



The future of anticoagulation management in atrial fibrillation in Europe

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

Annexes

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Annex A Methodology

The study employed a multi-method approach to explore the current and future management of atrial fibrillation (AF) in Europe, with a focus on anticoagulation (Figure A.1). It involved a rapid evidence assessment of the literature, interviews with experts and the use of future scenarios as a tool for refining our understanding of future developments. 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 across 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 scenarios that were further refined and developed 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.

In the following sections we outline in more detail the methods used for each of these activities.

The research focussed on six countries in order to cover a range of European healthcare contexts: Belgium, France, Germany, Italy, Spain and the UK (Figure A.2).

Rapid evidence assessment

The rapid evidence assessment (REA) of the current literature had the following objectives:

1. To explore current AF management techniques across the six focus countries, both in terms of official guidance and how this guidance is employed in practice.
2. To assess ageing population trends and how they are likely to impact on the prevalence of AF and management options.

Figure A.1: Summary of research approach

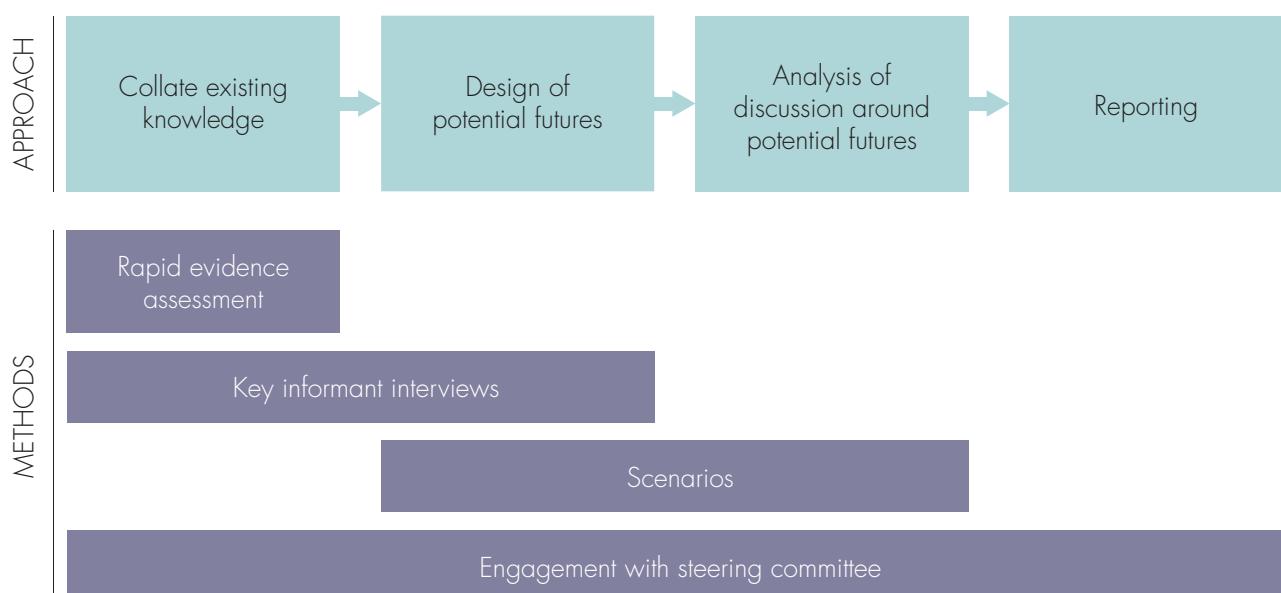
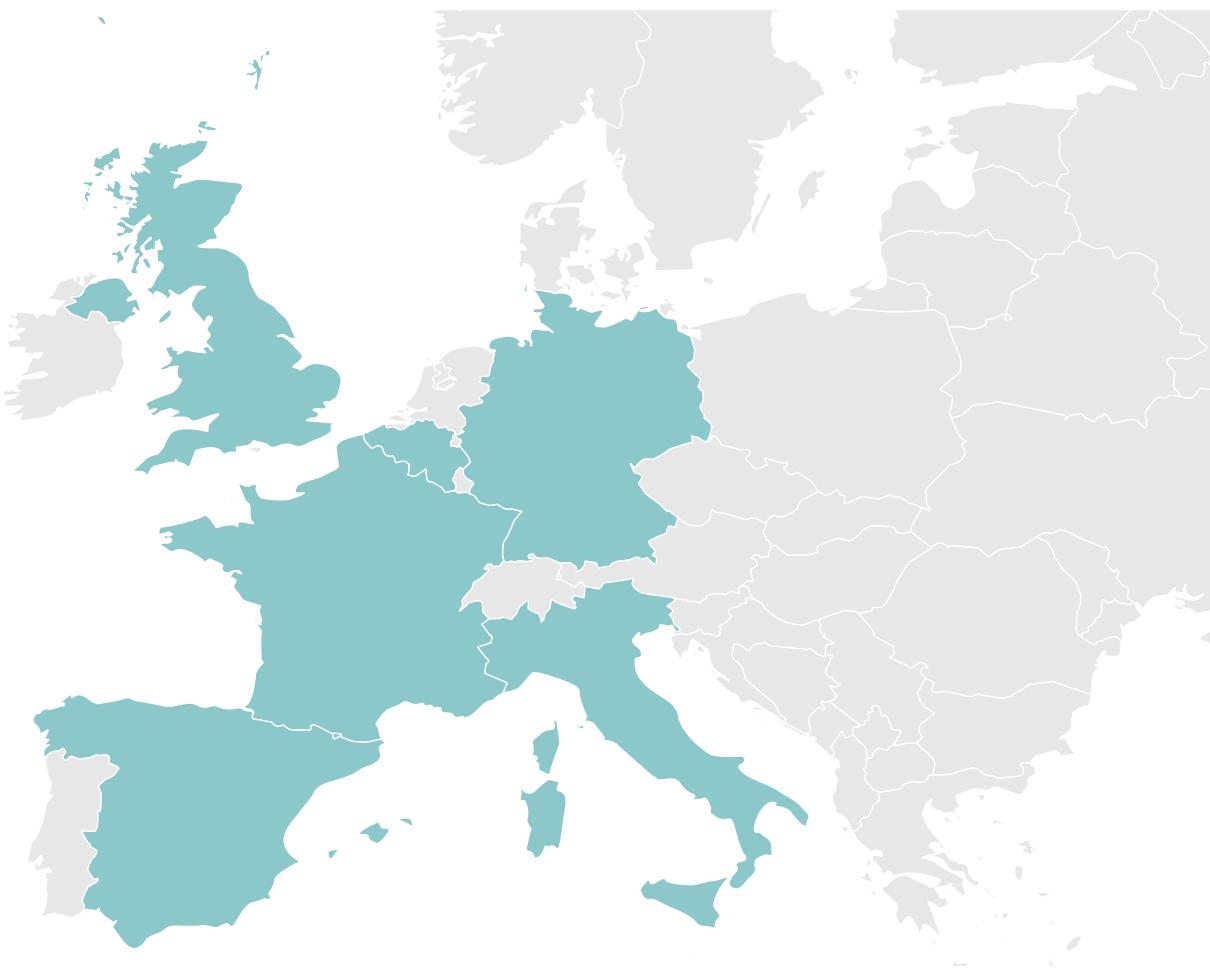


Figure A.2: The six focus countries were Belgium, France, Germany, Italy, Spain and the UK



3. To examine the barriers in identifying and accessing untreated patients and how these have been addressed in the six focus countries.
4. To understand how new treatment and management techniques for AF are likely to develop over the next five years.

Our team took a three-pronged approach to the evidence assessment:

1. First, to capture academic literature, the team performed searches of the PubMed database using a search strategy devised for each of the focus questions. This returned a total of 4,564 results (Table A.1). Following the search, all articles were screened using their titles and abstracts, categorised based on their content and long-listed based on their relevance to the REA objectives. Finally, we selected approximately 25 highly relevant articles for review for each of the four questions outlined above. Where appropriate, these articles were

supplemented with additional references from the reviewed articles through a snowballing process.

2. Second, the team reviewed official national guidelines, where available, for each of the six focus countries, as well as European guidelines, to determine their approach to AF management.
3. Third, the team reviewed key reports from patient organisations and professional bodies in each focus country.

The data were then synthesised, identifying common themes addressing each objective across Europe and the specific countries of focus, as well as elements unique to the focus countries.

Table A.1: Search term strategy for PubMed

Inclusion for different questions	Category	Terms
All questions (link: Disease AND Countries AND Treatment) ¹	Disease	"Atrial Fibrillation" OR "Atrial Fibrillation" (MESH) OR AF
	Countries	"European Union" OR Europe OR Belgium OR France OR Germany OR Italy OR Spain OR "United Kingdom" OR "Great Britain" OR Europe (MESH) OR Belgium (MESH) OR France (MESH) OR Germany (MESH) OR Italy (MESH) OR Spain (MESH) OR Great Britain (MESH)
	Treatment	Anticoagulant OR Anticoagulants (MESH) Treatment OR therapy OR Management
How new treatments and management techniques are likely to develop over the next five years	Question specific: Forward looking	Change OR Future OR Development OR Innovation
The barriers in identifying and accessing untreated patients and how these issues have been addressed across Europe, focussing particularly on France, Italy, Germany, UK, Spain and Belgium	Question specific	Barriers OR "untreated population" OR "under-treatment" OR "undertreatment" OR challenge OR "under-diagnosis" OR "underdiagnosis" OR "under-diagnosed" OR "underdiagnosed" OR identification OR diagnosis OR diagnosis (MESH) OR (physician AND decision)
Aging population trends and how they are likely to impact on the prevalence and treatment options for AF	Question specific	Population OR prevalence estimate OR aging OR ageing OR elderly OR (er AND (patient OR people))
Current AF management techniques across the six focus countries, including prevention strategies, both in terms of official guidance and how this guidance is employed in practice.	Question specific	Compliance OR guideline, OR monitoring OR "dose adjustment" "guideline adherence" (MESH)

Key informant interviews

During the study, a total of 60 telephone interviews were carried out (in the period from November 2014 to February 2015). The aim was to gather a range of perspectives on the current landscape and future of AF. Interviews were conducted using semi-structured interview protocols in the native or preferred language of the interviewee and according to the European regulations in force on adverse event reporting.² The English versions of these protocols are included at the end of this Annex. Each interview lasted between 45 and 60 minutes. Interviewees were identified through desk research according to a pre-set list of desired profiles and contacted via e-mail. They were required to sign confidentiality and consent documentation and received a financial incentive for their participation.

Interviews with key informants were employed at two points in the research. Initially they were used to complement the literature in helping the project team to gain an understanding of the AF landscape in each of the six focus countries, including the healthcare system and preferred management options. During this stage the team interviewed:

- For each focus country, one each of the following profiles:
 - Cardiologist
 - Patient representative
 - Policymaker/influencer
- Six members of our Steering Committee, from a range of focus countries and perspectives.

¹ These terms were required when searching for publications for all four objectives.

² The team used the appropriate national adverse event reporting guidelines for each interview. See (as of 19 March 2015): http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000176.jsp&mid=WC0b01ac058002ddcb

Following this, key informant interviews were used to explore the drivers of change shaping the future of AF, with a particular focus on the use of OACs in the prevention of AF-related stroke. During this stage the team interviewed five individuals for each focus country, including:

- Cardiologists
- GPs
- Nurses
- Policymakers
- Health economists
- Patient advocates.

These were complemented by six interviews which aimed to provide a pan-European perspective on the issues facing AF by focusing on general trends across Europe.

The geographical coverage of the interviews is illustrated in Table A.2. The breakdown of the professional profiles of the interviewees is illustrated in Table A.3.

Table A.2: Breakdown of key informant interviews by geography and steering committee membership

Belgium	8
France	8
Germany	8
Italy	8
Spain	8
UK	8
EU ³	6
Steering committee	6

Table A.3: Breakdown of Key Informant interviews by area of expertise

Cardiology, electrophysiology or neurology (including interviewees identifying mainly as clinicians and/or researchers)	26
Patient representation	14
Policy	8
Health economics	4
Primary care (including nurses)	4
Other (legal, technology, etc.)	4

Data was collected by taking written notes, as well as audio recordings. Verbatim transcripts were not made, but detailed notes were developed through review of the recordings. These were then analysed by type of

respondent, focus country and the objectives identified at the start of the REA, and these themes were reviewed and fed into the PESTLE analysis described below.

PESTLE analysis

A PESTLE analysis is a framework used to review factors affecting the environment and context an organisation is operating in. The factors covered (and defined in the acronym) are political, economic socio-cultural, technological, legal and environmental. In this instance we added an additional factor of population trends, understanding that the ageing population will have an impact on the future of AF management. Using this structured framework, we could identify the key drivers of change which should be included in the scenario development.

Evidence and analysis from the REA and key informant interviews were used to populate the PESTLE framework. This was carried out at a country level, as well as at an aggregated European level. The areas identified for consideration in the future of AF management are illustrated in Table A.4. The sub-topics were established and mapped through consideration of themes in the REA and analysis of the interview reports and discussions with the steering committee, noting where appropriate country specific comments (as illustrated in Table A.5).

Comments and findings were further categorised according to whether they represent i) a statement about the current situation and area where change is needed, ii) a possible type of change, or iii) a change that may already be emerging in certain areas. Finally, the impact and likelihood of change in each area were considered on the basis of interviewee comments, evidence of change beginning and the extent that consensus was observed about issues to be addressed.

Scenario building

We cannot predict with certainty what will happen in the future, but we can use our understanding of the present to think about what might occur. By constructing scenarios – logical and consistent pictures of the future – we can explore the implications of decisions made today. Scenarios help us to provide insight into potential developments and how they might impact AF prevention, treatment and management. While the scenarios as described may be exaggerated versions

³ EU interviewees were based in Belgium (3 people), Spain and the UK (2).

Table A.4: Sub-topics of PESTLE analysis

Area of review	Sub-topics
Political	<ul style="list-style-type: none"> • Policymaker awareness • AF as a political priority
Economic	<ul style="list-style-type: none"> • NOAC costs • Incentives for AF diagnosis • Subsidies for diagnostic tools or NOAC antidote • Cost-effectiveness analyses looking at wider system costs • Pressure on healthcare budgets
Social	<ul style="list-style-type: none"> • Public awareness • Patient compliance • Patient education • Patient preference and engagement • HCP education (primary or secondary care)
Technological	<ul style="list-style-type: none"> • NOACs and antidotes • Other interventions (ablation, LAOO, anti-arrhythmic drugs, etc.) • Digital devices (home monitoring, pulse/ECG check) • Research on AF
Legal	<ul style="list-style-type: none"> • Level of adherence to clinical guidelines • Other regulatory/liability issues
Environmental	<ul style="list-style-type: none"> • Screening and detection • Patient pathway (role of primary vs. secondary care) • Level of access to care • Community care

Table A.5: Example of how data was analysed focusing on each of the PESTLE factors and sub-topics identified

	Policy		Population trends			Economic		Social	
	Awareness of policymakers	AF as a policy priority	Elderly	Renal dysfunction	Younger people	Costs (including cost-effectiveness in decision making, NOAC costs, etc.)	Subsidies and incentives	Education	Patient preference
KII 1									
KII 2									

KII: Key informant interview

of possible developments, the real future is likely to contain elements from each scenario. By thinking through these changes, we can explore the implications of choices made today – in terms of both risks and opportunities – and prepare for the future.

The research team aimed to make the draft scenarios logically consistent based on current evidence, but pushing beyond what we expect will definitely happen. The scenarios sought to deliberately exaggerate each future so that it was possible to explore the impacts of specific changes. They are thus a tool for exploring the implications of change, not for making predictions about the future. To develop three scenarios, insights from the literature, interviews and the PESTLE analysis were used. The PESTLE framework allowed us to explore how

specific factors or drivers of change may work together in order to create a plausible future. These links can be illustrated if we summarise the process we used in developing *Scenario One: Advancing a patient-centric approach through awareness and education*. This scenario envisages a world where there are large public health campaigns to raise awareness of AF, all actors are educated about AF (including the public, patients and healthcare professionals (HCPs)), individuals feel empowered to test their own pulse, and primary care takes primary responsibility for AF patients. We arrived at this scenario as follows:

- **Political factors:** The majority of interviewees felt that policy buy-in and public health campaigns to raise awareness about AF would be very impactful

and beneficial in managing AF in the future. Many stated that public health campaigns for AF are not likely although we also heard that the majority of governments are likely to prioritise prevention.

Outcome: A future where there is investment in public health campaigns to make the public, patients and HCPs aware of AF, reducing the number of AF-related strokes. The rationale is that individual empowerment helps individuals identify AF in themselves, enabling early detection.

- **Population trends:** Estimates suggest that there will be increased prevalence of AF in the future due to an ageing population, improved longevity of those with AF and increases in other risk factors. (This factor features across all of the scenarios, as mentioned above).

Outcome: There is increased prevalence of AF.

- **Economic factors:** We gathered data on the importance of making cost-effective (long-term) decisions and how this relates to the prevention of AF and AF-related stroke. A number of interviewees highlighted the importance of finding the cause of AF in the future as well as managing AF before it causes AF-related stroke (e.g. through screening, self-identification or other means).

Outcome: There is investment in public health campaigns to raise awareness (with a rationale to improve lifestyles and enable early detection) as well as research to find the cause of AF.

