management of AF in Europe, with a focus on anticoagulation. The aim was to improve understanding of the dynamics and issues that will impact on the future landscape for the use of anticoagulation in AF, and to develop recommendations that will enable better patient outcomes.

In the course of this research, we have identified challenges both in AF management and in reducing the occurrence of AF-related stroke. Addressing these challenges – which relate to awareness and detection of the condition, education of patients about the condition and therapies, and education of healthcare professionals about AF and management options – would help reduce the burden of AF-related stroke at individual and population levels. Through assessment of the current landscape and discussion of the risks and opportunities associated with future scenarios, we have developed a set of immediate and longer-term recommendations for improving AF management.

In terms of more immediate and AF-specific recommendations, we recommend that action to improve awareness of AF among the public and policymakers be increased or continued. The level of awareness is low at present, but increased awareness (focussed on the idea that AF increases the risk of preventable stroke) could lead to earlier detection and intervention. There is also a need to support education for both patients and HCPs about AF management. Improved education can lead to better adherence to guidelines among HCPs and better-informed decisionmaking around AF patient management. Among patients, education can result in better understanding of the condition and need for therapy, leading to improved compliance and better patient outcomes. Finally, to ensure that progress continues in understanding AF and developing

management options, it is important to maintain engagement in AF-related research from all parts of the health services, involving primary, secondary and tertiary care as well as policymakers and patient groups.

There are also wider trends and systemic changes that, if they occurred, would have broad implications for healthcare delivery and these will be relevant for AF management even though they are not specific to AF. First, a longer-term view on spending decisions is important for ensuring improved outcomes in the longer term. In AF, such a view could lead to increased AF awareness and education, and could also lead to an increase in the adoption of NOACs in certain healthcare settings. Second, there is a wider trend towards patient stratification and more individualised care (based on an individual's medical characteristics and personal preferences), and continued improvement in these aspects is also relevant for improving AF patient management and outcomes. Third, increased interaction between the range of actors involved in caring for AF patients would enable more continuity of care and allow a wider range of players to contribute to AF-related awareness, education and patient care and management. Finally, it is important to monitor and take advantage of developments in the availability and use of patient data and digital devices for detecting AF or monitoring AF patients. Technological developments can enable better care by facilitating at-home monitoring or providing large patient datasets to inform research and risk stratification in AF.

References

- AFA. 2012. 'Guidance on new Quality and Outcomes Framework measures for AF.' AF Association, UK.
- AFA. 2014. 'Grasp the initiative.' AF Association, UK.
- AFA. 2015a. 'The Heart of AF.' As of 14 March 2015: <http://www.heartofaf.org>
- AFA. 2015b. 'Healthcare Pioneers Booklet.' AF Association, UK.
- AIFA. 2013. 'Comunicazione relativa ai nuovi anticoagulanti orali Eliquis®, Pradaxa®, Xarelto®: Importante informativa sui fattori di rischio di sanguinamento – Prestare attenzione alla posologia, alle controindicazioni e alle avvertenze speciali e precauzioni d'impiego per ridurre il rischio di sanguinamento.' Communication of the Italian Agency for Pharmaceuticals.
- ALFA. 2014. 'La fibrillazione atriale conoscerla per evitarne i rischi.' Associazione Lotta Fibrillazione Atriale.
- Alonso-Coello, P., et al. 2008. 'Values and preferences in oral anticoagulation in patients with atrial fibrillation, physicians' and patients' perspectives: protocol for a two-phase study.' *BMC Health Services Research* 8: 21.
- Alonso-Coello, P., et al. 2014. 'Values and preferences for oral antithrombotic therapy in patients with atrial fibrillation: Physician and patient perspectives.' *Health Expectations*.
- AM. 2013. 'Nouveaux anti-coagulants oraux: une étude de l'Assurance Maladie souligne la dynamique forte de ces nouveaux médicaments et la nécessité d'une vigilance accrue dans leur utilisation.' Assurance Maladie.
- Anderson, N., et al. 2007. "Rules of thumb" or reflective practice? Understanding senior physicians' decision-making about anti-thrombotic usage in atrial fibrillation.' *QJM* 100: 263–69.
- ANSM. 2014. 'Les anticoagulants en France en 2014: Etat des lieux, synthèse et surveillance.' As of 19 March 2015: http://ansm.sante.fr/var/ansm_site/storage/original/application/26ed375830c56499badf0014eb3bb81b.pdf
- Avonts, M. 2010. 'Is screenen voor voorkamerfibrillatie zinvol?' As of 19 March 2015: <http://www.domusmedica.be/vorming/wetenschapsdag/abstracts-2010/2872-is-screenen-voor-voorkamerfibrillatie-zinvol.html>
- Babaeizadeh, S., et al. 2009. 'Improvements in atrial fibrillation detection for real-time monitoring.' *Journal of Electrocardiology* 42(6): 522–26.
- Baena-Díez, J.M., et al. 2014. 'Prevalence of atrial fibrillation and its associated factors in Spain: An analysis of 6 population-based studies. DARIOS Study.' *Revista Clínica Española* 214(9): 505–12.
- Barcellona, D., et al. 2000. 'Management of oral anticoagulant therapy: The patient's point of view.' *Thrombosis and Haemostasis* 83: 49–53.
- Barcellona, D., et al. 2002. 'Patient education and oral anticoagulant therapy.' *Haematologica* 87: 1081–86.
- Barco, S., et al. 2013. 'New oral anticoagulants in elderly patients.' *Best Practice and Research Clinical Haematology* 26(2): 215–24.
- Battigelli, D., et al. 2013. 'La gestione della Fibrillazione atriale In Medicina Generale.' Società Italiana di Medicina Generale.