- **Social factors:** The key social issues we identified through our data related to education (for the population, HCPs and patients), patient preference, patient compliance and the importance of screening. We identified the drivers within those themes that would fit with the world we had started to create. In this scenario, education would be addressed through large public health campaigns, the issue of patient compliance would be reduced due to increased education (given the majority of interviewees felt education would directly address the issue) and individuals would feel empowered to check their own pulse on a regular basis. This individual empowerment would be reinforced through the school curriculum, education in pharmacies and innovations to aid pulse checking. These factors were suggested across the interviews, although are more likely in some countries than others. For example, German interviewees did not believe there was a role for pharmacies to play in AF management (and this

has been noted in the country evidence table for this scenario).

Outcome: Public health campaigns educate all, screening happens at the individual level and is facilitated through a range of support mechanisms, and education improves patient compliance.

- **Technological factors:** A broad number of potential technological developments emerged from our data. The development incorporated into this scenario is innovations to aid individuals in testing their own pulse. We focused on this driver given its fit with the rest of the scenario. Other key technological developments are explored in other scenarios.

Outcome: Innovations to aid individuals in testing their pulse are developed and marketed on a wide scale across Europe.

- **Legal factors:** Our research identified very few regulatory or legal factors relevant to the development of AF diagnosis and care. However, related to devices to help individuals test their pulse, we did hear that there may be legal obstacles related to accountability – e.g. if a device fails to detect AF in a person who goes on to suffer an AF-related stroke.

Outcome: There are legal worries in this area which remain unresolved, although they have stifled further innovation.

- **Environmental factors:** A large number of interviewees (particularly in the UK, Spain and Italy) emphasised the role of primary care in managing AF and the likelihood of this expanding in the future. Many specifically noted the potential for nurses and pharmacies to expand their involvement. Given the focus on individual empowerment and identification of AF in this scenario, the notion of primary care managing AF seems feasible. Early intervention is likely to reduce the number of AF-related strokes and therefore hospital cardiologists are less likely to be the first HCP contact in dealing with AF along the patient pathway. Of course this will not be the case in every country (the role of primary care in this area is less pronounced in Germany) and indeed there are a number of risks to this approach.

Outcome: Primary and community care providers are the key players in managing AF and educational messages are reinforced by pharmacies, nurses and GPs.

Scenarios workshop and development of recommendations

Once the project team at RAND Europe had developed the scenarios, they were shared with the steering committee at a one-day workshop held in Brussels in February 2015. During the workshop, the members of the steering committee worked in groups to review the scenarios and develop a pathway of steps that would be required to achieve the situation described in each scenario. These pathways included key developments and milestones that would need to happen for each scenario to become reality. Following this, attendees discussed as a whole group the risks and opportunities that would arise within each scenario, looking for ways to mitigate the risks and promote benefits. These discussions formed the basis for formulating the recommendations outlined in the main section of this report.

The scenarios were refined in light of these discussions and the final versions, including lists of risks and opportunities discussed, are presented in Annex 4. Key themes emerging from the discussion of risks and opportunities were used as the basis for the recommendations.

Steering committee

As part of the study, an expert steering committee was set up to provide expert perspectives on the research findings and bring consensus around steps required to change and improve AF management, with a focus on anticoagulation. Members, listed below, were selected to ensure representation from key disciplines across the fields of cardiology and neurology, as well as health economists, pharmacologists, primary care and patient groups.

The steering committee met twice in person and once virtually during the project. On the first occasion they reviewed the results of the REA, and provided input to the interview protocols. On the second occasion they reviewed and refined the scenarios. In addition, they provided input by telephone and email at several points in the project, including on the results of the interview analysis prior to the development of the scenarios and on the structure of the final report following the second workshop. Finally, a number of the steering committee members were interviewed individually.

Name	Professional role and affiliation
Professor John Camm (Chair)	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	Chief Executive Officer of 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

Phase 1 interview protocol

Interviewee participation

Taking part in the interview is entirely voluntary. You have the right to withdraw from the research at any point and the right not to give an answer to a question. Throughout the interview written notes will be taken, and with your permission the interview will be recorded. The recordings will only be used for note-taking purposes to ensure we have captured your points and perspective accurately and will be destroyed after analysis is complete. The research is being conducted in accordance with the European Market Research Association Code of Conduct and British Healthcare Business Intelligence Association guidelines. A payment is available to reimburse you for your time.

Confidentiality

All information collected about you and your organisation will be kept strictly confidential and will not be passed on to the company sponsoring the research or any other third party. Interview recordings and transcripts will only be available to the investigator and will be kept in a secured file. Original recordings will be destroyed within six months of conducting the interviews. No comments will be directly attributed to a particular person in our reporting and where quotes are used there will be no reference to your name or organisation. You also have the option of not being quoted at all.

We are required to pass on to our client details of adverse events and/or product complaints that are mentioned during the course of market research. Although what you say will, of course, be treated in confidence, should you raise during the discussion an adverse event and/or product complaint, we will need to report this even if it has already been reported by you directly to the company or the regulatory authorities using the MHRA's 'Yellow Card' system. In such a situation you will be asked whether or not you are willing to waive the confidentiality given to you under the Market Research Codes of conduct specifically in relation to that adverse event and/or product complaint. Everything else you say during the course of this interview will continue to remain confidential, and you will still have the option to remain anonymous if you so wish. Are you happy to participate with the interview on that basis? [See text at end of protocol for use if an adverse event is reported]

Introduction

1. Please could you tell us a bit about your role (and organisation if appropriate) and the work you do in relation to atrial fibrillation?

For cardiologists only:

2. Please outline how your role regarding atrial fibrillation fits within the wider health service delivery approach in this area

Explore how AF is usually treated – whether through primary or secondary care – and who the main players are.

Overview of treatment options

3. Are there particular AF treatments (in relation to preventing AF-related stroke or more broadly) that are favoured for use in your country? (*Compare with guideline review and see if there are any differences*)
4. Do you believe official guidelines reflect the reality of practice regarding the treatment of atrial fibrillation in your country?

The delivery of care

5. How is care for atrial fibrillation delivered in your country? (*e.g. through hospital-based clinics, etc.*)
6. Who are the key players in providing this care? (*e.g. cardiologists, GPs, nurses, etc.*)
7. How time and resource intensive is the provision of this care?
8. How likely do you think it is that advances in treatment options could change the way in which care is delivered? (*e.g. a shift away from monitoring clinics towards increased home testing, etc.*)
9. Do you think a shift away from this system would be desirable?

Barriers to treating AF patients

10. How are patients with atrial fibrillation identified at present?
11. How well is that system of identifying patients working?
12. Are there particular systems in place to identify vulnerable individuals at risk of AF?

13. How do you think processes of identification will change in future and what changes would you personally like to see to this system?

For both questions probe in relation to medical advances, regulatory/political changes, costs and economic developments and social/psychosocial factors

How physicians make decisions

14. Do you believe anticoagulants are currently under- or over-prescribed in your country?
15. If so, why do you think this is? *Probe on risk aversion (including risks of falling and bleeding), age, contraindications, interactions with drugs, foods and alcohol and how important each of these factors are in affecting physician decisions.*
16. How important are the costs of treatment and resource constraints in determining physician decisions to treat?
17. How important is the healthcare setting in determining physician decisions to treat?

Patient preference

18. How important do you believe patient preferences are in determining the approach to treating AF?
19. Do you have a sense of whether certain treatments are preferred over others?
20. How significant is the issue of patient non-compliance to anticoagulant therapy in your country? Why do you think non-compliance occurs?
21. Do you believe that patients' perceptions of risks in relation to strokes and anticoagulants are in line with how physicians assess those risks? (*i.e. are patients less risk averse than physicians re bleeding risks and more risk averse re stroke risks than physicians?*)
22. More broadly, how large a role do you think patient preference will play in determining the future of treatments for preventing AF-related stroke?

Futures

23. What is likely to change in relation to anticoagulant therapy in the next 3–5 years? (*including other AF-related stroke prevention strategies which may affect the way anticoagulants are prescribed*)
24. What is likely to change in relation to anticoagulant therapy in the next 10 years and beyond? (*including other AF-related stroke prevention strategies which may affect the way anticoagulants are prescribed*)

Additional questions just for policymakers

1. Do you think AF is a priority for policymakers?
2. Why/why not?
3. If not, what would it take to make it priority for policymakers?

Additional questions just for patient reps

1. How would you characterise the level of patient engagement in this area? (e.g. high, medium, low)
2. Why do you think that is?
3. What support systems are in place for patients, outside of the healthcare setting?
4. Do you have particular support mechanisms for different groups (e.g. younger patients, the elderly)?
5. How widely are these support services taken up?
6. What do these support systems offer? (e.g. support with side effects, emotional support, etc.)

Suggested text, should a HCP respondent raise an adverse event or product complaint:

'Doctor, [what you have just said]/[what you said earlier in the interview] is classified as an adverse event/ product complaint. The company commissioning this market research has a legal obligation to report this as part of their ongoing benefit risk management. I would like to spend a couple of minutes with you now to collect the necessary details of the adverse event/product complaint, so that the company can report this and meet their legal obligations. Are you willing to assist with the reporting of this adverse event/product complaint?'

If yes:

"Thank you. The information you provide will be sent to the company's Drug Safety department who may contact you directly for further information. Please note that if you provide your name during the adverse event/ product complaint reporting, this will not be linked in any way to your responses given during the interview."

Note: If respondent subsequently says no, then go to the 'If no' section.

If no: ‘Because I have become aware of this reportable adverse event/ product complaint I am obliged to report this to the company. I will file this report without giving any of your details, but if the Drug Safety department requires more information, may we contact you again (without identifying you to the company)?’

If still no: ‘Thank you doctor – I’ve made a note of that.’

Phase 2 interview protocol

Interviewee participation

Taking part in the interview is entirely voluntary. You have the right to withdraw from the research at any point and the right not to give an answer to a question. Throughout the interview written notes will be taken, and with your permission the interview will be recorded. The recordings will only be used for note-taking purposes to ensure we have captured your points and perspective accurately and will be destroyed after analysis is complete. The research is being conducted in accordance with the European Market Research Association Code of Conduct and British Healthcare Business Intelligence Association guidelines.

Confidentiality

All information collected about you and your organisation will be kept strictly confidential and will not be passed on to the company sponsoring the research or any other third party. Interview recordings and transcripts will only be available to the investigator and will be kept in a secured file. Original recordings will be destroyed within six months of conducting the interviews. No comments will be directly attributed to a particular person in our reporting and where quotes are used there will be no reference to your name or organisation. You also have the option of not being quoted at all.

We are required to pass on to our client details of adverse events and/or product complaints that are mentioned during the course of market research. Although what you say will, of course, be treated in confidence, should you raise during the discussion an adverse event and/or product complaint, we will need to report this even if it has already been reported by you directly to the company or the regulatory authorities using the MHRA’s ‘Yellow Card’ system. In such a situation you will be asked whether or not you are willing to waive the confidentiality given to you under the Market Research Codes of conduct specifically in relation to that adverse event and/or product complaint. Everything else you say during the course of this interview will continue to remain confidential, and you will still have the option to remain anonymous if you so wish. Are you happy to participate with the interview on that basis? [See text at end of protocol for use if an adverse event is reported]

Opening question

- What are the top 3 factors that will influence AF diagnosis, treatment and management in the near (3–5 years) and medium (10 years and beyond) terms?

Political

- Are policymakers aware of AF and the challenges it brings?
- How important are AF awareness campaigns for the general public? *[Particularly for policymakers: Probe on whether policymakers view AF as a problem particular to the elderly which does not affect the working population, etc.]*
- How important are public health campaigns in preventing AF *[e.g. to tackle obesity, alcohol intake and other population risk factors?]*
- [For policymakers only:]* How likely is it that decisionmakers will invest in AF awareness campaigns within the next 3–5 years and beyond?
- [For policymakers only:]* How likely is it that decisionmakers will invest in public health campaigns to prevent AF within the next 3–5 years and beyond? *[e.g. focusing on awareness re risk factors for AF such as obesity, alcohol intake, etc.]*
- If it is unlikely, what would it take to get this on the political agenda? *[Educating policymakers, a certain number of AF-related strokes/fatalities, public campaigns, etc.]*

Population trends

- How important is routine screening in identifying AF? Why is this the case? *[Probe on whether early diagnosis is important]*
- Do you think advances are needed in treating/managing the elderly with AF? If so, what might those treatments/management strategies look like?
- Do you think advances are needed in treating/managing those with AF and renal dysfunction? If so, what might those treatments/management strategies look like?

Economic

- How significant is the cost of NOACs in prescription decisions?

- Would a reduction in the cost of NOACs increase NOAC uptake? If so how much of a reduction would be needed?
- Would a subsidy in the [potential] antidote cost increase NOAC uptake? If so, how significantly?
- [If not already covered in Qs 11–13]* How significant is the budget system within your healthcare system as a barrier to prescribing NOACs? *[Probe on whether the disconnect between budgets for different departments acts as a disincentive to think about long-term holistic costs – i.e. the long-term cost-effectiveness of NOACs]*
- Could financial incentives for diagnosing AF for GP surgeries/pharmacies/other healthcare providers play an important role in the future of AF?
- How important would the financial subsidy of diagnostic tools be in determining the future of AF?

Social

- Is a lack of patient understanding regarding the symptoms of AF significant in preventing timely diagnosis?
- How important is further education for HCPs regarding the effective use of OACs? *[Probe on whether some HCPs would benefit from further education more than others].* What other factors are important?
- How significant is the issue of patient compliance? Is this likely to change with the use of NOACs versus the use of warfarin? Is this likely to change with better education for patients?

Technological

- What scientific breakthroughs do you think are likely in the next 3–5 years? *[e.g. biomarkers and clinical predictors for diagnosis, antidotes, breakthroughs in LAAO, others?]*
- What scientific breakthroughs do you think would have the most impact in the next 3–5 years?
- What might be the factors affecting NOAC use versus use of the alternative vitamin K antagonists currently in development?
- How far will ablation techniques or other AF treatments impact on the use of OACs and NOACs in the next 3–5 years and beyond?

24. Are there the necessary skills in your country to enable ablation techniques to have a large impact in the next 3–5 years?

Legal

25. Are there any regulatory factors which may impact on the diagnosis, treatment and management of AF?
26. Are there any regulatory factors which may specifically impact on the use of OACs or NOACs?

Environmental (healthcare setting)

27. Will responsibility for the AF patient along the patient pathway change in the next 3–5 years? Why/why not?
28. Would a change be desirable? Why/why not?
29. Are there broader changes in the way care is delivered in treating/managing AF that would have a significant impact?
30. What is the level of access to care for AF in your country and how might this change in the next 3–5 years? *[e.g. in the UK only a small number of centres of excellence can perform left atrial appendage occlusion. Are there other situations elsewhere which may have a significant impact on the types of care that are accessed?]*

Suggested text, should a HCP respondent raise an adverse event or product complaint:

'Doctor, [what you have just said]/[what you said earlier in the interview] is classified as an adverse event/ product complaint. The company commissioning this market research has a legal obligation to report this as part of their ongoing benefit risk management. I would like to spend a couple of minutes with you now to collect the necessary details of the adverse event/product complaint, so that the company can report this and meet their legal obligations. Are you willing to assist with the reporting of this adverse event/product complaint?'

If yes: 'Thank you. The information you provide will be sent to the company's Drug Safety department who may contact you directly for further information. Please note that if you provide your name during the adverse event/ product complaint reporting, this will not be linked in any way to your responses given during the interview.'

Note: If respondent subsequently says no, then go to the 'If no' section.

If no: 'Because I have become aware of this reportable adverse event/ product complaint I am obliged to report this to the company. I will file this report without giving any of your details, but if the Drug Safety Department requires more information, may we contact you again (without identifying you to the company)?'

If still no: 'Thank you doctor – I've made a note of that.'

Annex B

Rapid evidence assessment – mapping the AF landscape

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). Those who suffer AF are at higher risk of heart failure, stroke and other embolic complications (Sullivan et al. 2013). The prevalence of AF increases with age and is therefore expected to increase alongside population ageing in Europe (see Section 1.4).

In this annex, we present findings from an assessment of academic and grey literature on AF prevalence, diagnosis, treatment and management, as well as a review of clinical guidelines for AF treatment and management. The focus of the work is on stroke prevention in AF patients, and anticoagulation therapy in particular. We concentrate on evidence from the six focus countries: Belgium, France, Germany, Italy, Spain and the UK.

Types of atrial fibrillation

Clinical guidelines categorise AF into four types, as described in Zamani & Verdino (2014):

1. Paroxysmal atrial fibrillation – defined as recurrent AF (two or more episodes) that terminates spontaneously within 7 days, usually within less than 48 hours.
2. Persistent atrial fibrillation – defined as continuous AF lasting for more than 7 days or AF that was electrically or pharmacologically converted more than 48 hours after initiation.
3. Long-standing persistent atrial fibrillation – defined as continuous AF lasting more than one year.⁴

4. Permanent atrial fibrillation – refers to AF in patients who have decided not to restore sinus rhythm.

AF can also be valvular or non-valvular. Valvular AF refers to cases whereby AF is caused through mitral stenosis, the hardening and narrowing of the heart's mitral valve. Non-valvular AF refers to AF that is not associated with mitral stenosis. Treatment options differ according to whether AF is valvular or non-valvular as well as according to the four types of AF.

Current treatment options for the management of AF

AF can be treated in multiple ways – through rhythm or rate control strategies as well as through antithrombotic treatments or surgical options to reduce the risk of stroke. A brief overview of treatment options for AF is below, followed by a review of clinical guidelines from the European Society of Cardiologists and the six focus countries. As the focus of this work is on stroke prevention (and anticoagulation therapy in particular), the review of guidelines concentrates on stroke prevention.

Rate and rhythm control

Rate and rhythm control strategies are employed to directly address the irregular rhythm of the heartbeat in AF in order to alleviate symptoms. They can be pharmacological and non-pharmacological in nature. Rate control strategies include AV-node blocking drugs such as digoxin, beta-blockers or calcium channel blockers (Zamani & Verdino 2014).

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.

Treatments for rhythm control include anti-arrhythmic drugs such as amiodarone, sotalol or flecainide, as well as electrical cardioversions, surgical or catheter ablation and cardiac resynchronization therapy (Zamani & Verdino 2014). In terms of pharmacological approaches to rhythm control, ‘pill in the pocket’ strategies exist, where patients take a dose of the drug without visiting a hospital or healthcare professional. This approach enables patients to self-manage their condition, but is only recommended for those with infrequent episodes and few symptoms (and would therefore fall in category 1 according to Zamani & Verdino (2014)) (NICE 2014; Battigelli et al. 2013).

In terms of non-pharmacological interventions, electrical cardioversion consists of mild electric shocks that are intended to trigger the heart to return to its normal rhythm. In catheter ablation, catheters are inserted into blood vessels in the arms or legs and threaded through to the heart, where radio waves are then emitted to destroy small areas of heart tissue that may be contributing to the arrhythmia. Achieving pulmonary vein isolation is currently considered the main approach among curative AF ablation procedures, although a number of other approaches are being explored. In addition, although radiofrequency energy using bipolar catheters is the mainstay of ablation technologies, there are advances in alternative methods such as cryoballoons, multipolar ablation catheters, direct visual guidance and lasers (Marcus et al. 2013).

Clinical trials have explored the benefit of restoring a sinus rhythm using anti-arrhythmic drugs for the general AF population. For example, the large-scale Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial included 4,060 patients with recurrent AF and enrolled them either into a rate-control or rhythm-control strategy, with mandatory oral anticoagulation (Wyse et al. 2002). After follow-up of 3.5 years, there were no significant differences in overall mortality for patients on rate versus rhythm control (Zamani & Verdino 2014). Findings were similar for the Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE) trial, which also compared rhythm control and rate control (Van Gelder et al. 2002): no benefit was identified for rhythm control, which involved drug therapy and repeated electrical cardioversions (Zamani & Verdino 2014). Meta-analyses have confirmed the lack of benefit of rhythm-control in the general AF population, although there may be less evidence available on impacts in younger and highly symptomatic patients (Zamani & Verdino 2014).

Stroke prevention in AF

Stroke prevention treatment in AF can also be pharmacological or non-pharmacological. Non-pharmacological approaches consist of various methods to close the left atrial appendage (LAA) in the heart. Among patients with AF, the LAA is the prominent site of thrombus formation due to its anatomical location and the diminished blood flow it receives during AF. However, roughly 25 per cent of thromboembolic events take place outside the LAA and therefore patients can still be at risk of thromboembolisms after LAA closure (Han et al. 2012).

There are numerous ways to approach LAA closure. One is surgical ligation or amputation of the LAA, although this is usually only undertaken in patients who are undergoing cardiac surgery for other indications (Han et al. 2012). Second, endocardial LAA occlusion can be performed through percutaneous catheter-based methods. To date, four devices with a purely endocardial approach have been investigated for LAA occlusion (Camm et al. 2014a). Epicardial LAA occlusion is also being explored and a number of devices are in development (Han et al. 2012). These techniques are examined further below in relation to the development of future treatment options.

Pharmacological approaches to stroke prevention can be categorised into two primary categories: Anticoagulant therapy (the focus of this research) and antiplatelet therapy. Dual antiplatelet therapy with aspirin and clopidogrel is advised in some European guidance, although this is generally for patients who refuse anticoagulants or for whom anticoagulants are contraindicated. In the UK, antiplatelet therapy has been undertaken with aspirin, but the 2014 NICE guidelines state that aspirin monotherapy should not be prescribed for the sole purpose of stroke prevention in patients with AF.

Pharmacological approaches to anticoagulation have mainly used 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 a number of problems with this type of treatment, 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 range for coagulation, one study (Cotté et al. 2014) looked at the length of time patients spend in the target range of VKAs in four European countries: France (which mainly uses the VKA fluindione), Germany (which mainly uses phenprocoumon), and Italy and the UK (which mainly use warfarin). It 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; this difference may be attributable to the use of specialised ‘warfarin clinics’ for monitoring treatment in the UK. In these specialised clinics, patients are more closely followed, INR is frequently controlled and the dose of VKA is adapted in a more responsive manner than in the other countries included in the study. Poorly controlled treatment is 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.

In recent years, non-VKA oral anticoagulants (NOACs) have been developed which have been shown to overcome a number of these problems. 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, p. 1), making long-term treatment with NOACs more accessible than treatment with VKAs. 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.

A number of studies have compared NOACs with VKAs and have found the former to be more effective for stroke prevention for 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 anti-coagulation 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).

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. ROCKET-AF 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.

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. Of primary 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), but no such antidote exists for NOACs – although a number are being investigated. 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).

Two additional issues are cost and whether there is a need for monitoring. 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). While the fact that NOACs would not require monitoring has been

seen as an advantage because it makes the drugs more convenient, a scientific opinion issued by France's health authority cites the lack of a means in current practice to monitor the level of anticoagulation as a reason that NOACs should be considered as a second-choice option to be used when VKAs are not appropriate (HAS 2015). The authority also noted that there is evidence of variability in INR after one month of dabigatran treatment, and that this variability raises a question about whether there may be a need for monitoring with dabigatran in some patients (HAS 2014b).

A review of guidelines

We reviewed current national guidelines from the countries of focus for this study as well as those of the ESC (Camm et al. 2012). France (Haute Autorite de Sante 2014a, 2014b, 2014c and 2014d), Italy (Raviele et al. 2011 and 2013), Spain⁵ and the UK (NICE 2014) have established national guidelines. Germany uses ESC guidelines,^{6,7} while Belgium does not have official national guidelines.⁸

Our review concentrated on recommendations for when and how to use stroke prevention therapies. The main points are presented in Table B.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, but key differences exist regarding the use of aspirin, oral anticoagulants and LAAO.

- Assessing stroke risk – CHADS₂ vs.**

CHA₂DS₂-VASc: The guidelines refer to two tools for estimating stroke risk: CHADS₂ and CHA₂DS₂-VASc. 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 and female sex (Odum et al. 2012).

ESC guidelines recommend the use of CHADS₂ unless a patient has a CHADS₂ score of 0–1, in which case the CHA₂DS₂-VASc is to be used. Guidelines from France, Italy, Spain and the UK recommend using CHA₂DS₂-VASc from the outset.

CHA₂DS₂-VASc scores for risk stratification in atrial fibrillation

- Congestive heart failure (1 point)
- Hypertension* (1 point)
- Age ≥ 75 (1 point)
- Diabetes (1 point)
- Stroke or transient ischaemic attack (2 points)
- Vascular disease (1 point)
- Age 65–75 (1 point)
- Sex category (1 point for female)

*Defined as systolic blood pressure > 160 mmHg

- Assessing bleeding risk – HAS-BLED:** The ESC guidelines, along with all of the country guidelines reviewed, recommend the use of the HAS-BLED system to assess bleeding risk.

HAS-BLED scores for risk stratification in atrial fibrillation

- Hypertension (1 point)
- Abnormal liver or renal function (1 point each)
- Stroke (1 point)
- Bleeding (1 point)
- Labile INR (1 point)
- Elderly – greater than 65 years (1 point)
- Drugs or alcohol (1 point each)

- The use of aspirin:** The French guidelines recommend aspirin coupled with clopidogrel for patients with a CHA₂DS₂-VASc score of 1, for patients with AF who have refused anticoagulant treatment or for patients with any contraindication to anticoagulants. This recommendation is similar

⁵ Sociedad Espanola de Cardiologia (2012).

⁶ The German Society for Cardiology (DGK) has published pocket guidelines in German summarising the ESC guidelines. See (as of 19 March 2015): http://leitlinien.dgk.org/files/Pocket_Leitlinien_Vorhofflimmern_Update2013.pdf

⁷ German physicians are also aware of guidelines from the Drug Commission of the German Medical Association (AkdÄ), which discuss prescription of VKAs versus NOACs, but these guidelines are not often used (AkdÄ, pers. comm., 20 Jan 2015) and so this review takes the German guidelines to be the ESC guidelines.

⁸ Belgium does have in-country guidance, but because there is variation across the country in terms of guidelines followed, this guidance has not been included in this review.

Table B.1: Guidelines review – summary

Recommended practice	ESC	France	Italy	Spain	UK
Use of CHA₂DS₂-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

to that in the ESC guidelines, which state that the use of aspirin-clopidogrel therapy or aspirin monotherapy should be limited to the few patients who refuse anticoagulation therapy. French guidelines also recommend aspirin monotherapy for patients undergoing biotherapy. In contrast, the UK guidelines state that aspirin monotherapy should not be used for stroke prevention in AF patients, but does not comment on dual-antiplatelet therapy. The Italian guidelines state that aspirin should not be prescribed for low–medium risk patients, but recommend it for patients with vascular disease.

- **VKAs vs. NOACs:** ESC guidelines state that NOACs are broadly preferable to VKAs for most non-valvular AF patients, but they also state that one NOAC cannot be recommended over another. The Italian and UK guidelines advocate using either NOACs (apixaban, rivaroxaban and dabigatran) or VKAs for patients with non-valvular AF. In Italy, NOACs are recommended in patients who have not been taking VKAs and who have a history of stroke or intra-cranial haemorrhages, or would have difficulty with monitoring, among other factors.⁹ The Spanish guidelines recommend the VKAs acenocumarol

and warfarin in the first instance, only suggesting NOACs for those contraindicated for VKAs or for whom VKAs have been unsuccessful. In France as well, VKAs are considered the first choice unless they are contraindicated or have resulted in poor INR control in the patient, or if the patient prefers NOACs (HAS 2014b-d).¹⁰ For selecting from among the three NOACs marketed in France, the HAS has ranked the drugs 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.

- **Compulsory anticoagulation:** In France, anticoagulation is considered compulsory for patients receiving electrical or pharmacological cardioversion. However, other guidelines emphasise the importance of patient preference in choosing anticoagulant therapy, and the need for physicians to explain the pros and cons of the treatment options to patients.

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

⁹ The Italian guidelines also recommend changing the medication from VKAs to NOACs for patients for whom treatment with a VKA has given suboptimal results (<60% of the time spent in therapeutic range), among other conditions.

¹⁰ This situation reflects a recent change in the HAS position based on a re-evaluation of data. The 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.

NOACs: the RE-LY trial (dabigatran), ROCKET-AF (rivaroxaban) and ARISTOTLE (apixaban) (Camm et al. 2012). The ESC guidelines were updated in 2012, just two years after the previous edition issued (Camm et al. 2010). A major change from 2010 to 2012 was in guidance on the use of NOACs versus VKAs.

In the 2010 guidelines, the recommendation was that the NOAC dabigatran could be considered as an alternative to VKA therapy (Camm et al. 2010). The 2012 guidelines say that NOACs are considered preferable to VKAs in most patients with non-valvular AF. 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.

The use of anticoagulation in practice and guideline adherence

A number of studies have found that anticoagulation therapy is under-prescribed in practice (e.g. Lopes et al. 2010; Dores et al. 2011; Gorin et al. 2011; Diez-Mangano et al. 2014). Ogilvie et al. (2010) undertook a systematic review of literature published between 1997 and 2008 across all world regions. They found that, in all but 4 of 29 studies, among patients with prior stroke or transient ischaemic attack (who should all receive oral anticoagulation therapy according to treatment guidelines), less than 70 per cent received it. They also found that oral anticoagulation therapy treatment levels were suboptimal (<70 per cent) for patients with a CHADS₂ score of ≥2. Studies reporting the under-use of anticoagulation suggest a number of possible causes, including the narrow therapeutic range of VKAs and inconvenience of INR monitoring, patient preference and compliance, a fear of bleeding and experience of bleeding events, and a large number of contraindications (Ogilvie et al. 2010). To complement the ESC guidelines published in 2012, the European Heart Rhythm Association (EHRA) published a practical guide to physicians in their use of the different NOACs with their patients (Heidbuchel et al. 2013).

Age has also been found to be a predictor of reduced guidance adherence. A systematic review by Pugh et al.

(2011) found that physicians often did not prescribe anticoagulation for patients over the age of 70 who were otherwise healthy, and that physicians became even more reluctant to prescribe it for patients over the age of 80. Diez-Mangano (2014) also found that age was a predictor of reduced adherence to anticoagulant guidelines, as were other factors such as a history of stroke and higher bleeding risk.

The combination of increased age in people presenting with AF and the frequent presence of contraindications may be key to understanding the under-prescription of anticoagulants in practice. Pugh et al. (2011) point out that physicians may argue that it is unusual to see a patient over 70 years of age with no health problems other than AF, and that advanced age often goes hand in hand with other risk factors for bleeding such as polypharmacy, cognitive impairment and risk of falls. Moreover, in response to Ogilvie et al. (2010), Pechlaner (2011) wrote a letter saying that the term ‘under-use’ regarding anticoagulation prescription ignores ‘contraindicating evidence and considerable uncertainty’ that physicians often have to face. According to Pechlaner, contraindications are rarely clear-cut and usually require significant physician judgment.

The Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) has explored physician practices regarding contraindications to oral anticoagulation in AF (O’Brien et al. 2014), given that evidence suggests anticoagulation decisions are more likely to be driven by perceived risks (such as adverse bleeding events) than by perceived benefits (such as stroke risk reduction). The study enrolled 10,130 patients with AF, 1,330 of whom had contraindications. Overall, the most commonly reported contraindications were prior bleed (27.7 per cent) and patient refusal (27.5 per cent), followed by high bleeding risk (18 per cent) and frequent falls/frailty (18 per cent). Some 30 per cent of patients with a documented contraindication were taking oral anticoagulants compared with 83 per cent of those without one. Among patients with documented contraindications taking oral anticoagulants, those most commonly listed were prior bleed (25.8 per cent), need for dual antiplatelet therapy (24.3 per cent) and high bleeding risk (15.4). Overall, in 30 per cent of people with contraindications, oral anticoagulants had been prescribed, suggesting that decisions about using oral anticoagulants – despite the presence of contraindications – are subjective.

O’Brien et al. (2014) point out that a ‘major challenge in implementing proper anticoagulation strategies in

AF is the overlap between risk factors for bleeding and risk factors for stroke' (p.607). Illustrating this issue is the appearance of multiple risk factors – such as hypertension, previous experience of stroke and an age over 65 years – in both the CHA₂DS₂-VASc and HAS-BLED frameworks. This challenge results in complexity for prescribing anticoagulants and a need to balance perceived risk with clinical judgment. Nevertheless, a number of studies have shown that anticoagulants are prescribed despite contraindications and risk factors, and indeed that neither age alone nor a predisposition for falls should be seen as automatic contraindications for using oral anticoagulants.

In addition, GPs can vary greatly in their assessments of the risks and benefits of different antithrombotic treatment choices for AF (Anderson et al. 2007; Oswald & Bateman 2000, as cited in Fay & Montana 2012), and there may be a mismatch in patient and physician perceptions of risk. Patients at high risk of AF have been found to place more value on avoiding stroke and less value on avoiding bleeding than their physicians (Devereaux et al. 2001, as cited in Fay & Montana 2012). Similarly, a study conducted in Spain found that patients, compared to physicians, were more stroke averse, and/or less bleeding averse (Alonso-Coello et al. 2014).

There may be still other reasons for the under-use of anti-coagulants. Gerber et al. (2012) found that physicians in ambulatory care reported low use of guidelines (never or seldom) compared with those that work in a hospital setting. Moreover, Fay & Montana (2012) found that physicians' awareness of the relevant guidelines and recommendations is not always sufficient to influence practice. Although the literature has found that anticoagulants are arguably under-prescribed relative to other treatments, a number of studies have found that inappropriately high levels of anticoagulants have been prescribed in some individual cases. This issue is explored in more detail in relation to our countries of focus below.

Countries in focus

The approach to stroke prevention treatment as well as the presentation of AF across Europe has recently been explored. Lip et al. (2014) collected data in nine countries, which were then divided into European regions. Belgium, Denmark, the Netherlands and Norway were categorised as the West; Poland and Romania as the East; and Greece, Italy and Portugal as the South. They found some variation with regards to usage of oral anticoagulation (either as monotherapy or in conjunction with antiplatelet therapy). Overall, 72 per cent of

patients in the West, 75 per cent of patients in the East and 76 per cent in the South use oral anticoagulation. In terms of presentation, patients from the South and East had higher CHA₂DS₂-VASc and HAS-BLED scores than those in the West (Lip et al. 2014).

The PREvention oF thromboembolic events – European Registry in Atrial Fibrillation (PREFER-AF) study (Kirchhof et al. 2014) explored the management of AF in seven European countries after the publication of the 2010 ESC guidelines. The study collected data from France, Italy, Spain, the UK, and Germany, Austria and Switzerland (grouping the last three together in the analysis). The study found high use of anticoagulants – with these being prescribed in 85.6 per cent of patients with a CHA₂DS₂-VASc score ≥2, 70.1 per cent of patients with a CHA₂DS₂-VASc score of 1 and 62.5 per cent of patients without any CHA₂DS₂-VASc stroke risk factor (Kirchhof et al. 2014).