- Belgisch Centrum voor Farmacotherapeutische Informatie (BCFI). 2014. 'Antistollingsbehandeling bij voorkamerfibrillatie: vitamine K-antagonisten of nieuwe orale anticoagulantia?' *Folia Pharmacotherapeutica* 41.
- Becker, S. 2013. 'Mobile Smartphone-Applikationen - Möglichkeiten der Therapieunterstützung.' As of 19 March 2015: <http://cardiohilfe.de/2013/03/mobile-smartphone-applikationen-moglichkeiten-der-therapieunterstuetzung/>
- Berisso, M.Z., et al. 2014. 'Antiarrhythmic strategies in patients with atrial fibrillation managed by cardiologists and internists: Antithrombotic Agents in Atrial Fibrillation (ATA-AF) survey.' *Journal of Cardiovascular Medicine* 15(8): 626–35.
- Bilato, C., et al. 2009. 'Prevalence, functional impact, and mortality of atrial fibrillation in an older Italian population (from the Pro. VA study).' *American Journal of Cardiology* 104(8): 1092–97.
- Bitton, A., et al. 2013. 'The impact of medication adherence on coronary artery disease costs and outcomes: A systematic review.' *American Journal of Medicine* 126 (4): 357.e7–e27.
- Bundesministerium für Bildung und Forschung. 2011. 'Aktuelle Ergebnisse der Gesundheitsforschung.' Newsletter 53: 8–9.
- Camm, J.A., et al. 2010. 'Guidelines for the management of atrial fibrillation.' *European Heart Journal* 31: 2369–429.
- Camm, J.A., et al. 2012. '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.' *European Heart Journal* 33: 2719–47.
- Camm, J.A., et al. 2014a. 'Left atrial appendage closure: A new technique for clinical practice.' *Heart Rhythm* 11: 514–21.
- Camm, J.A., et al. 2014b. 'The Route Map for Change & the European Atlas on the Prevention of AF-Related Stroke.' As of 19 March 2015: <http://www.anticoagulationeurope.org/files/files/Interactive%20Route%20Map%20for%20Change%2011Nov14%20final.pdf>
- Canestaro, W.J., et al. 2013. 'Cost-effectiveness of oral anticoagulants for treatment of atrial fibrillation.' *Circulation: Cardiovascular Quality and Outcomes* 6: 724–31.
- Carmen, A., et al. 2014. 'Situacion de la anticoagualcion en Espana en 2014, Presentation for RED, La salud del paciente por delante.'
- Cavallo, A., et al. 2009. 'Trattamento della fibrillazione atriale per via mini-invasiva mediante ablazione ad ultrasuoni (HIFU).' Horizon Scanning report No.3. Rome: Agenzia nazionale per i servizi sanitari regionali.
- Chan, P.S., et al. 2006. 'Cost-effectiveness of radiofrequency catheter ablation for atrial fibrillation.' *Journal of the American College of Cardiology* 47(12):2513–20.
- Charlemagne, A., et al. 2011. 'Epidemiology of atrial fibrillation in France: Extrapolation of international epidemiological data to France and analysis of French hospitalization data.' *Archives of Cardiovascular Diseases* 104(2): 115–24.
- Chugh, S.S., et al. 2014. 'Worldwide epidemiology of atrial fibrillation. A global burden of disease 2010 study.' *Circulation* 129: 837–47.
- Claes, N., et al. 2012. 'Prevalence of atrial fibrillation in adults participating in a large-scale voluntary screening programme in Belgium.' *Acta Cardiologica* 67(3): 273–78.
- Clua-Espuny, J., et al. 2013. 'Prevalence of Undiagnosed Atrial Fibrillation and of That Not Being Treated With Anticoagulant Drugs: the AFABE Study.' *Revista Española de Cardiología* 66(7): 545–52.
- Clua-Espuny, J., et al. 2014. 'Diagnosed, undiagnosed and overall atrial fibrillation research on population over 60 year-old. AFABE study.' *Cardiovascular System* 2(1): 2.
- Connolly, S.J., et al. 2009. 'Dabigatran versus warfarin in patients with atrial fibrillation.' *New England Journal of Medicine* 361: 1139–51.
- Cotté, F.E., et al. 2014. 'Vitamin K antagonist treatment in patients with atrial fibrillation and time in therapeutic range in four European countries.' *Clinical Therapeutics* 36(9): 1160–68.