However, the high level of anticoagulant prescription for eligible patients in the PREFER-AF study suggests that oral anticoagulation use that aligns with guideline recommendations has increased, as compared to prior data from European, national and international registries. The study reported that only 70 per cent of eligible patients received oral anticoagulants during 2005–2008, compared to over 85 per cent of eligible patients received oral anticoagulants in PREFER-AF. The use of NOACs in the PREFER-AF study was low, with an overall rate of approximately 6 per cent. This low rate resulted in part from limited availability of NOACs in the countries concerned. NOACs were only available and reimbursed in Germany and Spain in 2012 (when data was collected), and both had higher levels of use at 11 per cent. In contrast, the UK had local reimbursement limitations for NOACs. In France, NOACs only came on the market just before the study data were collected, and in Italy NOACs did not come on the market until 2013.

Belgium

While Belgium does not have official national guidelines, documentation from the Belgian Centre for Pharmacotherapeutic Information (BCFI) notes that on the basis of the available evidence, VKAs cannot yet be replaced systematically by NOACs (BCFI 2014). Current successful treatments with VKAs should therefore not be replaced with NOACs, it says, and NOACs should only be considered in certain situations as an alternative to VKAs, for example when INR values are difficult to keep in range. It also notes that there are no

comparative studies of NOACs, which makes it difficult to recommend one over the other.

A lot of attention has been given to the effectiveness of catheter ablation to treat AF. The number of catheter ablation operations in Belgium increased from 993 in 2008 to 2,064 in 2010, which led the Belgium Government to commission a Health Technology Assessment to understand the effectiveness and costs of the procedure (Van Brabandt et al. 2012a). The assessment, conducted by the Belgian Health Care Knowledge Centre (KCE), stated that the reimbursement of catheter ablations should be limited to 'patients suffering from paroxysmal AF with no or minimal structural heart disease and who feel that their symptoms could not be sufficiently controlled by means of prior therapy with antiarrhythmic and rate-control drugs.' This statement of caution followed from the conclusion that 'so far, there is no hard evidence as to the cost effectiveness of catheter ablation for AF' (Van Brabandt et al. 2012b, iv).

France

A study conducted in 2012 in France (the year NOACs were launched there) found that more than 1 million patients received anticoagulation via VKAs, while 265,000 received NOACs (AM 2013). However, the study found that the uptake of NOACs is increasing and, in less than one year, nearly half the patients starting oral anticoagulant therapy were prescribed NOACs.

The national health agencies also noted poor adherence to guidelines in AF treatment and management – particularly in terms of over-prescribing NOACs. For instance, national epidemiologic data from the National Health Insurance Agency revealed that some NOAC patients were prescribed concomitant treatments that increase the risk of bleeding. As a result, several measures have been implemented to ensure adherence to national guidelines. Since the summer of 2013, training on NOAC treatment has been organised in more than 100,000 GP practices. Memos, which are approved by the French National Authority for Health (HAS) and summarise recommendations on the role of NOACs in non-valvular AF, are given to physicians as part of the training. There has been an increasing effort from the HAS to centralise and provide up-to-date information on AF treatments on its website.¹¹

Germany

While anticoagulation via NOACs is seen in European and international guidelines as the new common treatment preference, many practitioners in Germany still have their doubts, staying hesitant about employing those guidelines in practice and often sticking to VKA treatment (especially for patients that are already stable on VKAs) (Ebner 2013). However, the 'Deutsche Gesellschaft für Kardiologie' (DGK/ German Cardiac Society) has criticised the AkdÄ (Drug commission of the German Medical Association) for repeatedly underlining the risks of new oral anticoagulants, without calling the attention to their utility. This, according to the DGK, irresponsibly led to a feeling of insecurity for the patient. The DGK points to studies which prove that for some patient groups NOACs are a better therapy than VKAs and not just an alternative. As NOACs are not as widespread as in other countries, there is still potential for NOAC use to grow in Germany.

Between 2003 and 2004, 361 patient case histories from 45 practices have been studied. Some 90 per cent were treated with VKAs. The INR was within the therapeutic range 56 per cent of the time, while 29 per cent of the time it was higher and 19 per cent of the time it was lower than the target range. Around 40 per cent of patients were not treated according to international guidelines: those under 60 were often, despite lacking risk factors, given anticoagulation and therefore 'over-treated', while those over 75 were, despite lacking contraindications, not receiving anticoagulation and were therefore 'under-treated' (Kobza & Paul 2007).

According to a study conducted by AFNET (the German competence network on AF) and the BMBF (Federal Ministry of Education and Research) investigating AF treatments in 72 clinics and 122 practices in Germany, the treatment of AF is not the same throughout different levels of healthcare in Germany. It was found that the majority of patients are treated according to the guidelines. However, especially concerning stroke prophylaxis, an undersupply was identified, meaning that not all patients received an antithrombotic treatment according to the guidelines. The percentage varies between different healthcare institution types. While in more specialised healthcare settings, such as hospital clinics and local cardiologists, 70 per cent of all patients were treated according to the guidelines, this only applied to less than 50 per cent of patients in less specialised regional hospitals and

¹¹ See (as of 19 March 2015): <http://www.has-sante.fr>

GP practices (Bundesministerium für Bildung und Forschung 2011).

Italy

Tilatti et al. (2014) found that 39.7 per cent of the AF patients in the region (44.4 per cent males and 35.6 per cent females) were subject to treatment with oral anticoagulants. However, the prevalence of patients receiving this therapy was lower in the more elderly patient groups (≥ 75 years). According to the guidelines, the reason for this can be found in a reduction of compliance in ageing patients, difficulties in managing the therapeutic range and the risk of adverse reactions in patients treated for multiple conditions.

Adherence to anticoagulant treatment is a risk factor, with the role of the GP fundamental in ensuring that the patient recognises the importance of the treatment according to Battigelli et al. (2013). The guidelines for GPs emphasize the need to closely follow patient adaptation to the treatment and to verify adherence at the point of renewing subscriptions.

The Italian Agency for Pharmaceuticals issued a warning in 2013 about the risks connected to haemorrhages when administering NOACs (AIFA 2013). According to the warning, prescribing doctors often don't have an adequate understanding of the haemorrhagic risks associated with these drugs.

According to the National Association for Pharmaceuticals (OSMED 2008), treatment levels with anticoagulants are to a certain degree inadequate in Italy. In the 2008 report it is stated that 15 per cent of patients with low risk of ictus are treated with oral anticoagulants; 32 per cent in the medium risk category, and 38 per cent in the high-risk category. In sum, some low-risk patients are receiving inappropriate therapy while some high-risk patients are under-treated (p.88, OSMED 2008). According to d'Angela et al. (2013), similar results have been found by the ATA-F study (AntiThrombotic Agents in AF Routine Management of AF: a Survey in Italian routine practice). This study worked with 164 cardiology centres and 196 centres of internal medicine on a total of 7,148 AF patients, and found that 44 per cent of those for whom an anticoagulant treatment would be indicated under the guidelines do not receive one, while approximately 50 per cent of those for whom it is not indicated are treated with anticoagulants (Berisso et al. 2014; d'Angela et al. 2013).

Spain

The first general recommendations for the use of NOACs were published in 2013 by the Spanish Ministry of Health (Informe de Pasacionamiento Terapeutico, Ministerio de Sanidad, Servicios Sociales e Igualdad, 23 December 2013). These recommendations were validated by the Interregional Health Council to ensure higher coordination and more equitable access to NOAC drugs across different provinces. However, the use of NOACs for AF treatment remains very uneven across provinces and under-use of NOACs has been observed at the national scale. Adherence to recommendations for NOACs prescription remains quite difficult to quantify as not all Spanish provinces collect data on this specific issue (Carmen et al. 2014).

According to 2013 data from the Spanish National Health Authority, 4.4 per cent of the total population suffers from AF. The prevalence of AF is higher for the population aged 60 years old and over. Some 80 per cent of the total population receives anticoagulants (mostly acenocumarol) but only 60 per cent of them have a stable INR (Lobos Bejarano, 2013). In a recent communication, the Spanish Ministry of Health estimated that although approximately 30 per cent of patients receiving anticoagulant treatments should be treated with NOACs only 8.8 per cent actually are. The Spanish Society of Cardiology is thus implementing a training/communication campaign to raise GP awareness of the benefits of anticoagulant therapy.

UK

Several studies have found oral anticoagulants to be used at a level lower than that suggested in clinical guidelines. Cowan et al. (2013) analysed data from the GRASP-AF program, which automatically analyses GP-level patient data for AF risk. Based on the review of 231,833 patients with a history of AF, they established that although uptake of anticoagulants has improved in comparison with previous studies, over one-third of high-risk patients remain untreated. Some 45.3 per cent of all patients at high risk (a CHADS₂ score of ≥ 2) did not receive an anticoagulant treatment. Even after allowing for patients for whom anticoagulants were contraindicated or declined, 34.0 per cent of patients with CHADS₂ ≥ 2 did not receive an anticoagulant.

Furthermore, the choice of medication appears to favour antiplatelet medication in situations where anticoagulants would be more appropriate. According to Cowan et al. (2013), the fact that 36.2 per cent of patients with CHADS₂ ≥ 2 were prescribed antiplatelet medication

without anticoagulant suggests an over-reliance on the former for stroke prevention in AF, despite the fact that the NICE guidelines recommend warfarin over aspirin for stroke prevention. While there is a slow increase of the number of patients receiving OAC treatment, the condition still appears to be under-treated or treated with antiplatelet medication. In May 2014, the available data from GRASP-AF indicated that only 57.32 per cent of people with a CHADS₂ score greater than one were being treated with anticoagulants. A slight decrease from the 2012 data, in 2014 33.98 per cent of AF patients at high risk of stroke (CHADS₂>1) have still been prescribed an antiplatelet but not anticoagulation. The available data also suggests great geographical variation in anticoagulation rates among patients with AF at high risk of stroke. In the 156 Clinical Commissioning Groups (CCGs) with at least one practice uploading data onto the system, the average percentage of high-risk AF patients receiving anticoagulation ranges from 36 per cent to 70 per cent (AFA 2014).

Cowan et al. (2013) suggest that the high use of anti-platelets may partly reflect the recommendations of the Quality and Outcomes Framework (QOF) of the NHS, which provided equal emphasis on anticoagulants and antiplatelets in stroke prevention throughout the study period. This may have contributed to the fact that 90.9 per cent of patients with CHADS₂ ≥2 were treated with either an anticoagulant or antiplatelet or both, thereby fulfilling the stated objectives of the QOF at that time. AFA (2012) also emphasises the effect of these recommendations in their review of the QOF guidelines, which set incentives for the prescription of aspirin in AF and enforce practices that do not reflect scientific evidence.

In the UK a web-based resource was established in June 2013 that provides healthcare professionals with state-of-the-art resources to better equip them with the skills and knowledge to improve diagnosis, treatment and management of patients with AF.¹² The site is aimed at all healthcare professionals who engage with AF patients in different settings. Resources provided include: guidelines, information on AF as a condition, treatment options, information on commissioning, real-life examples, and training resources, including signposting to relevant courses. Users also use it as a network and forum for exchange regarding good practice.

The future of AF management

The recent development and marketing of NOACs has changed the face of AF management in relation to preventing AF-related stroke and serves to demonstrate that this can be an area of rapid change and development in terms of management options. With this in mind, it is likely that there will be scientific developments in treatment over the near (3–5 years) and medium (10 years and beyond) terms. Other trends may also determine the future of AF. For example, a number of studies have drawn attention to the economic burden of AF. A study in 2004 identified annual AF-related costs of £459m in the UK (Stewart 2004, as cited in Wodchis et al. 2012). Wodchis et al. (2012) conducted a review of studies on the cost of AF and found that costs were high – primarily due to the high levels of hospitalisation but also due to anticoagulation management related to medications and INR testing. They also found that studies which included other care settings in their estimates identified additional substantial costs. Growing evidence of the economic burden of AF may influence the political agenda in terms of prioritising AF and public awareness in the future. Below we explore what the future may hold specifically for the use of anticoagulants in preventing AF-related stroke, as well as how other AF management options may develop.

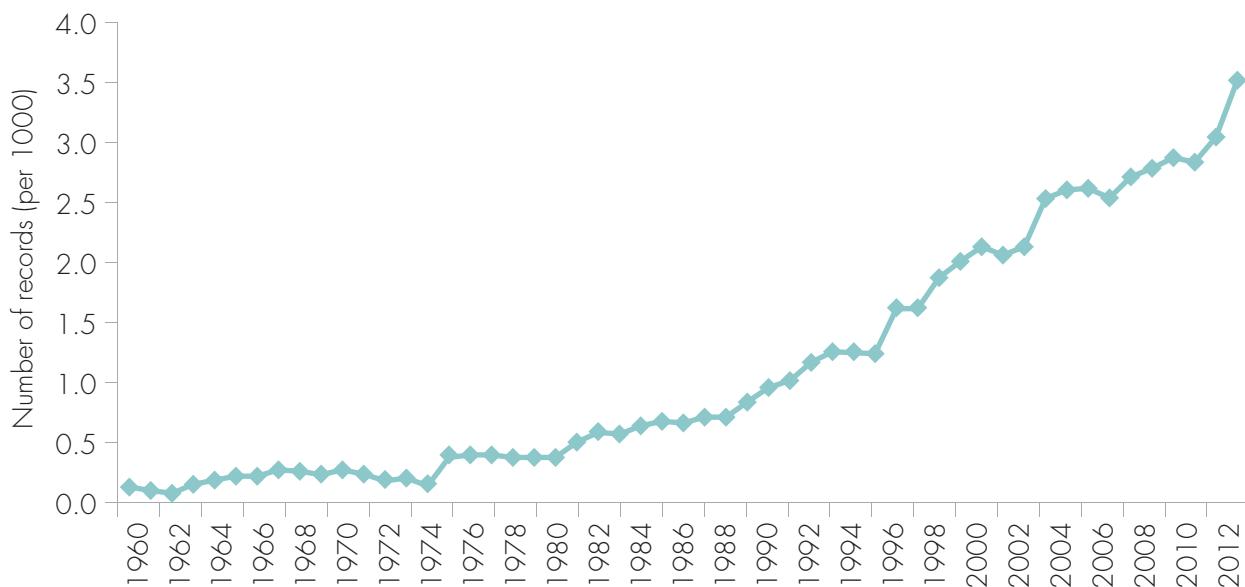
Research activity in AF

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 B.1). For every 1,000 records in the medical research database Medline in 2012, there are 3.5 records with 'atrial fibrillation' in the abstract or title, compared with 2.2 records in 2002 and 1.2 records 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

¹² See (as of 19 March 2015): <http://www.heartofaf.org/>

Figure B.1: 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



Note that complete data were only available up to 2012.

Source: NCBI (2015)

open and listed on the US National Institutes of Health clinical trials database at ClinicalTrials.gov.¹³ A number of these focus on aspects of NOAC use and compare 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 on reasons for variations in quality of life and symptom burden for AF patients,¹⁴ a US study on genomic risk markers for AF following extended heart rhythm monitoring,¹⁵ and a Dutch study on identifying a risk profile to guide AF therapy.¹⁶

The future of anticoagulant use

As outlined above, three NOACs have been approved and recommended for the treatment of non-valvular AF in Europe in recent years – apixaban, rivaroxaban and dabigatran. In addition to these it is likely that a fourth

NOAC – edoxaban – will join the list of available NOACs in the near future. As described below, these have had a significant impact in treatment to prevent AF-related stroke and have been recommended in a large number of European guidelines – including the ESC guidelines. As a result, NOACs are being used in clinical practice and this use looks likely to increase over the coming years, particularly when one takes cost-effectiveness into account. Indeed, in France the use of anticoagulants has been increasing in recent years, with a doubling of sales of OACs between 2000 and 2012. The increase has been sharper since 2011. In 2013, the National Agency for Pharmacovigilance estimated that at least 3.12 million patients received at least one anticoagulant. By contrast, although VKA sales doubled between 2000 and 2011, there was a decline in 2013. This decline appears to be linked to the recent availability (2009) in France of NOACs, for which sales grew rapidly (ANSM 2014).

NOACs have been shown to be cost-effective in comparison to warfarin in a number of studies. Harrington

¹³ Information accessed at ClinicalTrials.gov, using the general terms 'anticoagulation' and 'atrial fibrillation' as the condition search terms (accessed 15 March 2015).

¹⁴ 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.

¹⁵ Official title: THE GIRAFFE Study: Genomic Risk Markers for Atrial Fibrillation Following Extended Cardiac Rhythm Monitoring.

¹⁶ Official title: Identification of a Risk Profile to Guide Atrial Fibrillation Therapy.

et al. (2013) compared apixaban, rivaroxaban and dabigatran with warfarin and found that apixaban 5mg was the most cost-effective – given that compared with warfarin it provides an additional 0.5 QALYs at a cost of US \$7,500 – resulting in an incremental cost-effectiveness ratio (ICER) of US \$15,000 per QALY gained – well below the threshold of US \$50,000 per QALY gained. However, another study carried out by Canestaro et al. (2013) found that – compared with warfarin – dabigatran, rivaroxaban and apixaban cost US \$141,000, \$111,000 and \$93,000 per additional QALY gained respectively, showing they provided greater quality-adjusted life expectancy than warfarin but at a greater cost. Nevertheless, this shows that NOACs are more effective than warfarin and therefore may point to the likelihood of their increased use in future.

In addition to cost-effectiveness, patient preference for NOACs may play an important part in their use. The convenience of NOACs as opposed to VKAs is likely to make them a more appealing choice for patients. Moreover, in patients looking to minimise the number of doses of their medications, once-daily rivaroxaban or edoxaban rather than apixaban or dabigatran may be desired (Gonzalez-Quesada & Giugliano 2014).

However, despite the apparent advantages of NOACs in preventing AF-related stroke, there is evidence that healthcare professionals in Germany and Belgium have been hesitant about the rapid uptake of NOACs in place of VKAs. With this in mind, it is important to explore the factors that may inhibit the use of NOACs for this purpose in the future.

First, NOACs do not have a specific antidote available in the clinical setting and none of the routinely used coagulation tests can precisely quantify their anticoagulation effect (Kornej et al. 2013). This causes a number of concerns in relation to acute haemorrhagic stroke as well as the need for urgent surgery in those taking NOACs. In the case of the former, VKAs can be reversed using fresh frozen plasma and prothrombin complex concentrate, given that vitamin K acts too slowly in this case (Kornej et al. 2013). However, no such option is available for NOACs. In relation to urgent surgery in those taking anticoagulants, again VKAs can be reversed with vitamin K, fresh frozen plasma and prothrombin complex concentrate, whereas in those taking NOACs the drug should be discontinued and the surgery should be delayed until at least 12–24 hours after the last dose if possible (Kornej et al. 2013). A number of agents are being investigated as possible NOAC antidotes and several have proven effective in pre-clinical and clinical studies, so antidotes may

be developed and marketed in the near future, helping to alleviate concerns (Schneider 2014).

Second, Gheorghiade et al. (2013) point out the difficulties of using NOACs in patients with liver or renal dysfunction. The use of both rivaroxaban and dabigatran is limited in patients with renal insufficiency and it is still unclear whether apixaban can be used in patients with mild or moderate renal or hepatic dysfunction. Indeed the clinical trials for these drugs excluded patients with severe renal insufficiency and liver disease, meaning there is limited evidence on how far these drugs can be used within this sub-group (Gheorghiade et al. 2013). Relatedly, the trials for dabigatran and apixaban only included patients with one CHADS₂ risk factor (i.e. low-risk patients) and therefore there is limited evidence regarding the use of these drugs in higher-risk patients. This links back to the points made above regarding a hesitancy to prescribe anticoagulants due to contraindications. Although some of the problems associated with the under-prescription of warfarin may be addressed through NOACs (such as a reduced need for monitoring), there remains a lack of clarity regarding the frameworks used to prescribe anticoagulants. As outlined above there is a significant overlap between risk factors for stroke used in the CHA₂DS₂-VASc framework and risk factors for bleeding used in the HAS-BLED framework. This, combined with a lack of evidence for NOAC use in high-risk patients, may curb their use in the future.

Third, it is unclear how far there will be a transition from those already taking VKAs to NOACs. Luger et al. (2014) undertook a study in Germany and found that frequent reasons to prefer VKAs over NOACs were prior treatment with VKAs and a feeling that the patient was well acquainted with this form of anticoagulation. In addition to this, guidelines from some countries – such as France and Spain – recommend VKAs as the first treatment option.

Therefore, although NOAC use is likely to increase, it may be more pronounced in some countries than others.

Broader trends and their potential impact on anticoagulant therapy

Although the need for anticoagulation therapy looks set to continue in preventing AF-related stroke, it is also necessary to look beyond anticoagulation. This is because changes in the way AF is approached and managed more broadly may have implications for the way anticoagulants are prescribed. However, it should be noted that this review has been undertaken with

a specific focus on how future treatment options will impact on anticoagulant use and therefore advances in rate or rhythm control strategies such as technological developments in catheter ablation, for example, are not explored here. It is worthy of note that catheter ablation may increase in the future given technological advances in this area, although it is still not clear which segments of the AF population it is cost-effective for (Chan et al. 2006, McKenna et al. 2008, Reynolds et al. 2009, Van Brabandt 2012a, Reynolds et al. 2014).

A good example of this is the notion of a shift to individualized therapy for treating patients with AF. 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 (among other things). Therefore, instead of relying on stroke risk frameworks such as CHA₂DS₂-VASc and CHADS₂ as well as bleeding risk frameworks such as HAS-BLED, decisions could be made 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 & Ogin (2014) also note that more targeted approaches are needed to improve therapy of AF. They state that research should aim at ‘developing approaches to reduce the occurrence of incidence AF by preventing the development of the AF substrate [i.e. upstream therapies]; therapies that interrupt or reverse the pathophysiology of AF; anti-arrhythmic drugs that are atrial specific to limit side effects; and ablative approaches that require less ablation of tissue, are easier to perform, and have a higher success rate’ (p.1,533). They also note a combination of these approaches may be needed through personalised therapy.

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 & Ogin 2014). Biomarkers and other diagnostic techniques are discussed below. Another type of tool that could impact AF diagnosis would be devices that could measure the heart rate over months.

There may also be developments in non-pharmacological approaches to AF-related stroke prevention. As discussed above, left atrial closure can be performed through ligation or amputation, as well as through endocardial approaches for which several devices are in development (the Aegis System, the Cardioblate Closure system and the ligation of the LAA with the LARIAT system) (Han et al. 2012). In the UK, the left atrial appendage occlusion (LAAO) procedure has recently been commissioned under the National Health Service for England. However, only 10 centres have been selected to carry out the procedure across the country, which will limit its use in the near term.¹⁷

Countries in focus

Approaches to AF in the future may differ across countries. For example, in Germany there has been hesitancy about switching to NOACs from VKAs, perhaps in part because self-measurement of INR is common in Germany, reducing the patient burden associated with VKAs. Developments in self-monitoring by patients via smartphone apps, blood pressure monitors or loop recorders may be more important in Germany than elsewhere, especially as increasing proportions of ageing people use smartphones (Becker 2013, Gessner 2014, Kneife 2014). Self-monitoring via smartphones has also been introduced in a Spanish awareness campaign, and other apps have been suggested in France for use by physicians. These apps, available for tablets and smartphones, help physicians in calculating indicator scores as well as assessing and calculating appropriate doses of anticoagulants (Messika-Zeitoun 2013).

Information technology may also impact the diagnosis and treatment of AF by facilitating the screening of medical databases for patients who may be at risk. The GRASP-AF (Guidance on Risk Assessment and Stroke Prevention for AF) initiative in the UK is currently running in a third of medical practices. It screens patient databases for people with CHADS₂ and CHA₂DS₂-VASc scores that indicate they are

¹⁷ See (as of 19 March 2015): <http://www.england.nhs.uk/ourwork/commissioning/spec-services/npc-crg/comm-eval/>

candidates for anticoagulation therapy (GRASP-AF 2014). With the system facilitating adherence to the new NICE guidelines, we may see an increase of patients treated with NOACs and a decrease of high-risk patients receiving only platelet drugs (Cowan et al. 2013, GRASP-AF 2014).

As further clinical studies are conducted and with the emergence of additional clinical evidence on the use and efficacy of NOAC therapy, the recommendations may be updated to reflect these changes, leading to better awareness and stronger recommendations for the use of these medications (see, for example, classification of evidence levels for NOACs in the Italian guidelines, Raviele et al. 2013). In Italy, a Health Technology Assessment project has projected that the market share of rivaroxaban could grow from the present 8 per cent to approximately 30 per cent in 10 years, enabling the prevention of 4,182 cases of stroke and savings for the national health system amounting to €58m in the first three years (Ricciardi et al. 2013).

New treatment options may emerge for patients for whom current practices have been ineffective. The Italian government's Health Technology Foresight project lists the minimally invasive ultrasound ablation (HIFU) therapy as a potentially relevant new technological development for AF patients who are resistant to pharmacological treatment and for whom trans-catheter ablation interventions have proven ineffective (Cavallo et al. 2009).

The impact of an aging population on AF management

Prevalence in the elderly

AF is particularly relevant for the elderly, mostly affecting patients with a mean age of 75–85 years (Camm et al. 2012). Its prevalence increases exponentially with age, affecting less than 0.5 per cent of people under the age of 40, and 18 per cent of those over the age of 85 (Fumagalli et al. 2012). Although individuals with AF often have other diseases and disorders – including ischaemic heart disease, heart failure, hypertension, diabetes and hyperthyroidism – age has been

identified as the strongest independent risk factor for AF (Sankaranarayanan et al. 2013).¹⁸

The overall prevalence of AF is currently 1.5–2 per cent in the developed world, according to ESC guidelines (Camm et al. 2012), but a range of estimates of the prevalence and incidence of AF are available for specific regions. These data are based on data collected over a range of time periods, and estimates are made using a variety of approaches. Below, we present country-specific prevalence data obtained from the literature (but those data may not be comparable due to differences in the methodology used or time period addressed).

Several studies have indicated that the prevalence and incidence of AF are increasing. One factor driving this increase is the fact that populations are aging, and individuals of advanced age are more likely to have AF than younger people. There is also evidence that the incidence of AF is increasing by more than would be expected based on changes in age demographics alone; factors driving the increase may be comorbidities, cardiovascular risk factors and lifestyle factors (Chugh et al. 2014).

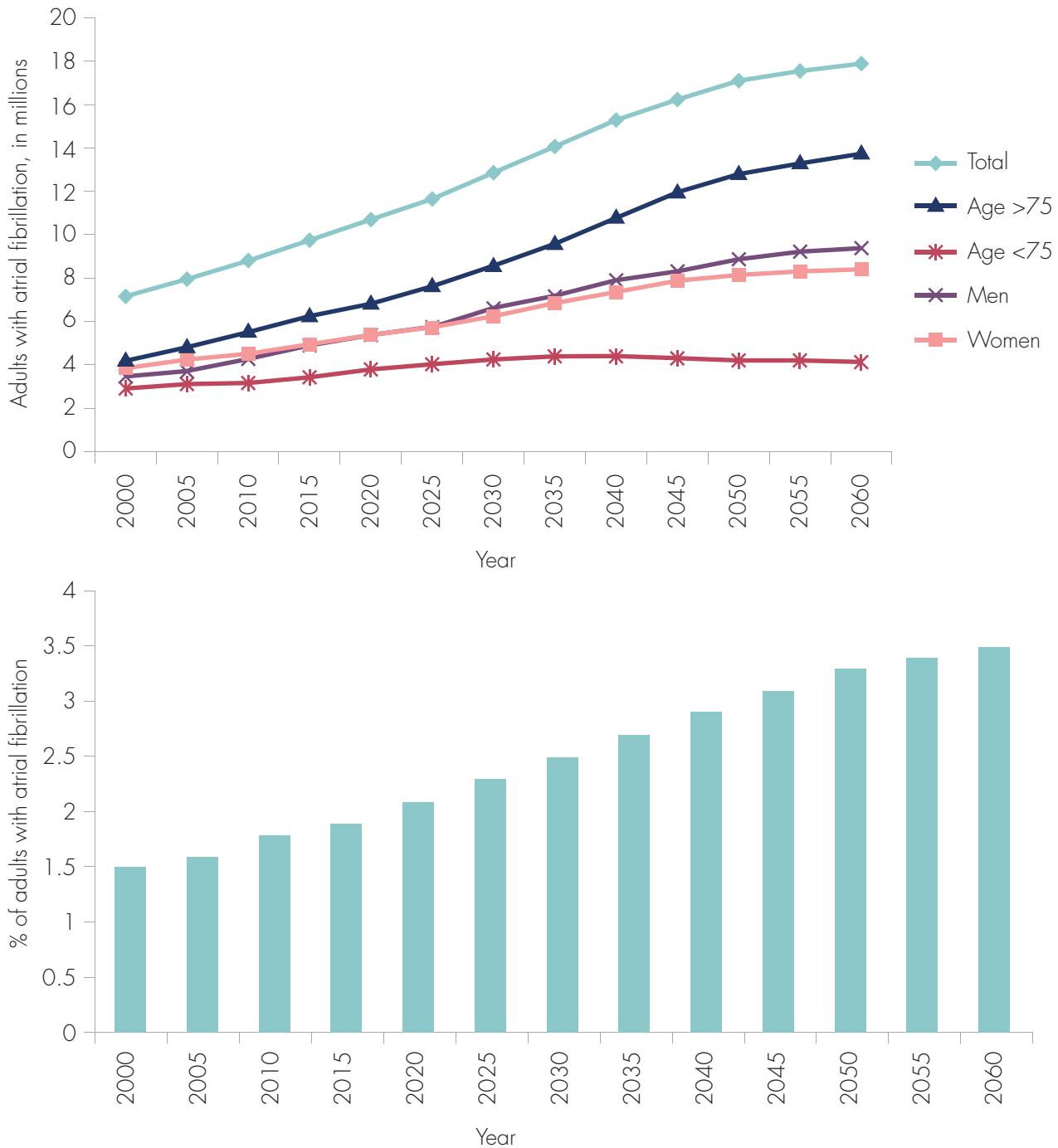
According to projections, the prevalence of AF in Europe may nearly double by 2060.¹⁹ Krijthe et al. (2013) estimated the prevalence of AF in Europe up to 2060 based on European figures for AF prevalence and EU population projections (Figure B.2). They calculated that the number of adults aged 55 and over with AF in the EU will double by 2060 to 17.9 million. Prevalence figures used by Krijthe et al. (2013) come from the Rotterdam Study, which ran from 1990–1999 and focussed on a population in the Netherlands. Prevalence figures from the Rotterdam Study (Table B.2) were consistent with two large-scale, longitudinal studies carried out in the US (the Framingham Study and the Cardiovascular Health Study) and with figures reported in Australia (Heeringa et al. 2006).

In Europe, the proportion of people above the age of 80 is currently 5.1 per cent, and is projected to increase to 9.0 per cent by 2040. According to the Rotterdam Study, prevalence of AF increases with age, as indicated in Table B.2. Combining demographic projections with prevalence data provides projections

¹⁸ Fumagalli et al. (2012) also found that patients of advanced age were underrepresented in their survey and were less likely to be enrolled in specialised health centres and universities.

¹⁹ According to figures from the US, where the projected shift in age structure is less pronounced than in Europe, AF prevalence is expected to increase 2.5 times by 2050 as compared to 2001 levels (Go et al. 2001). The authors calculated this increase based on projected population changes and current levels of AF prevalence for various age groups in the US.

Figure B.2: 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)

for future AF prevalence (Figure B.2). AF prevalence overall in Europe is due to increase from about 1.7 per cent in 2013 to 3 per cent in 2050. Among persons 55 and over in Europe, the increase in prevalence is more pronounced: it is currently 5.6 per cent and due to increase to 7.4 per cent by 2050. These projections do not take into account, however, increased incidence of AF due to factors other than age demographics,

such as increases in other AF risk factors or more AF patients being diagnosed.

Within the EU, projected changes in age demographics vary across member states. For example, in Germany and Spain populations are projected to decrease between 2013 and 2020, but both countries will see considerable increases in the proportion of their population that is at

least 60 years old, which will increase from 26 to 38 per cent in Germany and from 23 to 39 per cent in Spain. In both France and Italy, populations will increase, but this will be driven by an increase in numbers of older persons. In France, the proportion aged 60 and up will increase from 24 per cent in 2013 to 30 per cent in 2050; in Italy, it will increase from 27 per cent in 2013 to 36 per cent in 2050. Less notable increases are expected in the UK and Belgium. In both countries, the proportion of population aged 60 and over is projected to rise from 23 per cent in 2013 to 29 per cent in 2050.²⁰

Table B.2: AF Prevalence by age group

Age	Prevalence
55–59	0.7%
60–64	1.7%
65–69	4.0%
70–74	6.0%
75–79	9.0%
80–84	13.5%
85+	17.8%

Source: Heeringa et al. (2006)

As AF becomes more prevalent, issues related to its treatment and management will become increasingly important. The rise in AF prevalence may also have significant economic implications. One global estimate for the annual costs of the average AF patient was between €2,600 and €3,000 per year (Ochhetta et al. 2010). Taking into account that there are approximately 10 million patients with AF in the EU, this corresponds to a total of about €26–30bn per year in the EU.

AF symptoms and stroke risk change with age

A major risk associated with AF is stroke, and this risk goes up as patients age. AF is associated with a five-fold increase in risk for ischaemic stroke (Lotze et al. 2010). In one long-running study, the US-based Framingham Heart Study, attributable risk of stroke from AF increased from 1.5 per cent in patients aged 50–59 to 23.5 per cent in those aged 80–89 (Wolf et al. 1991). Confounding this situation, age is also a risk factor for mortality after stroke (Dekker 2011). The risk of stroke is significantly higher for women with AF than it is for men with AF (Rich 2012).

The primary symptoms of AF include palpitations, shortness of breath and dizziness, and possibly chest pain, but the presence of these symptoms may change depending on patients' age. Palpitations are less common in patients aged 65–80 than in those under 65 (Dekker 2011, Sankaranarayanan et al. 2013), and atypical chest pain is more common in younger AF patients (Sankaranarayanan et al. 2013). Indeed, up to 40 per cent of elderly hospital patients found to have AF have not been exhibiting symptoms. Many elderly patients are diagnosed by chance during health assessments carried out for other reasons (Sankaranarayanan et al. 2013). Symptoms such as shortness of breath (dyspnoea) and fatigue may be more common in the elderly than in younger patients (Dekker 2011, Fumagalli et al. 2012).

Treatment

As discussed above, the objectives of treatment for AF are to alleviate symptoms and reduce the risk of stroke (Rich 2012), and the main treatment approaches are rate control and rhythm control to relieve symptoms, and antithrombotic therapy (mainly OACs) to reduce the risk of stroke. Particular challenges arise in the treatment of elderly AF patients because they often have comorbidities and are often taking other medications, increasing their risk of side effects (Fumagalli et al. 2012).