- Cowan, C., et al. 2013. 'The use of oral anticoagulants in the management of atrial fibrillation among general practices in England.' *Heart*. As of 19 March 2015: <http://heart.bmj.com/content/early/2013/02/06/heartjnl-2012-303472.full>
- CPRD. 2015. 'Welcome to The Clinical Practice Research Datalink.' As of 25 March 2015: <http://www.cprd.com/intro.asp>
- Cramer, J.A. 2002. 'Effect of partial compliance on cardiovascular medication-effectiveness' *Heart* 88: 203–6.
- Cruss, D.G., et al. 2010. 'Patient attitudinal and behavioral factors associated with warfarin non-adherence at outpatient anticoagulation clinics.' *International Journal of Behavioral Medicine* 17(1): 33–42.
- d'Angelo, D., et al. 2013. 'Nuovi anticoagulanti orali (NAO).' In Spadonaro, F. (ed.), *Rapporto Sanita IX, Crisi economica e Sanità: come cambiare le politiche pubbliche*. Università degli Studi di Roma 'Tor Vergata'. Edizioni Health Communication.
- Davy, J.M. (on behalf of PROFIL FA investigators, Bureau I: V. Donio, N. Penalheux, N. Spiess, Y. Briand). 2014. 'The French screening campaign of Atrial Fibrillation (PROFIL FA®) in general practice: Assessment of predictive criteria for atrial fibrillation (AF).' Abstract no.82393. Barcelona: ESC. Summary available at (as of 19 March 2015): http://www.boehringer-ingenelheim.fr/actualites/CP_14-0552_FA_BOX/publie/presse_nouveau/CP_140691_profil.html
- De Breucker, S., et al. 2010. 'Could geriatric characteristics explain the under-prescription of anticoagulation therapy for older patients admitted with atrial fibrillation? A retrospective observational study.' *Drugs Aging* 27(10): 807–13.
- Deedwania, P.C. 2013. 'New oral anticoagulants in elderly patients with atrial fibrillation.' *American Journal of Medicine* 126(4): 289–96.
- Dekker, L.R. 2011. 'Treatment of atrial fibrillation in the elderly: Time for a change?' *Netherlands Heart Journal* 19(10): 403–4.
- Denoël, P., et al. 2014. 'Could some geriatric characteristics hinder the prescription of anticoagulants in atrial fibrillation in the elderly?' *Journal of Aging Research* 2014: 1–8.
- Devereaux, P.J., et al. 2001. 'Differences between perspectives of physicians and patients on anticoagulation in patients with atrial fibrillation: observational study.' *British Medical Journal* 323(7323): 1218–22.
- Dewar, R.I., & G.Y.H. Lip. 2007. 'Identification, diagnosis and assessment of atrial fibrillation.' *Heart* 93(1): 25–28.
- Di Minno, A., et al. 2014. 'Ensuring medication adherence with direct oral anticoagulant drugs: lessons from adherence with vitamin K antagonists (VKAs).' *Thrombosis Research* 133(5): 699–704.
- Diez-Mangano, J., et al. 2014. 'Adherence to guidelines and mortality in atrial fibrillation.' *International Journal of Cardiology* 176(2): 430–36.
- Disertori, M., et al. 2010. 'Clinical predictors of atrial fibrillation recurrence in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Atrial Fibrillation (GISSI-AF) trial.' *American Heart Journal* 159(5): 857–63.
- Dobreanu, D., et al. 2013. 'Current practice for diagnosis and management of silent atrial fibrillation: Results of the European Heart Rhythm Association survey.' *Europace* 15(8): 1223–25.
- Doliwa Sobocinski, P., et al. 2012. 'Improved screening for silent atrial fibrillation after ischaemic stroke.' *Europace* 14(8): 1112–16.
- Dores, H., et al. 2011. 'Atrial fibrillation and thromboembolic risk: What is the extent of adherence to guidelines in clinical practice?' *Revista Portuguesa de Cardiologia* 30(2): 171–80.
- Dweck, M.R., et al. 2012. 'Anticoagulation in atrial fibrillation: The present and the future.' *JRSM Cardiovascular Disease* 1(5): 13.
- Ebner, B. 2013. 'Orale Antikoagulation bei chronische Vorhofflimmern 2013.' *Arzt und Praxis*. As of 19 March 2015: http://www.arztundpraxis.at/index.php?id=262&ctx_ttnews%5Btt_news%5D=3053&cHash=d07a6da13be4422178959906c249587c
- EHRA. 2015. 'AFib Matters.' As of 16 March 2015: <http://www.afibmatters.org>

- Engdahl, J., et al. 2013. 'Stepwise screening of atrial fibrillation in a 75-year-old population: implications for stroke prevention.' *Circulation* 127(8): 930–37.
- Engel, G., & R.H. Mead. 2008. 'Remote monitoring for atrial fibrillation.' *Congestive Heart Failure* 14(5 Suppl 2): 14–18.
- EU EXPH (EU EXpert Panel on effective ways of investing in Health). 2014. 'Report on Definition of a frame of reference in relation to primary care with a special emphasis on financing systems and referral systems.' European Commission. As of 19 March 2015: http://ec.europa.eu/health/expert_panel/opinions/docs/004_definitionprimarycare_en.pdf
- Eurostat. 2014. 'Main scenario – Population on 1st January by sex and single year age. Code: proj_13npms.' As of 19 March 2015: http://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=proj_13npms&lang=en
- Fattore, G., et al. 2012. 'The social and economic burden of stroke survivors in Italy: a prospective, incidence-based, multi-centre cost of illness study.' *BMC Neurology* 12: 137.
- Fay, M.R., & C. Montana. 2012. 'What are the differences between physician and patient expectation with regard to the management of atrial fibrillation?' *Journal of the Royal College of Physicians Edinburgh* 42(Suppl 18): 45–54.
- Fitzmaurice, D.A., et al. 2007. 'Screening versus routine practice in detection of atrial fibrillation in patients aged 65 or over: Cluster randomised controlled trial'. *British Medical Journal* 335: 383.
- Fitzmaurice, D.A., et al. 2014. 'Is screening for AF worthwhile? Stroke risk in a screened population from the SAFE study.' *Family Practice* 31(3): 298–302.
- Flint, A.C., et al. 2012. 'Detection of paroxysmal atrial fibrillation by 30-day event monitoring in cryptogenic ischemic stroke: The Stroke and Monitoring for PAF in Real Time (SMART) registry.' *Stroke* 43: 2788–90.
- Fumagalli, S., et al. 2012. 'Characteristics, management and prognosis of elderly patients in the Euro Heart Survey on atrial fibrillation.' *Aging Clinical and Experimental Research* 24(5): 517–23.
- Gage, B.F., et al. 1995. 'Cost-effectiveness of warfarin and aspirin for prophylaxis of stroke in patients with nonvalvular atrial fibrillation.' *Journal of the American Medical Association* 274(23): 1839–45.
- Gage, B.F., et al. 1996. 'The effect of stroke and stroke prophylaxis with aspirin or warfarin on quality of life.' *Archives of Internal Medicine* 156(16): 1829–36.
- Gage, B.F., et al. 1998. 'Cost-effectiveness of preference-based antithrombotic therapy for patients with nonvalvular atrial fibrillation.' *Stroke* 29: 1083–91.
- Gerber, B., et al. 2012. 'The health care setting rather than medical speciality impacts on physicians adherence to guideline-conform anticoagulation in outpatients with non-valvular atrial fibrillation: A cross sectional survey.' *BMC Cardiovascular Disorders* 12: 12.
- Gessner, C. 2014. 'Screening auf Vorhofflimmern lohnt sich!' As of 19 March 2015: <http://www.medical-tribune.de/medizin/fokus-mezizin/artikeldetail/screening-auf-vorhofflimmern-lohnt-sich.html>
- Gheorghide, M., et al. 2013. 'Anticoagulation in heart failure: Current status and future direction.' *Heart Failure Reviews* 18(6): 797–813.
- Giugliano, R.P., et al. 2013. 'Edoxaban versus warfarin in patients with atrial fibrillation.' *New England Journal of Medicine* 369(22):2093–104.
- Go, A.S., et al. 2001. '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.' *Journal of the American Medical Association* 285(18): 2370–75.
- Gonzalez-Quesada, C.J., & R.P. Giugliano. 2014. 'Comparison of the phase III clinical trial designs of novel oral anticoagulants versus warfarin for the treatment of nonvalvular atrial fibrillation: Implications for clinical practice.' *American Journal of Cardiovascular Diagnoses* 14: 111–27.
- Gorin, L., et al. 2011. 'Prognosis and guideline-adherent antithrombotic treatment in patients with atrial fibrillation and atrial flutter: Implications of undertreatment and overtreatment in real-life clinical practice; the Loire Valley Atrial Fibrillation Project.' *Chest* 140(4): 911–17.

- Granger, C.B., et al. 2011. 'Apixaban versus warfarin in patients with atrial fibrillation.' *New England Journal of Medicine* 365(11): 981–92.
- Griffo, R., et al. 2013. 'Effective secondary prevention through cardiac rehabilitation after coronary revascularization and predictors of poor adherence to lifestyle modification and medication. Results of the ICAROS Survey.' *International Journal of Cardiology* 167(4): 1390–95.
- Guize, L., et al. 2007. 'Atrial fibrillation: Prevalence, risk factors and mortality in a large French population with 15 years of follow-up.' *Bulletin de l'Académie Nationale de Médecine (Paris)* 191(4–5): 791–803.
- Gumbinger, C., et al. 2012. 'Continuous monitoring versus HOLTER ECG for detection of atrial fibrillation in patients with stroke.' *European Journal of Neurology* 19(2): 253–57.
- Han, J., et al. 2012. 'Pharmacologic and nonpharmacologic therapies for stroke prevention in nonvalvular atrial fibrillation.' *Pacing and Clinical Electrophysiology* 35(7): 887–96.
- Hanon, O., et al. 2013. 'Expert consensus of the French Society of Geriatrics and Gerontology and the French Society of Cardiology on the management of atrial fibrillation in elderly people.' *Archives of Cardiovascular Diseases* 106(5): 303–23.
- Harrington, A.R., et al. 2013. 'Cost-effectiveness of apixaban, dabigatran, rivaroxaban, and warfarin for stroke prevention in atrial fibrillation.' *Stroke* 44: 1676–81.
- Hart, R.G., et al. 2007. 'Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation.' *Annals of Internal Medicine* 146(12): 857–67.
- Haute Autorité de Santé (HAS). 2008. 'Prise en charge des surdosages des situations à risque hémorragique et des accidents hémorragiques chez les patients traités par antivitamines K en ville et en milieu hospitalier.'
- Haute Autorité de Santé (HAS). 2014a. 'Guide parcours de soins fibrillation atriale.'
- Haute Autorité de Santé (HAS). 2014b. 'Commission de la transparence, Avis, 17 Décembre 2014, Pradaxa.'
- Haute Autorité de Santé (HAS). 2014c. 'Commission de la transparence, Avis, 17 Décembre 2014, Zarelto.'
- Haute Autorité de Santé (HAS). 2014d. 'Commission de la transparence, Avis, 17 Décembre 2014, Eliquis.'
- Haute Autorité de Santé (HAS). 2015. 'Les "NACO", anticoagulants d'action directe, n'ont pas tous démontré la même efficacité.' As of 23 April 2015: http://www.has-sante.fr/portail/jcms/c_2008955/en/les-naco-anticoagulants-daction-directe-nont-pas-tous-demontre-la-meme-efficacite
- Healey, J.S., et al. 2012. 'Subclinical atrial fibrillation and the risk of stroke.' *New England Journal of Medicine* 366: 120–29.
- Heeringa, J., et al. 2006. 'Prevalence, incidence and lifetime risk of atrial fibrillation: The Rotterdam study.' *European Heart Journal* 27: 949–53.
- Heidbuchel, H., et al. 2013. 'European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation'. *Europace* 15(5): 625–651.157.
- Helms, T.M., et al. 2014. 'Prediction and personalised treatment of atrial fibrillation – stroke prevention: consolidated position paper of CVD professionals.' *EPMA Journal* 5: 15.
- Hobbs, F.D., et al. 2005. '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 Technology Assessment* 9(40): 1–74.
- Holding, S., et al. 2013. 'Opportunistic screening for atrial fibrillation.' *Nursing Times* 109(30): 12–15.
- Ifop/Bayer. 2014. 'Les Français et l'accident vasculaire cérébral. Vague 3: Sondage Ifop pour Bayer'. As of 19 March 2015: http://www.ifop.fr/media/poll/2819-1-study_file.pdf
- Ingelgard, A., et al. 2006. 'What are the barriers to warfarin use in atrial fibrillation?: Development of a questionnaire.' *Journal of Thrombosis and Thrombolysis* 21: 257–65.