Another complicating factor is that less evidence has generally been available about AF treatment options for very elderly and very frail patients. Elderly patients were underrepresented in randomised trials of OACs until the Birmingham AF Treatment of the Aged Study trial (BAFTA), published in 2007, was carried out (van Walraven et al. 2009). An evaluation of the Euro Heart Survey, a Europe-wide evaluation of clinical data on clinical practice in cardiovascular diseases, found that patients over age 80 were not adequately studied and treated compared to younger patients. It found that patients of more advanced age were underrepresented in that survey and were less likely to be enrolled in specialised health centres and universities (Fumagalli et al. 2012). In addition, patients outside of anticoagulant trials are generally at higher risk of bleeding than those approved to participate, which could reduce the applicability or perceived applicability of trial results to real-world cases (van Walraven et al. 2009).

²⁰ Calculated using data from Eurostat (2014).

Antithrombotic therapy

As noted above, the situation of stroke prevention treatment for elderly AF patients is complicated at present, with several studies showing that physicians do not prescribe anticoagulants for their elderly AF patients even when clinical guidelines indicate that they should do so. Difficulties arise because the most commonly used anticoagulants – VKAs such as warfarin – increase the risk of bleeding and pose other challenges. However, a number of articles have stressed that it is wrong to withhold anticoagulants from elderly patients who qualify to receive it and who are most at risk of stroke.

VKAs are burdensome to use because they put patients at risk of major haemorrhage and this risk is higher in patients of more advanced age (Zarraga & Kron 2013). In addition, as discussed earlier, VKAs are burdensome due to their requirements for monitoring, their varying responses and narrow therapeutic windows, and their potential for food and drug interactions, which require patients to adhere to dietary restrictions (Deedwania 2013).

The under-prescribing of anticoagulants in the elderly relative to what is suggested by clinical guidelines 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 (Sociedad Espanola de Cardiologia 2013). These studies observed that decisions not to treat patients with anticoagulants appear to be based mainly on age, and not on recommendations in clinical guidelines related to patient stroke risk (as calculated by, for instance, CHA₂DS₂-VASc scores).

One reason cited for this under-prescription is that physicians are concerned about the bleeding risk associated with VKAs, particularly among elderly patients that seem at risk of falls or have a history of bleeding (Lip & Lane 2013, Strong & Halperin 2007). However, it has been suggested that physicians may have a biased perception of the relevant risks and are more alert to the chance that they could cause a haemorrhage by prescribing warfarin than the chance that they could allow a stroke to occur by not doing so (Zarraga & Kron 2013). Another reason for under-use of warfarin may be physicians' concerns that some patients of advanced age, e.g. those with cognitive impairments, would struggle to comply with the treatment requirements (Strong & Halperin 2007, Yates 2013).

Authors stress that decisions should not be based solely on age or perceived fall risk because the significant benefits of stroke prevention that are offered by anticoagulant use may outweigh the bleeding risks (Lafuente-Lafuente et al. 2012). Decisions, they say, should be based on stroke risk (estimated with tools such as CHADS₂ and CHA₂DS₂-VASc) (Zarraga & Kron 2013),²¹ as well as on individual patient preferences and needs (Lip & Lane 2013). Supporting the notion that anticoagulation treatment decisions should not be based on age or perceived fall risk, studies have failed to identify an increased incidence of major bleedings in patients of advanced age, and have found that the incidence of major bleedings is acceptably low in patients over age 80 treated with anti-coagulants (Fumagalli et al. 2012).

While antiplatelet agents such as aspirin may be seen as an alternative to VKAs for anticoagulation, they may not be as effective in patients of advanced age. Some guidelines recommend aspirin be used for stroke prevention in AF patients at low risk of stroke or who have contraindications for VKAs (Table B.1), but evidence suggests it has little effect in reducing thromboembolic events in patients who are at low risk of stroke and it may increase bleeding risk (Yates 2013). Moreover, combining VKA treatment with antiplatelet agents can significantly increase bleeding risk for elderly patients as compared to using a VKA alone (Zarraga & Kron 2013).

One study compared the relative efficacy of antiplatelet therapy against OACs for ischaemic stroke prevention across 12 clinical trials, and it found that the efficacy of antiplatelet agents for preventing ischaemic stroke went down significantly as patient age increased, becoming near ineffectual for those over 80 (van Walraven et al. 2009). However, the efficacy of OACs changed very little with age, and so OACs became relatively more beneficial as patients age and their risk of stroke becomes higher. Nonetheless, an analysis of the Euro Heart Survey found that in patients over the age of 80, OACs were used least often as compared to younger age groups: it was used in 50 per cent of patients over age 80, but in 60 per cent of patients age 65–80 and 57 per cent of patients under 65; antiplatelet agents were used most often, in 33 per cent of patients over 80, compared with 25 per cent of patients aged 65–80 and 23 per cent of patients under 65 (Fumagalli et al. 2012).

²¹ There is evidence that CHADS₂ and CHA₂DS₂-VASc have the best predictive power for thromboembolism among the elderly as compared with other risk prediction schemes (Poli et al. 2011).

New anticoagulants

It is important to consider whether conclusions drawn about the safety and effectiveness of NOACs hold true for particularly elderly patients. A meta-analysis has been carried out to assess use of NOACs in the elderly that covered 10 randomised control trials on dabigatran, rivaroxaban and apixaban, focussing on patients over the age of 75 (Sardar et al. 2014). The results indicated that the drugs did not lead to more major bleeding or clinically relevant bleeding than conventional antithrombotic drugs, and significantly reduced stroke or systemic embolism. The meta-analysis concluded that the new anticoagulants are more effective than conventional anticoagulants and that they should not be withheld from patients on the basis of age.

A similar analysis looked at results from trials of the three NOACs to test whether conclusions – that stroke prevention benefits from these drugs outweigh bleeding risks – also applied to frail, elderly patients (Barco et al. 2013). The analysis indicated that the findings were consistent for the elderly sub-group, and the authors concluded that using the new drugs in place of conventional warfarin treatment in the very elderly may lead to higher absolute risk reduction because elderly patients have more frequent stroke events.

Rate and rhythm control

An analysis of the Euro Heart Survey found that use of rhythm control strategies (pharmacological and non-pharmacological) and rate control drugs declined as patients aged (Fumagalli et al. 2012). It also found that rate control was preferred over rhythm control in ageing patients, which the authors suggest could be due to AF more often being accepted as a permanent condition in these patients. Evidence has shown that rate control may be more effective than rhythm control and lead to better outcomes for patients over 65 years of age (Rich 2012), and that rhythm control drugs are associated with a high incidence of adverse effects (Fumagalli et al. 2012).

The use of cardioversion or ablation for non-pharmacological rhythm control has not been associated with a greater incidence of adverse effects in ageing patients (Fumagalli et al. 2012). There is limited evidence about the benefits of catheter ablation in terms of mortality or stroke prevention and most trials have included only patients under age 65 (Sankaranarayanan et al. 2013). However, 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 this treatment is safe and effective, reduced stroke risk and mortality, and enabled warfarin treatment to be safely stopped (Nademanee et al. 2014). The Euro Heart Survey analysis indicated that patients under the age of 80 received cardioversion and catheter ablation more frequently than those over 80, and the authors stress that elderly patients should not be denied these interventions (Fumagalli et al. 2012).

Countries in focus

Belgium

In terms of AF prevalence in Belgium, a 2012 study assessed the feasibility and effectiveness of a voluntary, national screening programme for the general population (Claes et al. 2012). It screened 13,564 participants, of which 10,758 were more than 40 years of age. All participants had a CHADS₂ or CHA₂DS₂-VASc evaluation and underwent a one-lead electrocardiogram. The results showed that 228 participants had AF (125 women and 103 men), implying a prevalence of 2.2 per cent in the screened population.

Two studies on the use of anticoagulants among ageing patients in Belgium found that use of these treatments was limited, but neither study revealed any impairments or geriatric characteristics among patients that would serve as a barrier to anticoagulant use. The first study showed that, of 111 patients identified with AF, 49 per cent did not receive VKA treatment before admission to hospital (De Breucker et al. 2010). However, no differences were detected between those that did and those that did not receive treatment, in terms of either geriatric or CHADS₂ characteristics. The focus of the second study was slightly different, but the results were relatively similar. It showed that among the AF patients to whom anticoagulation therapy had been recommended (73 per cent), only 61 per cent were actually being treated (Denoël et al. 2014). Again, neither geriatric characteristics nor CHADS₂ score correlated with the presence or absence of therapy.

Regarding the economic cost of AF, little evidence is available for Belgium. However, in a study comparing the cost-effectiveness of the NOAC dabigatran with the VKA warfarin, Wouters et al. (2013) estimated total costs per patient at €13,333 for dabigatran and €12,454 for warfarin. Data was based on the RE-LY trial and a network meta-analysis, and assumed routine clinical practice in Belgium. The analysis did not include long-term costs for clinical events in Belgium, as these data were reportedly not available.

Table B.3: Projected age demographics (Belgium), 2013–2050

Age Group	Belgium				
	2013	2020	2030	2040	2050
Number of persons (m)					
All	11.2	11.8	12.9	13.9	14.8
60–79	2.0	2.3	2.7	2.8	2.9
80+	0.6	0.6	0.8	1.0	1.3
Age Group	Belgium				
	2013	2020	2030	2040	2050
Percentage of total population					
60–79	18.1%	19.5%	21.2%	20.3%	19.6%
80+	5.3%	5.5%	6.0%	7.5%	8.6%

Source: Eurostat (2014)

France

It has been estimated that between 600,000 and 1 million people are affected by AF in France, two thirds of whom are aged 75 years and above, and there are 110,000–230,000 new cases each year (Charlemagne et al. 2011; Hanon et al. 2013). As the population ages, AF is becoming a major public health concern (Moubarak et al. 2012). AF prevalence rates are much higher in the population over 80 years of age, affecting 6.05 per cent of men and 5.2 per cent women (figures for the population below 50 years of age are 0.05 per cent for men and 0.01 per cent for women) (Guize et al. 2007). The number of people age 60 and over in France is projected to rise from 15.6m in 2013 to 22.5m in 2050 (see Table B.4). Demographic projections from the French Society of Cardiology (2014) indicate that nearly 2 million people in France will be affected by AF in the next 40 years. Society representatives have indicated that France might lack the number of cardiologists needed to ensure efficient treatment and management of the disease going forward because there are currently only 20 specialised centres (Haute Autorité de Santé 2014).

A 2013 expert consensus document released by the French Society of Geriatrics and Gerontology and the French Society of Cardiology acknowledges the potential of NOACs for the treatment of patients aged 75 years or above with non-valvular AF and indicates that more efforts should be made to increase NOAC treatment for people aged over 80 with AF (Hanon et al. 2013). However, recent figures from the National Health Insurance Information Centres indicate that among the total population receiving NOAC treatment, 33.8 per cent are aged 80 or over; as for people receiving VKA

treatment, 41.9 per cent of the total patient population is aged 80 or over (SNIIRAM 2013).

The economic cost of stroke and haemorrhage complications that arise in patients with AF has been recently estimated for France (Cotté et al. 2014). The study reviewed data of about 62,000 patients with AF from the French National Hospital database (Programme Médicalisé des Systèmes d'Information). It found that the incidence of stroke was 32.1 cases per 1,000 patients with AF over a two-year period, and the mean cost of these strokes ranged from about €5,000 to nearly €30,000 depending on severity. The mean costs of haemorrhages ranged from €2,600 to €7,300 depending on type.

Table B.4: Projected age demographics (France), 2013–2050

Age Group	France				
	2013	2020	2030	2040	2050
Number of persons (m)					
All	65.6	67.7	70.4	72.8	74.3
60–79	11.9	13.6	15.3	15.3	14.8
80+	3.7	4.1	5.2	6.8	7.7
Percentage of total population					
60–79	18.2%	20.1%	21.8%	21.1%	19.9%
80+	5.6%	6.0%	7.3%	9.3%	10.4%

Source: Eurostat (2014)

Germany

The number of Germans with AF is expected to increase from 1.8 million in 2009 to 2.1 million in 2020 (Wilke et al. 2013). Around 2–4 per cent of individuals over 60, 10 per cent of individuals over 65 and up to 12 per cent of those over 75 years are affected (Lüderitz 2009). As in other countries, the increase in prevalence is due to significant demographic changes and an increase in risk factors such as high blood pressure and obesity. In Germany, the proportion of people above the age of 80 is expected to more than double from 4.5 per cent of the total population in 2013 to 10.5 per cent in 2050 (see Table B.5). With this rise in prevalence, AF presents a considerable healthcare burden at present and for the future in Germany, highlighting the need for preventive measures such as improving diets, encouraging exercise and careful management when AF risk factors are present (Wilke et al. 2013).

A recent study (Ohlmeier et al. 2013) estimated prevalence and incidence of AF among individuals aged 65 years and above in Germany, and was based on health insurance data for 800,000 people from the period

2004–2007. It found that the prevalence of AF in this group was 7.7 per cent in 2004, and it rose each year to reach 10.3 per cent in 2007. The incidence rate was 27.4 per 1,000 person-years in 2007.

Ohlmeier et al. (2013) also found that a significant number of patients who were newly diagnosed with AF did not receive antithrombotic drugs, and that use of this treatment declined with age. Among patients aged 65–69, 60.2 per cent were prescribed antithrombotic medication; for patients aged 90 and above, the proportion dropped to 32.2 per cent. Though previous studies indicated that a large proportion of AF patients do in fact receive antithrombotic treatment, the authors suggest that this difference could be due to previous studies focussing mainly on patients enrolled in specialised centres, whereas the Ohlmeier et al. (2013) study covered a very large sample.

Another German study, focussing on clinical data from 169 patients aged 80 years and above admitted to a cardiology ward during a one-year period, also found that ageing patients were less often prescribed OACs (Lotze et al. 2010). Patients over age 84 were prescribed OACs less frequently than those aged 80–84 (7 per cent vs 36 per cent). Contrary to guidelines, just 27.5 per cent of patients with a CHADS₂ score of at least 2 (high risk of stroke) were prescribed OACs at hospital discharge. Reasons given for not prescribing treatment were that the patients were expected to have poor compliance, had other clinical conditions, or were seen as at risk of a fall. The overall clinical situation appeared to influence the decision about whether to use OAC more than the patient's stroke risk, as calculated by the CHADS₂ score. Lotze et al. (2010) conclude that there is a need for education of staff to help create conditions that enable more elderly patients to receive OAC therapy.

McBride et al. (2009) estimated the costs of AF patient care in Germany through a six-month, multicentre observational study in physicians' practices, with additional retrospective data collection. The study was based on observation of 361 patients in 45 practices. Mean annual AF-related cost was €827 ± 1,476 per patient (median €386). Half of the total costs were incurred by just 11 per cent of patients, with these costs driven by AF-related hospitalisation (44 per cent). Anti-arrhythmics and stroke prophylaxis accounted for a further 20 per cent and 15 per cent of expenditure, respectively.

Stroke cost data in Germany were compiled by Lindig et al. (2010) in a retrospective review of data on insurance claims from a German statutory health insurance

database including around 5 million insured persons. Summarising all the charges for patients with stroke over a one-year period after the initial event, the study estimated mean total costs per patient to be €11,800, with half the costs occurring in the first four weeks after the stroke event and being incurred for acute care.

Table B.5: Projected age demographics (Germany), 2013–2050

Age Group	Germany				
	2013	2020	2030	2040	2050
	Number of persons (m)				
All	82.0	80.6	79.8	77.8	74.7
60–79	17.6	18.4	22.1	20.8	18.2
80+	4.5	5.8	6.5	8.1	10.5
Percentage of total population					
60–79	21.5%	22.9%	27.8%	26.7%	24.4%
80+	5.4%	7.2%	8.1%	10.4%	14.1%

Source: Eurostat (2014)

Italy

According to Italy's official guidelines, data on the prevalence of AF in Italy is scarce. According to figures from d'Angelo et al. (2013), there are around 900,000 people with AF in Italy, and this number is expected to rise to about 1.4m by 2050. The official guidelines, on the other hand, cite the prevalence of AF in the Veneto region (Raviele et al. 2011). Patients showed a prevalence of 4.2 per cent for those aged 65–74 years, 9.4 per cent for those between 75–84 years, and 17 per cent in those above age 85 in that region (Bilato et al. 2009). The guidelines estimate that, assuming AF prevalence to be approximately 1 per cent of the total population, AF affects approximately 600,000 people and the number of new patients is 120,000 per year. Some other regional studies also estimate the incidence of AF at the level of single Italian regions. For instance, the Friuli Region AF Guidelines estimate the prevalence of AF at 2.1 per cent of the population, based on hospital data (Tilatti et al. 2014). The 2013 Report on Health from the University of Rome Health Research group (d'Angelo et al. 2013) estimates that due to demographic aging, the number of patients with AF will grow by 50,000 to 80,000 every five years.

At present, people aged 60–79 make up 21 per cent of the Italian population and people aged 80 and over make up 6 per cent, but these figures are expected to increase to 24 per cent and 12 per cent, respectively, by 2050 (see Table B.6). Based on the conditions for recommending treatment with non-VKA oral anticoagulants,

the number of patients who would be eligible for this kind of treatment is estimated to be between 600,000 and 930,000 (d'Angelo et al. 2013).