- Johnston, J.A., et al. 2003. 'Predictors of warfarin use among Ohio medicaid patients with new-onset nonvalvular atrial fibrillation.' *Archives of Internal Medicine* 163: 1705–10.
- Keech, M., et al. 2012. 'Trends in atrial fibrillation hospitalisation in Scotland: an increasing cost burden.' *British Journal of Cardiology* 19(4): 173.
- Kirchhof, P., et al. 2014. 'Management of atrial fibrillation in seven European countries after the publication of the 2010 ESC Guidelines on atrial fibrillation: Primary results of the PREvention of thromboembolic events – European Registry in Atrial Fibrillation (PREFER in AF).' *Europace* 16(1): 6–14.
- Kneeland, P.P., & M.C. Fang. 2010. 'Current issues in patient adherence and persistence: Focus on anticoagulants for the treatment and prevention of thromboembolism.' *Journal of Patient Preference and Adherence* 4: 51–60.
- Kneife, G. 2014. 'Gesundheits-Apps ante portas: Krankenkassen finanzieren sie nur selten.' As of 19 March 2015: <http://praxis.medscapemedizin.de/artikel/4902453>
- Kobza, R. & E. Paul. 2007. 'Wird in der Praxis konsequent antikoaguliert?' *Ars Medici Dossier*.
- Kompetenznetz Vorhofflimmern. 2014a. 'Volkskrankheit Vorhofflimmern.' As of 19 March 2015: <http://www.kompetenznetz-vorhofflimmern.de/de/vorhofflimmern/patienteninformation-vorhofflimmern/volkskrankheit-vorhofflimmern>
- Kompetenznetz Vorhofflimmern. 2014b. 'Volkskrankheit Vorhofflimmern.' <http://www.kompetenznetz-vorhofflimmern.de/de/volkskrankheit-vorhofflimmern-rechtzeitig-behandeln-komplikationen-verhindern>
- Kornej, J., et al. 2013. 'Anticoagulation management in nonvalvular atrial fibrillation: Current and future directions.' *Polish Archives of Internal Medicine* 123(11): 623–34.
- Krijthe, B.P., et al. 2013. 'Projections on the number of individuals with atrial fibrillation in the European Union from 2000 to 2060.' *European Heart Journal* 34(35): 2746–51.
- Lafuente-Lafuente, C., et al. 2012. 'Long term treatment of atrial fibrillation in elderly patients: A decision analysis.' *International Journal of Cardiology* 155(1): 102–9.
- Lee, G., & C. Campbell-Cole. 2014. 'Recognising and managing atrial fibrillation in the community.' *British Journal of Community Nursing* 19(9): 422–26.
- Leong, D.P., et al. 2012. 'Imaging for Atrial Fibrillation.' *Current Problems in Cardiology* 37: 7–33.
- Liao, J., et al. 2007. 'Noninvasive cardiac monitoring for detecting paroxysmal atrial fibrillation or flutter after acute ischemic stroke: A systematic review.' *Stroke* 38: 2935–40.
- Liard, F., et al. 2013. 'Fibrillation atriale et traitement anticoagulant: Point de vue du médecin généraliste, du cardiologue et du patient.' *La Presse Médicale* 42(7): e259–e270.
- Limantoro, I., et al. 2012. 'The impact of atrial fibrillation on quality of life of the elderly: the calm before the storm?' *Europace* 14(10): 1379–80.
- Lindig, C., et al. 2010. 'Die Kosten des Schlaganfalls – eine Längsschnittdanalyse.' *PharmacoEconomics – German Research Articles* 8(2): 97–107.
- Lip, G.Y.H., & D.A. Lane. 2013. 'Stroke prevention with oral anticoagulation therapy in patients with atrial fibrillation – focus on the elderly.' *Circulation Journal* 77(6): 1380–88.
- Lip, G.Y.H., et al. 2014. 'A prospective survey in European Society of Cardiology member countries of atrial fibrillation management: Baseline results of EURObservational Research Programme Atrial Fibrillation (EORP-AF). Pilot General Registry.' *Europace* 16: 308–19.
- Lobos Bejarano, J., 2013. 'Fibrilacion auricular: presente y futuro.' Presentation at the Spanish Society for Cardiology (Sociedad Espanola de Cardiologia).
- Lorenzoni, G., et al. 2014. 'Cost-effectiveness of early detection of atrial fibrillation via remote control of implanted devices.' *Journal of Evaluation in Clinical Practice* 20(5): 570–77.