The under-use of antithrombotic treatment has also been identified as an issue in Italy. One study reviewed medical records from administrative databases of around 25,000 patients aged 65 and over who were hospitalised in Italy in 2002 (Monte et al. 2006). It found that antithrombotic treatments (both antiplatelet and anticoagulation therapies) were under-used. Contrary to recommendations, anticoagulants were not prescribed to up to two thirds of patients following their hospitalisation with AF. Moreover, the presence of cardiovascular conditions was not associated with receiving antithrombotic treatment, but the presence of non-cardiovascular comorbidities was significantly associated with decreased likelihood of receiving the treatment. The study confirmed that the use of anti-thrombotic treatment was associated with reduced mortality and the use of anticoagulants was associated with a reduction in thromboembolic events.

The official guidelines cite the following trends in the future incidence of AF:

1. Population growth.
2. Fast aging of the global population with significant growth in the number of elderly people, who are at a higher risk of developing AF.
3. Lengthened survival of patients affected by conditions that can be associated with AF, such as arterial hypertension, congestive heart failure and coronary disease (Raviele et al. 2011).

The economic cost of treating AF in Italy has been estimated by Occhetta et al. (2010) based on a review of AF cases in three Italian regional health centres. The mean annual cost per patient was estimated to be €2,685, including €2,235 (83 per cent) for hospitalisation, with the rest for GP or specialist and diagnostic exams, and drug costs. An analysis of general stroke costs estimated the costs of hospital treatment for stroke at about €3,400, but ranging from €2,850 to €4,000 depending on severity of the stroke and increasing significantly when follow-up treatments were taken into account (Lucioni et al. 2010). Fattore et al. (2012) found that AF increased the cost of hospitalisation for strokes as compared to strokes not due to AF, however this difference was not statistically significant.

In addition, Ringborg et al. (2008) used data from the Euro Heart Survey to estimate the costs associated with

AF care for five European countries, including Italy and Spain, for the years 2003–2004. The study looked at the costs of initial admission to clinics and hospitals and costs incurred in the year following admission. It estimated the annual cost of AF in Italy to be €3,286m overall. Mean costs of admission for inpatient care in Italy were estimated at €5,300 per patient, with mean costs incurred in the following year estimated at €3,200 and including an average of two consultations with a doctor over the year. Inpatient care and interventional procedures were identified as the main cost drivers, accounting for more than 70 per cent of total annual costs and indicating that reducing the incidence of serious cardiovascular events among AF patients could be highly cost-effective. There was found to be a wide range (9–26 days) in the mean number of work days lost due to AF symptoms among employed patients (Ringborg et al. 2008).

Table B.6: Projected age demographics (Italy), 2013–2050

Age Group	Italy				
	2013	2020	2030	2040	2050
	Number of persons (m)				
All	59.7	62.	64.1	66.2	67.1
60–79	12.5	13.4	15.8	17.3	16.0
80+	3.8	4.4	5.2	6.1	7.9
Percentage of total population					
60–79	21.0%	21.5%	24.6%	26.1%	23.9%
80+	6.3%	7.1%	8.0%	9.2%	11.8%

Source: Eurostat (2014)

Spain

In Spain, a recent study reported the overall prevalence of AF to be 1.5 per cent, ranging from 0.5 per cent for patients aged 45–59 to 6.3 per cent for those above 75 (Baena-Díez et al. 2014). According to the 2012 ESFINGE study, the prevalence of AF in patients over age 70 of both sexes in Spain is 31.3 per cent. With Spain's population aged 60 years of age or above set to rise from 23 per cent to 39 per cent by 2050 (see Table B.7), this prevalence is expected to increase.

Recent data from the Spanish Society of Cardiology (SSC 2013) show that only 50 per cent of elderly patients who met guideline requirements for OAC treatment were prescribed OACs. This low prescription rate is attributed to GPs fearing that the risk of bleeding in these patients is higher, and being reluctant to prescribe OACs. The Spanish Society of Cardiology is, as a result, currently implementing a training and

communication campaign to raise awareness regarding the benefits of anticoagulation across GP practices.

In response to concerns about the rising number of individuals affected by AF in Spain, the first consensus document on the ‘Management of vascular risk factors in patients older than 80’ was presented at the Annual Congress on Geriatric Cardiology in 2014. It has the backing of the four medical societies involved in the management of AF patients: the Spanish Society of Internal Medicine (SEMI), the Spanish Society of Cardiology (ESC), the Spanish Society of Geriatrics and Gerontology (SEGG) and the Spanish Society of Family and Community Medicine (SEMFYC). It aims to provide guidance on implementing the correct treatment of cardiovascular risk factors in the octogenarian population to facilitate the clinical decisionmaking around issues such as lifestyle modification, treatment of hypertension, dyslipidaemia or anticoagulation.

As mentioned above, Ringborg et al. (2008) used data from the Euro Heart Survey to estimate the costs associated with AF care for five European countries, including Italy and Spain, for the years 2003–2004. They estimated the annual cost of AF in Spain to be €1,545m overall. Mean costs of admission for inpatient care in Spain were estimated at €6,400 per patient, with mean costs incurred in the following year estimated at €2,300 and including an average of two consultations with a doctor over the year. Inpatient costs in Spain were higher than those in other countries (Greece, Italy and Poland) and similar to those in the Netherlands, and this difference was attributed mainly to a higher mean length of stay for patients. Meanwhile, Souto et al. (2013) estimated the costs of self-management of VKAs in Spain at €420 per year and per patient, including technology, reagents, supervision and data centralisation.

Table B.7: Projected age demographics (Spain), 2013–2050

Age Group	Spain				
	2013	2020	2030	2040	2050
Number of persons (m)					
All	46.7	45.8	44.5	44.6	45.5
60–79	8.2	9.2	11.2	13.	11.9
80+	2.6	2.8	3.4	4.3	5.7
Percentage of total population					
60–79	17.6%	20.1%	25.1%	29.2%	26.1%
80+	5.5%	6.1%	7.6%	9.7%	12.6%

Source: Eurostat (2014)

UK

The Stroke Prevention in Atrial Fibrillation Expert (SAFE) study, a UK-based multicentre randomised control trial of elderly (≥ 65 years) patients with AF, showed an overall prevalence of 7.2 per cent, and 10.3 per cent in those aged 75 years and above, with a 1.6 per cent yearly incidence of new AF (Hobbs et al. 2005).

In the UK, there is debate about whether to introduce an AF screening programme. In the current guidelines of the UK National Screening Committee (UKNSC 2014), screening for AF in the over 65-year-old population is not recommended. However, in the written responses submitted to the Committee’s consultation, the British Heart Foundation (BHF), the Arrhythmia Association, the AF Association and the Royal College of Physicians of Edinburgh supported the introduction of such a screening programme. The reason for the policy not recommending screening, according to the update document, is that treatment and care for people with AF is not optimal. It also said that better evidence is needed about whether AF detected at screening carries the same long-term risk of stroke as AF found in the context of other conditions; and the test needs to be improved and standardised (UKNSC 2014).

In the absence of efficient prevention and treatment processes, demographic ageing in the population is likely to go hand in hand with an increasing number of AF-related events. Yiin et al. (2012) explore whether greater awareness of the need for stroke prevention in AF, more screening and increased availability of VKAs over the past 2 decades reduced the incidence of AF-related stroke despite population ageing. Their review of data in one UK region showed no reduction in age-adjusted incidence of AF-related ischaemic stroke over the last 25 years and found that absolute numbers increased substantially. The study concludes that under-use of anticoagulation for stroke prevention in eligible patients is a major barrier to effective stroke prevention in the face of an ageing population with high rates of AF.

Using data from a study in the Oxfordshire region in the UK carried out from 2002 to 2012 and a related study from the 1980s, Yiin et al. (2014) found that the number of AF-related ischaemic strokes at age ≥ 80 nearly tripled from the period 1981–1986 to the period 2002–2012, and that this increase was partly caused by an increase in age-specific incidence and occurred despite the introduction of anticoagulants. The cost of potentially preventable AF-related embolic events in patients over age 80 was estimated to be £374m per

year for the UK. At current rates, the study estimates that numbers of AF-related events in patients over age 80 will triple again by 2050, and that 84 per cent of all events will occur in this age group. Therefore, Yiin et al. (2014, 1) recommend that improved stroke prevention in ageing people with AF be made ‘a major public health priority’.

UK studies have also addressed changes in quality of life that result from AF. They find that AF may not significantly diminish quality of life in elderly patients, but it can lead to more serious events. Based on data from 1,762 patients with AF aged more than 75 years collected in the Birmingham AF Treatment of the Aged (BAFTA) study, Roalfe et al. (2012, 1) concluded ‘In the absence of comorbidity, chronic AF has little impact on generic quality of life in an elderly non-acutely ill population.’ Limantoro et al. (2012) suggest that this limited impact may have unfortunate consequences. While elderly AF patients are at highest risk of stroke, a limited impact on quality of life will probably not prompt them to seek medical attention, potentially leading to lack of antithrombotic treatment and the occurrence of strokes that could have been prevented. Furthermore, despite the fact that elderly patients seem to have increased benefit from OACs as opposed to placebo or antiplatelet medication, compared to their younger counterparts, many physicians remain reticent to prescribe OAC to ageing patients. Risk of falls and previous bleeding seem to be barriers to prescription (Manning et al. 2014).

The prevalence of AF also represents a growing burden on UK hospitals. Keech et al. (2012, 1) concluded that ‘AF presents a significant and increasing burden on hospital care in Scotland’. They found that AF-related costs represent one quarter of the total cardiovascular burden and are increasing relatively faster than overall costs for cardiovascular conditions.

Stewart et al. (2004) extrapolated 1995 data on AF to 2000 to estimate the burden of the disease for the NHS. According to the study, there were about 534,000 people with AF in the UK in 1995 and the ‘direct’ cost of healthcare for these patients was £244m (0.62 per cent of total NHS expenditure). Hospitalisations and drug prescriptions accounted for 50 per cent and 20 per cent of this expenditure, respectively, and long-term nursing home care after hospital stays cost an additional £46.4m. Based on these figures, it was estimated that the direct cost of AF rose to £459m in 2000, equivalent to 0.97 per cent of total NHS expenditure, and nursing home costs rose to £111m. In addition, as mentioned

above, Yiin et al. (2013) estimated potentially preventable AF-related events of those aged ≥80 to cost the UK £374m per year.

Table B.8: Projected age demographics (UK), 2013–2050

Age Group	United Kingdom				
	2013	2020	2030	2040	2050
	Number of persons (m)				
All	63.9	66.7	70.5	73.8	77.2
60–79	11.6	12.8	14.8	15.5	15.7
80+	3.0	3.4	4.6	5.6	7.1
Percentage of total population					
60–79	18.1%	19.2%	21.0%	21.0%	20.4%
80+	4.7%	5.1%	6.5%	7.6%	9.3%

Source: Eurostat (2014)

Barriers in identifying and accessing untreated patients

Identification of AF

AF is often under diagnosed (Fitzmaurice et al. 2007, as cited in Scowcroft & Cowrie 2014), although AF identification in the UK increased between 2000 and 2012, potentially because of the NICE guidance and the GRASP-AF initiative on AF treatment (Scowcroft & Cowrie 2014).

A survey completed by respondents from 33 European Heart Rhythm Association Research Network partners in 16 countries found that there is currently no consensus regarding the screening methods for asymptomatic AF (Dobrea et al. 2013). Opportunistic and systematic screening were equally effective at detecting patients at risk for stroke; the CHADS₂ stroke risk scores of patients detected via both screening methods were similar (Fitzmaurice et al. 2014).

Continuous ECG monitoring is considered superior to intermittent ECG monitoring (Ziegler et al. 2006, as cited in Babaeizadeh et al. 2009). In Germany, continuous monitoring was found to be more effective than a 24-hour Holter ECG (Gumbinger et al. 2012). The median detection time of 43 hours underscored the need for longer continuous monitoring (Gumbinger et al. 2012).

Remote monitoring offers clinical value in terms of diagnosis of AF and stroke prevention, monitoring of medical therapy and identification of asymptomatic AF (Engel & Mead 2008). However, the potential

downsides of remote monitoring are the increased workload and volume of data (Engel & Mead 2008). The healthcare organisational model needs to be restructured for optimal handling of remote monitoring data (Engel & Mead 2008), with new management strategies for patient follow-up (Lorenzoni et al. 2014).

Single time-point screening

Opportunistic screening

Opportunistic screening, in the form of a peripheral pulse check, should be carried out regularly with adults 65 years and above (Dobreanu et al. 2013; Lee & Campbell-Cole 2014). Opportunistic screening in this group is recommended by the European Society of Cardiology (Camm et al. 2012, as cited in Lowres et al. 2013) and in the United Kingdom by the Royal College of Physicians of Edinburgh (Stott et al. 2012, as cited in Lowres et al. 2013). Indeed, opportunistic screening (compared to targeted screening) was the only strategy that improved on routine practice (Hobbs et al. 2005, as cited in Dewar & Lip 2007). A systematic review found that single time-point screening in adults 65 years or above identified previously unknown AF in 1.4 per cent of the screened population (Lowres et al. 2013).

Opportunistic checks could occur in hypertension, diabetes, asthma and ischaemic heart disease primary care clinics, as well as during home visits and consultations (Dewar & Lip 2007; Lee & Campbell-Cole 2014). Pulse checks carried out at flu-jab sessions were beneficial as these patients are in the high-risk category (Campbell & Jackson 2011, as cited in Holding et al. 2013). It is also considered good practice to check the blood pressure and pulse of all patients presenting with breathlessness, dyspnoea, palpitations, syncope/dizziness or chest discomfort (Dewar & Lip 2007). For those with an irregular pulse, a 12-lead electrocardiogram (ECG) should be performed to confirm the diagnosis (Lee & Campbell-Cole 2014). If there is no evidence of AF from the 12-lead ECG, a Holter monitor may be ordered to confirm the diagnosis and assist in the identification of AF type (Lee & Campbell-Cole 2014).

In Italy, a scheme has been in place since 2011 to offer pulse checks alongside blood pressure monitoring for free to the general public in 3,000 pharmacies across the country during the week of World Stroke

Day (in October).²² The initiative estimates that 5–6 per cent of people assessed were suspected to have AF and is thought to have raised awareness on the link between AF and AF-related stroke. In addition, a complete physical assessment and detailed medical history should be obtained from the patient, to document the onset and effect of symptoms for the patient (Lee & Campbell-Cole 2014). An echocardiogram may also be ordered to determine cardiac function and any myocardial damage, depending on other signs and symptoms reported by the patient (Lee & Campbell-Cole 2014).

Systematic screening

Systematic screening identifies similar numbers of previously undiagnosed AF as opportunistic screening, but current guidelines do not recommend widespread population screening (Lowres et al. 2013). However, systematic screening may be necessary given the asymptomatic nature of AF (Lowres et al. 2013).

Although economic analysis suggests that systematic screening costs more than opportunistic screening (Hobbs et al. 2005, as cited in Fitzmaurice et al. 2014), new methods could provide a viable cost-effective alternative to pulse check and 12-lead ECG for AF screening. Such methods include hand-held ECGs (e.g. an iPhone ECG device), blood pressure machines and finger-probe instruments (Lowres et al. 2013). These new technologies are low cost and simple to use, and have higher sensitivity and specificity than pulse palpation (Lowres et al. 2013).

Monitoring

In patients with suspected paroxysmal AF, ambulatory ECG recordings can be useful for confirming the diagnosis and documenting the frequency of the arrhythmia, especially as many AF episodes are asymptomatic (Dewar & Lip 2007). Multiple screening identified a higher incidence of paroxysmal AF (Engdahl et al. 2013; Flint et al. 2012; Healey et al. 2012; Liao et al. 2007, all as cited in Lowres et al. 2013), as paroxysmal AF is problematic to identify with single-time point screening because patients may be in sinus rhythm at the point of screening (Lowres et al. 2013).

Patients who frequently experience symptoms can be diagnosed with a 24-hour or 48-hour Holter monitor (Dewar & Lip 2007). However, these short-term

²² See (as of 19 March 2015): www.aliceitalia.org

Holter recordings have a low diagnostic yield, especially in detecting paroxysmal AF, and they generate a large amount of ECG information without diagnostic interest (Engdahl et al. 2013).

Patients with less frequent episodes may require a 7-day Holter or an event recorder, which is either patient- or ECG-triggered (Dewar & Lip 2007). Implantable loop recorders and pacemakers can record continuously for prolonged periods (Dewar & Lip 2007). Event and loop recorders with intermittent and continuous ambulatory ECG recording have a better diagnostic yield than Holter recordings when detecting paroxysmal AF in stroke patients (Doliwa Sobocinski et al. 2012).

Currently, there is no consensus on the optimal ambulatory ECG method (Engdahl et al. 2013). Ambulatory ECG recordings are limited and provide useful information in only up to 20 per cent of cases (Dewar & Lip 2007). Mobile Cardiac Outpatient Telemetry and implantable loop recorders, while demonstrating high diagnostic yield, are expensive methods and the latter requires minor surgery (Doliwa Sobocinski et al. 2012; Engdahl et al. 2013).

New modalities of remote monitoring

A study conducted in Italy found that new-onset AF was detected significantly earlier in patients followed remotely (median = 2 days) than in patients with scheduled follow-up clinic visits (median = 78 days); this translated to a likelihood of detection that was twofold higher for remote monitoring versus clinic visits (Lorenzoni et al. 2014). Three different systems of remote monitoring were considered: Home Monitoring[®] (Biotronik, Berlin, Germany), CareLink[®] Network (Medtronic, Inc., Minneapolis, MN, USA) and LATITUDE[®] Patient management system (Boston Scientific, Natick, MA, USA) (Lorenzoni et al. 2014). Costs were estimated to be lower for remote monitoring than for traditional check-ups (Lorenzoni et al. 2014).