- Lopes, R.D., et al. 2010. 'Highlights from the II international symposium of thrombosis and anticoagulation (ISTA), October 22–23, 2009, Sao Paulo, Brazil.' *Journal of Thrombosis and Thrombolysis* 29(4): 395–408.
- Lotze, U., et al. 2010. 'Medical treatment of patients with atrial fibrillation aged over 80 years in daily clinical practice: Influence of age and CHADS(2) score.' *Archives of Gerontology and Geriatrics* 50(1): 36–41.
- Lowres, N., et al. 2013. 'Screening to identify unknown atrial fibrillation. A systematic review.' *Thrombosis and Haemostasis* 110(2): 213–22.
- Lowres, N., et al. 2014. 'Feasibility and cost-effectiveness of stroke prevention through community screening for atrial fibrillation using iPhone ECG in pharmacies. The SEARCH_AF study.' *Thrombosis and Haemostasis*: 111(6):1167–76.
- Lucioni, C., S. Mazzi, G. Micieli, M.L. Sacchetti & D. Toni. 2010. 'Valutazione economica del trattamento con alteplase di pazienti con ictus ischemico in fase acuta, con riferimento all'Italia.' *Pharmacoeconomics – Italian Research Articles* 12(2): 91–103
- Lüderitz, B. 2009. 'Pharmakologische Konzepte zur Therapie des Vorhofflimmerns.' *Clinical Research in Cardiology Supplements* 4: 170–75.
- Luger, S., et al. 2014. 'Prescription frequency and predictors for the use of novel direct oral anticoagulants for secondary stroke prevention in the first year after their marketing in Europe – a multicentric evaluation.' *International Journal of Stroke* 9(5): 569–75.
- MacLean, S., et al. 2012. 'Patient values and preferences in decision making for antithrombotic therapy: a systematic review: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines.' *Chest* 141(2 Suppl): e1S–e23S.
- Man-Son-Hing, M., et al. 2001. 'Differences in treatment preferences between persons who enroll and do not enroll in a clinical trial.' *Annals of the Royal College of Physicians and Surgeons Canada* 345: 292–96.
- Manning, L., et al. 'Atrial fibrillation.' *Geriatric Medicine*. As of 19 March 2015: http://www.gmjjournal.co.uk/atrial_fibrillation_78635.aspx
- Marcus, G.M., et al. 2013. 'The year in review of clinical cardiac electrophysiology.' *Journal of the American College of Cardiology* 61(7): 772–82.
- McBride, D., A.M. Mattenklotz, S.N. Willich & B. Brüggenjürgen. 2009. 'The costs of care in atrial fibrillation and the effect of treatment modalities in Germany.' *Value in Health* 12(2): 293–301.
- McKenna, C., et al. 2008. 'Cost-effectiveness of radiofrequency catheter ablation for the treatment of atrial fibrillation in the United Kingdom.' *Heart* 95:542–49.
- Messika-Zeitoun, D. 2013. 'Les smartphones en cardiologie.' *La Lettre du Cardiologue*.
- Monte, S., et al. 2006. 'Antithrombotic treatment is strongly underused despite reducing overall mortality among high-risk elderly patients hospitalized with atrial fibrillation.' *European Heart Journal* 27(18): 2217–23
- Moubarak, G., et al. 2012. 'Electrocardiographic Abnormalities in Centenarians and Octogenarians: A Case-Matched Study.' *Annals of Noninvasive Electrocardiology* 17(4): 372–77.
- NHS. 2000. National Service Framework for Coronary Heart Disease.
- Nademanee, K., et al. 2014. 'Benefits and risks of catheter ablation in elderly patients with atrial fibrillation.' *Heart Rhythm* 12(1): 44–51.
- NCBI. 2015. PubMed. National Center for Biotechnology Information (US). As of 19 March 2015: <http://www.ncbi.nlm.nih.gov/pubmed>
- NICE. 2014. *Atrial fibrillation: The management of atrial fibrillation*. NICE Clinical Guideline 180. Issued June 2014; last modified August 2014.
- NIH National Heart, Lung and Blood Institute. 2015. 'What is Atrial Fibrillation?' NIH Health Information for the public. As of 19 March 2015: <http://www.nhlbi.nih.gov/health/health-topics/topics/af>

- Nieuwkerk, P.T., et al. 2012. 'Intervention to improve adherence to lipid-lowering medication and lipid-levels in patients with an increased cardiovascular risk.' *American Journal of Cardiology* 110: 666–72.
- O'Brien, E.C., et al. 2014. 'Physician practices regarding contraindications to oral anticoagulation in atrial fibrillation: findings from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry.' *American Heart Journal* 167(4): 601–609.e1.
- Occhetta, E., P. Diotallevi & L. Venegoni. 2010. 'I costi sanitari della Fibrillazione Atriale. Follow-up a un anno dello studio EPICARDIA.' *GIAC* 13(3): 232–42.
- OECD. 2013. 'Consultations with doctors.' OECD Health Statistics 2013. As of 30 March 2015: <http://dx.doi.org/10.1787/888932917218>
- Ogilvie, I.M., et al. 2010. 'Underuse of oral anticoagulants in atrial fibrillation: A systematic review.' *American Journal of Medicine* 123(7): 638–645.e4.
- Ohlmeier, C., et al. 2013. 'Incidence, prevalence, and antithrombotic management of atrial fibrillation in elderly Germans.' *Europace* 15(10): 1436–44.
- Orensky, I.A., & D.A. Holdford. 2005. 'Predictors of noncompliance with warfarin therapy in an outpatient anticoagulation clinic.' *Pharmacotherapy* 25(12): 1801–8.
- OSMED. 2008. *L'uso dei Farmaci in Italia Rapporto nazionale anno 2008*. Rome: Istituto Superiore di Sanità.
- Oswald, N., & H. Bateman. 2000. 'Treating individuals according to evidence: Why do primary care practitioners do what they do?' *Journal of Evaluation in Clinical Practice* 6: 139–48.
- Pechlaner, C. 2011. 'Anticoagulation for Atrial Fibrillation: Underuse?' *American Journal of Medicine Letter* e11.
- Poli, D., et al. 2011. 'Stroke risk stratification in a "real-world" elderly anticoagulated atrial fibrillation population.' *Journal of Cardiovascular Electrophysiology* 22(1): 25–30.
- Pollard, L., et al. 2015. 'A study of role expansion: a new GP in cardiology care.' *BMC Health Services Research* 14:205.
- Pugh, D., et al. 2011. 'Attitudes of physicians regarding anticoagulation for atrial fibrillation: A systematic review.' *Age and Ageing* 40: 675–683.
- Raviele, A., et al. 2011. 'Linee guida AIAC 2010 per la gestione e il trattamento della fibrillazione atriale.' *Giornale Italiano di Cardiologia* 12(1 Suppl 1): 7–69.
- Raviele, A., et al. 2013. Linee guida AIAC per la gestione e il trattamento della fibrillazione atriale: aggiornamento 2013. *Giornale Italiano di Cardiologia* 14(3): 215–240.
- Reynolds, M.R., et al. 2009. 'Cost-effectiveness of radiofrequency catheter ablation compared with antiarrhythmic drug therapy for paroxysmal atrial fibrillation.' *Circulation* 2:362–69.
- Reynolds, M.R., et al. 2014. 'Cost-effectiveness of cryoballoon ablation for the management of paroxysmal atrial fibrillation.' *Europace* 16:652–59.
- Ricci, R.P., et al. 2009. 'Remote control of implanted devices through Home Monitoring technology improves detection and clinical management of atrial fibrillation.' *Europace* 11(1): 54–61.
- Ricciardi, W., et al. 2013. 'Rivaroxaban per la prevenzione dell'ictus in pazienti con fibrillazione atriale: risultati di una valutazione di HTA.' *QJPH* 2: 7.
- Rich, M.W. 2012. 'Atrial fibrillation in long term care.' *Journal of the American Medical Directors Association* 13(8): 688–91.
- Ringborg, A., R. Nieuwlaat, P. Lindgren, B. Jönsson, D. Fidan, A.P. Maggioni, et al. 'Costs of atrial fibrillation in five European countries: results from the Euro Heart Survey on Atrial Fibrillation.' *Europace* 10: 403–11.
- Roalfe, A.K., et al. 2012. 'A cross-sectional study of quality of life in an elderly population (75 years and over) with atrial fibrillation: secondary analysis of data from the Birmingham Atrial Fibrillation Treatment of the Aged study.' *Europace* eus102.

- Sankaranarayanan, R., et al. 2013. 'Comparison of atrial fibrillation in the young versus that in the elderly: A review.' *Cardiology Research and Practice* 2013 (976976).
- Sanmartín, M., et al. 2013. 'A campaign for information and diagnosis of atrial fibrillation: Pulse Week.' *Revista Española de Cardiología (English Edition)* 66(1): 34–38.
- Sardar, P., et al. 2014. 'New oral anticoagulants in elderly adults: Evidence from a meta-analysis of randomized trials.' *Journal of the American Geriatric Society* 62(5): 857–64.
- Schauer, D.P., et al. 2005. 'Psychosocial risk factors for adverse outcomes in patients with nonvalvular atrial fibrillation receiving warfarin.' *Journal of General Internal Medicine*, 20: 1114–1119.
- Schmidt, H., et al. 2009. 'What can we learn from German health incentive schemes?' *British Medical Journal* 339: b3504.
- Schneider, G. 2014. 'An antidote on the horizon? An update on the progress toward achieving reversibility for the new oral anticoagulants.' *Clinical Correlations*. As of 19 March 2015: <http://www.clinicalcorrelations.org/?p=7373>
- Shenasa, M., et al. 2012. 'Individualized therapy in patients with atrial fibrillation: New look at atrial fibrillation.' *Europace* 14(Suppl 5): v121–v124.
- SNIIRAM Database, 2013 data.
- Snowcroft, A.C., & M.R. Cowie. 2014. 'Atrial fibrillation: Improvement in identification and stroke preventive therapy – data from the UK Clinical Practice Research Datalink, 2000–2012.' *International Journal of Cardiology* 171(2): 169–73
- Sociedad Espanola de Cardiologia. 2012. *Manejo de los pacientes con fibrilacion auricular en los servicios de urgencias hospitalarios (actualización 2012)*.
- Societe Francaise de Cardiologie. 2014. *Les nouveaux anticoagulants oraux dans la fibrillation auriculaire: Ce qu'il faut savoir*.
- Souto, J.C., X. Ruyra & A. Bayes-Genis. 2013. 'Self-management of Vitamin K Antagonists Is More Cost-effective Than Dabigatran for Stroke Prevention in Non-valvular Atrial Fibrillation in Spain.' *Revista Española de Cardiología* 66(06): 510–11.
- Stewart, S. 2004. 'Cost of an emerging epidemic: An economic analysis of atrial fibrillation in the UK.' *Heart* 90: 286–92.
- Stiftung Deutsche Schlaganfall-Hilfe. 2012. 'Vorhofflimmern: Patienteninformation.' As of 19 March 2015: http://www.schlaganfall-hilfe.de/c/document_library/get_file?uuid=9c2ffe57-9f3a-4956-9bec-681ef2f34796&groupId=10156
- Stott, D.J., et al. 2012. 'RCPE UK Consensus Conference on "Approaching the comprehensive management of atrial fibrillation: evolution or revolution?"'. *Journal of the Royal College of Physicians Edinburgh* 42(Suppl 18): 3–4.
- Strong, S.H., & J.L. Halperin. 2007. 'Confronting atrial fibrillation in the elderly: Stroke risk stratification and emerging antithrombotic therapies.' *Geriatrics* 62(3): 22–27.
- Sullivan, S.D., et al. 2013. 'Interventions for the treatment of atrial fibrillation: A systematic literature review and meta-analysis.' *International Journal of Cardiology* 165(2): 229–36.
- UK National Screening Committee (UK NSC). Note of the meeting held on 18 June 2014.
- Universimed (2014). 'Kardiologie und Gefäßmedizin.' As of 19 March 2015: <http://kardiologie-gefaessmedizin.universimed.com/artikel/neuerungen-nach-dem-update-2012-richtlinien-zur-behandlung-von-v>
- Van Brabandt, H., et al. 2012a. 'Katheter-ablatie van voorkamerfibrillatie.' Health Technology Assessment (HTA). Brussels: Belgian Health Care Knowledge Centre (KCE). KCE Report 184A. D/2012/10.273/57
- Van Brabandt, H., et al. 2012b. 'Catheter ablation of atrial fibrillation.' Health Technology Assessment (HTA). Brussels: Belgian Health Care Knowledge Centre (KCE). KCE Report 184C. D/2012/10.273/57
- Van Gelder, I.C., et al. 2002. 'A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation.' *New England Journal of Medicine* 347(23): 1834–40.

- Van Walraven, C., et al. 2009. 'Effect of age on stroke prevention therapy in patients with atrial fibrillation: The atrial fibrillation investigators.' *Stroke* 40(4): 1410–16.
- Vilchez, J.A., et al. 2014. 'Biomarkers in atrial fibrillation: An overview.' *International Journal of Clinical Practice* 68(4): 434–43.
- Wasmer, K., & L. Eckhardt. 2011. 'Management of atrial fibrillation around the world: A comparison of current ACCF/AHA/HRS, CCS and ESC guidelines.' *Europace* 13: 1368–74
- Wiesel, J., et al. 2009. 'Detection of atrial fibrillation using a modified microlife blood pressure monitor.' *American Journal of Hypertension* 22(8): 848–52.
- Wiesel, J., et al. 2013. 'Screening for asymptomatic atrial fibrillation while monitoring the blood pressure at home: Trial of regular versus irregular pulse for prevention of stroke (TRIPPS 2.0).' *American Journal of Cardiology* 111(11): 1598–601.
- Wilke, T., et al. 2013. 'Incidence and prevalence of atrial fibrillation: An analysis based on 8.3 million patients.' *Europace* 15(4): 486–93.
- Wodchis, W.P., et al. 2012. 'A review of the cost of atrial fibrillation.' *Value Health* 15(2): 240–48.
- Wohlfahrt, J., et al. 2014. 'Clinical predictors to identify paroxysmal atrial fibrillation after ischaemic stroke.' *European Journal of Neurology* 21(1): 21–27.
- Wolf, P.A., et al. 1991. 'Atrial fibrillation as an independent risk factor for stroke: The Framingham Study.' *Stroke* 22(8): 983–88.
- Wouters, H., V. Thijs, & L. Annemans. 2013. 'Cost-effectiveness of dabigatran etexilate in the prevention of stroke and systemic embolism in patients with atrial fibrillation in Belgium.' *Journal of Medical Economics* 16(3): 407–14.
- Woods, C.E., & J. Olgin. 2014. 'Atrial fibrillation therapy now and in the future: Drugs, biologicals, and ablation.' *Circulation Research* 114(9): 1532–46.
- Wyse, D.G., et al. 2002. 'A comparison of rate control and rhythm control in patients with atrial fibrillation.' *New England Journal of Medicine* 347: 1825–33.
- Yates, S.W. 2013. 'Novel oral anticoagulants for stroke prevention in atrial fibrillation: a focus on the older patient.' *International Journal of General Medicine* 6: 167–80.
- Yiin, G., et al. 2012. 'Population-based study of temporal trends in atrial fibrillation related incident ischaemic stroke: evidence of substantial failure of primary prevention.' *Journal of Neurology, Neurosurgery & Psychiatry* 83(3): e1.
- Yiin, G., et al. 2014. 'Age-specific incidence, outcome, cost and projected future burden of atrial fibrillation-related embolic vascular events: a population based study.' *Circulation* 130(15): 1236–44.
- Zamani, P., & R.J. Verdino. 2014. 'Management of Atrial Fibrillation.' *Journal of Intensive Care Medicine* 1–15.
- Zarraga, I.G., & J. Kron. 2013. 'Oral anticoagulation in elderly adults with atrial fibrillation: integrating new options with old concepts.' *Journal of the American Geriatric Society* 61(1): 143–50.
- Zoppo, F., et al. 2014. 'Improving Atrial Fibrillation Detection in Patients with Implantable Cardiac Devices by Means of a Remote Monitoring and Management Application.' *Pacing and Clinical Electrophysiology* 37(12): 1610–18.