The Microlife blood pressure monitor (model BPM BP3MQ1-2D; Microlife USA, Inc., Dunedin, Florida) automatically detects AF using an algorithm that analyses the mean and standard deviation of pulse beat intervals (Wiesel et al. 2013). The monitor achieved 99 per cent sensitivity and 93 per cent specificity for detecting AF with daily readings (Wiesel et al. 2013). However, prolonged home monitoring increased the likelihood of false-positive readings (Wiesel et al. 2013).

The Zenicor-EKG[®] is a hand-held ECG recorder that transfers ECG recordings to an Internet database for

investigators to evaluate at their discretion (Doliwa Sobocinski et al. 2012). The hand-held ECG device was found to be superior to 24-hour Holter monitoring, and the majority of AF episodes were detected within the first 20 days of using the intermittent ECG recorder (Doliwa Sobocinski et al. 2012). However, AF prevalence may be exaggerated; the device was only able to make 10-second recordings, while current AF guidelines deem only AF episodes of over 30 seconds to be clinically relevant (Doliwa Sobocinski et al. 2012).

Home Monitoring[®] technology provides automatic daily transmission of data stored on a pacemaker to a service centre. Physicians can then access the data online. Automatic alerts also inform clinical staff of any trigger events (11, as cited in Ricci et al. 2009). Remote monitoring with Home Monitoring[®] detected AF and led to unscheduled follow-up visits 148 days earlier, on average, than scheduled follow-up visits (Ricci et al. 2009).

The Microlife AF detection blood pressure monitor modified with a new algorithm had a sensitivity of 95 per cent and a specificity of 89 per cent for three-sequential readings (Wiesel et al. 2009). However, the effectiveness of the device with paroxysmal AF is unknown (Wiesel et al. 2009).

A new R-R Markov algorithm was able to achieve 92 per cent sensitivity and 97 per cent positive predictive value in detecting AF episodes, and 93 per cent sensitivity and 98 per cent positive predictive value in quantifying AF segment duration, an improvement over previously published algorithms (Babaeizadeh et al. 2009). In Italy, the web-based Discovery Link AFinder application was successful in improving AF detection when applied on top of standard hospital and remote monitoring (Zoppo et al. 2014). In addition, this new web-based technology may also improve adherence to antithrombotic therapy recommendations (Zoppo et al. 2014).

Clinical predictors

Clinical risk scores, such as the CHADS₂ and CHA₂DS₂-VASc, have been developed to aid decisionmaking in thromboprophylaxis, but are only moderately capable in predicting thromboembolic events (Vilchez et al. 2014).

A prospective study conducted in Germany found that clinical predictors for the detection of paroxysmal AF included advanced age, clinical symptoms lasting for over 24 hours and a history of coronary artery disease (Wohlfahrt et al. 2014).

A study analysing Italian clinical trial data (GISSI-AF) found that, independent of the modality of sinus rhythm restoration, the risk factors for time to first AF recurrence and at least one AF episode within a one-year follow up were first, a history of two or more AF episodes in the preceding 6 months, and second, a lower heart rate during sinus rhythm (Disertori et al. 2010). Additionally, patients treated with amiodarone had a lower risk, while those on diuretics had a greater risk (Disertori et al. 2010).

Biomarkers, whether imaging-based or measured in the blood or urine, may improve the prediction power of clinical risk scores and help assess AF prognosis (Vilchez et al. 2014). Biomarkers include (Vilchez et al. 2014):

- Cardiac biomarkers (myocardial injury and myocyte wall stress).
- Inflammation biomarkers (C-reactive protein, tumour necrosis factor- α , interleukins and monocyte chemoattractant protein-1 (MCP-1)).
- Biomarkers related to prothrombotic state in AF (D-dimer (DD) and β -thromboglobulin).
- Biomarkers of endothelial damage and dysfunction (plasma levels of soluble E-selectin (sE-sel), von Willebrand factor (vWF) and soluble thrombomodulin (sTM)).
- Changes in platelets (amounts of β -thromboglobulin and CD62P (P-selectin)).
- Adipokines and resistin levels.
- Renal function (chronic kidney disease, estimated glomerular filtration rate (eGFR), Cystatin C and β -trace protein).
- Specific genetic polymorphisms.²³

Patient compliance as a barrier to treating diagnosed patients

Impact on quality of life

Ingelgard et al. (2006) identified patient concerns about the adverse effect on quality of life as a barrier to warfarin use (as cited in Fay & Montana 2012). While the current literature revealed great variability of individual lifestyle experiences on warfarin, warfarin appeared to have at most a modest negative impact on patients' quality of life (Kneeland & Fang 2010). Therefore, individual patient preferences need to be taken into account when making warfarin treatment

decisions (Kneeland & Fang 2010). Factors that may influence the impact of long-term warfarin therapy on quality of life are the inconvenience of taking the medication, the inconvenience of frequent blood monitoring and clinic visits, anxiety related to side-effects of the medication, anxiety about potential drug-drug interactions, the impact of the medication on physical activities, and dietary and alcohol restrictions (Kneeland & Fang 2010).

Other potential factors were the perceived efficacy of the medication in preventing adverse outcomes, the extent of shared decisionmaking between the physician and patient, and the quality of information given to patients by physicians (Kneeland & Fang 2010).

The apparent minimal impact of warfarin as perceived by patients may be related to the value placed on preventing adverse health outcomes over the risk of negative drug effects and the inconvenience of the warfarin regimen (Devereaux et al. 2001, as cited in Kneeland & Fang 2010). Although patients' concerns about the risk of bleeding may be a barrier to warfarin use (Ingelgard et al. 2006, as cited in Fay & Montana 2012), patients tend to place a higher disutility (associated burden or negative outcome) on stroke than non-fatal bleeding (Alonso-Coello et al. 2008, Devereaux et al. 2001, Man-Son-Hing et al. 2001, all as cited in MacLean et al. 2012), and a much greater disutility on stroke than treatment burden (Gage et al. 1995, 1996, 1998, all as cited in MacLean et al. 2012). VKA therapy does not pose negative effects on quality of life for most patients, although many worry about its side effects (MacLean et al. 2012). However, aversion to warfarin treatment may decrease over time once treatment begins (MacLean et al. 2012). Other antithrombotic interventions, such as injection treatments and compression stockings are well tolerated, though the former is preferable to the latter (MacLean et al. 2012).

The limitations of the current evidence are that little is known about the quality of life of patients who did not start warfarin and those who discontinued warfarin (Kneeland & Fang 2010). Moreover, although patient preferences are a key determinant of warfarin therapy, there is no data on patient objections to being prescribed warfarin (Fay & Montana 2012).

²³ FGA T331A polymorphism (rs6050), FGB g.4577G >A polymorphism (rs1800790), F13A1V34L polymorphism, F7 g.4727_4728ins10 (rs5742910) polymorphism, and the integrin α 2 gene (ITGA2).

Risk factors for discontinuation, non-adherence and non-compliance

Discontinuation and non-adherence rates in clinical trials were not consistently higher in warfarin than in control patients, although elderly patients may be more likely to discontinue warfarin than aspirin because of the greater perceived burdens of warfarin monitoring (Kneeland & Fang 2010). In observational studies, however, demographic risk factors affecting adherence included younger age, male sex, race and ethnicity, disability, higher educational attainment, employment and low income (Di Minno et al. 2014, Kneeland & Fang 2010).

Patient-related medical conditions that influenced medical adherence were comorbidities, poor baseline health, low overall stroke risk, dementia and poor cognitive function (Di Minno et al. 2014, Kneeland & Fang 2010). Although cognitive functioning has not been consistently linked with adherence, studies examining this relationship may have been confounded by caregiver involvement (Kneeland & Fang 2010).

Psychosocial determinants associated with poor warfarin adherence included alcohol and drug abuse, psychiatric disease, homelessness, social isolation, depression and lack of caregiver support (Di Minno et al. 2014, Kneeland & Fang 2010). Specifically, substance abuse, psychiatric disease, homelessness and lack of support were inversely related to VKA use (Johnston et al. 2003, Schauer et al. 2005, both as cited in Di Minno et al. 2004).

Attitudinal factors such as patients' perceptions of barriers to taking warfarin correlated to worse compliance (Kneeland & Fang 2010). Such barriers included taking too many pills, that taking warfarin increased worry about bad health outcomes, and that taking warfarin increased bruising and bleeding (Dantas et al. 2004, Orensky & Holdford 2005, both as cited in Kneeland & Fang 2010). In addition, patients' reluctant receptiveness to medical information was also associated with poor warfarin adherence (Cruess et al. 2010, as cited in Kneeland & Fang 2010, Di Minno et al. 2014). Other causes of non-adherence to VKAs included forgetfulness, priorities, personal decisions to omit doses, dosing misunderstandings and emotional factors (Cramer 2002, as cited in Di Minno et al. 2004).

Studies conducted in Italy found that a good doctor-patient relationship is considered very important by

most patients and therefore doctor-patient interaction and patient education may improve patient adherence (Barcellona et al. 2000, 2002, both as cited in Di Minno et al. 2004). In addition, other studies suggested that good communication (Griffo et al. 2013, as cited in Di Minno et al. 2004), rehabilitation programmes (Bitton et al. 2013, as cited in Di Minno et al. 2004) and nurse counselling (Nieuwkerk et al. 2012, as cited in Di Minno et al. 2004) may improve medical adherence.

Countries in focus

Belgium

The role of screening is the subject of some debate in Belgium. The Belgian Heart Rhythm Association, with the contribution of two pharmaceutical industry sponsors, organises the yearly Week of the Heart Rhythm, which involves free mass screening events and distribution of information leaflets about self-administered pulse checks.²⁴ A study on the free mass screenings, involving 69 hospitals that screened a total of 13,564 patients, found that these screenings are feasible and effective in detecting AF in approximately 2.2 per cent of the screened individuals (Claes et al. 2012). However, a group of Belgian GPs (from Deurne-Borgerhout) carried out a literature review concluding that there is no scientific argument for mass screening for AF, and stated that they do not feel the screening event is useful (Avonts 2010).

France

There is recognition from French national health agencies that more effort should be made to identify and diagnose AF patients, especially by increasing GPs' training in using and interpreting ECG results (HAS 2008). The HAS guidelines also recommend that systematic AF auscultation be done in subjects over 65 years of age. The guidelines suggest that the GPs be responsible for performing ECG tests in the first instance but need to refer to a cardiologist in case of doubt or inability to interpret ECG results (HAS 2014a). Liard et al. (2013) interviewed physicians, cardiologists and patients about how they treat AF. A total of 394 patients on VKAs and 130 patients not receiving VKAs were included in the study, as well as 65 cardiologists and 68 GPs. The study found that, for more than one in three patients, AF was diagnosed incidentally in

²⁴ Semaine du Rythme Cardiaque website, available at <http://www.monrythmecardiaque.be/> last accessed 20/10/2014

a medical consultation for another reason. It also underlined the lack of oversight physicians have on patient compliance. According to doctors, their patients systematically take their treatment in 91 per cent of cases. However, patient interviews revealed that 60 per cent of non-compliant patients were thought to be compliant by their physician.

Attention has been dedicated to the use of AF treatments, in particular OAC treatment, in geriatric patients. According to the expert consensus of the French Society of Geriatrics and Gerontology and the French Society of Cardiology on the management of AF in elderly people (Hanon et al. 2013), diagnosis can be limited by the different presentation of symptoms. In the elderly, AF is often asymptomatic and found by chance, and palpitations are less frequent in elderly patients compared with younger adults. Although oral anticoagulation is recommended for these patients, in practice treatment is limited by restrictions posed by the patients' renal function and mental frailty.

On the patient side, a pharmaceutical sponsor and the French AVC Association launched a campaign to raise awareness about AF in reaction to a recent survey in France that showed that 87 per cent of people surveyed don't know what AF is (Ifop/Bayer Healthcare, 2014). In addition, another pharmaceutical industry sponsor supports the PROFIL FA campaign, which aims at discovering AF in the population above 60 years of age. In 2013, the campaign covered 4,592 patients in 16 French cities through educating general practitioners on AF and modes of detection. Some 585 patients (15.6 per cent) were referred to cardiologists and 129 new AF cases were confirmed (Davy 2014).

In 2014, the Alliance du Coeur launched a national heart day to coincide with Valentine's Day and which advocates the prevention of cardiovascular disease including raising awareness of AF. The achievements of this campaign have included: increased awareness of cardiovascular disease (including AF and AF-related stroke), integration of AF and AF-related stroke into a cardiovascular policy document, and a call for increased political engagement on cardiovascular disease (including AF and AF-related stroke) as part of a broader commitment to public health (Camm et al. 2014b).

Germany

The German Emergency Services guidelines cite estimates that one third of affected individuals do not notice any symptoms of AF (Stiftung Deutsche Schlaganfallhilfe 2012). Other patient guidelines (Kompetenznetz

Vorhofflimmern 2014a) emphasise that paroxysmal AF in particular passes without the patient noticing in 70 per cent of cases. Some professional organisations therefore advocate the screening of risk groups within the population (over 60 years, high blood pressure, coronary heart disease, cardiac weakness) to establish early treatment (Kompetenznetz Vorhofflimmern 2014b). On the other hand, the German Stroke Foundation (Stiftung Deutsche Schlaganfall-Hilfe) sees regular pulse self-measurement as the best way to find irregularities in the heart rate and identify AF early (Stiftung Deutsche Schlaganfall-Hilfe, 2012).

A pharmaceutical industry sponsor organises, in cooperation with the German Stroke Foundation, an awareness-raising tour through 38 cities in Germany. The tour focusses on stroke prevention addressing especially AF as one of the risk factors. In 2013 they reached 14,000 interested citizens (Vorhofflimmern 2013).

The German Stroke Foundation developed a test-kit for on-the-spot risk screening in collaboration with the company Roche. These kits can be used at fairs and events, as well as within company health management frameworks. During the 15-minute screening, an individual risk profile and prevention report are created (Stiftung Deutsche Schlaganfall-Hilfe 2013).

Italy

The guidelines on AF of the Italian Association for the Fight Against AF (ALFA 2014) note that often patients who do not present symptoms are not aware of their condition. They indicate that if all individuals with AF were identified, the number of patients would double. The association's patient information publication recommends self-monitoring of the pulse for patients, at least once a week (ALFA 2014). The association realised a campaign in 2014 to raise awareness on the importance of self-performed pulse checks.

Pulse checks are also recommended to GPs by Battigelli et al. (2013) in the case of patients referring symptoms of dyspnoea, palpitations, dizziness or postural instability or a sensation of pressure or pain in their chest, as well as regular routine screening pulse checks in all patients regardless of suspected AF, but paying particular attention to patients in groups presenting an elevated risk. The guidelines also indicate an opportunity to check patients' pulse at the moment of measuring blood pressure. Incorporating these encounters in daily practice (routine pulse check and routine pulse check when measuring blood pressure) ensures a wide coverage of patients, including outside the groups with the highest risk of AF.

The AF guidelines (Raviele et al. 2011) suggest that, due to the elevated prevalence of asymptomatic AF, it is necessary to consider oral anticoagulant therapy in patients at a high risk of ischaemic stroke even in the absence of abnormal rhythm.

Spain

The guidelines of the Spanish Society for Cardiology emphasise that there is a risk that GPs could fail to detect AF even in the presence of an ECG. This under-diagnosis would be due to the difficulty in interpreting the ECG and the possible absence of arrhythmia at the time the test is performed. Other difficulties in correctly diagnosing AF are the possibilities of confusing AF with other supraventricular arrhythmias, which may be regular or irregular, or that the arrhythmia may be of very short duration and may be present without related symptoms (Sociedad Espanola de Cardiologia 2014).

Clua-Espuny et al. (2014) estimated undiagnosed AF in a cross-sectional multicentre clinical study where 1,043 patients over 60 were screened in Catalonia. The screening found that the overall AF prevalence increased 10 times from patients in their 60s to those over 80 years of age. The prevalence of undiagnosed AF was 2.2 per cent. The study found that being more than 75 years of age, male, having a history of chronic heart failure, no ECG in the last two years and living in a rural environment were the major risk factors for having undiagnosed AF. Moreover, 23.5 per cent of the population diagnosed with AF in this study was found to not be receiving anticoagulation therapy. Clua-Espuny et al. (2013) found that the risk of not receiving OAC therapy increases with age at the time of AF diagnosis and is higher among women. However, Sanmartín et al. (2013) found that a local AF screening and outreach campaign had little effect on the diagnosis of previously undetected AF cases. They conclude that opportunistic screening is the best strategy for the early detection of this arrhythmia.

FEASAN, the Spanish Federation of Anticoagulant Associations, runs a digitally enabled patient awareness campaign on pulse monitoring, anticoagulants and AF in general. The campaign, sustained by a pharmaceutical industry sponsor, targets patients treated with

anticoagulants and offers printed material, a website and a mobile app allowing the patient to track their coagulation levels.²⁵

UK

Identifying and reaching out to patients who have already established cardiovascular diseases or are at significant risk of cardiovascular disease but have not developed symptoms are among the standards for GPs and primary healthcare teams established in the NHS Coronary Heart Disease Framework (NHS 2000). Suggested actions include advice on reducing lifestyle-related risk factors (such as obesity, diet or smoking) for all at-risk patients, and in the case of a positive diagnosis warfarin or aspirin for AF patients above the age of 60. The strategy identifies general practice consultations and cardiac prevention clinics as appropriate venues for this screening. However, systematic population screening is not recommended by the UK National Screening Committee as it is not clear that those identified as at risk through screening would benefit from early diagnosis.

A 2011 survey of NHS Primary Care Trusts (PCTs) found that while not compulsory, many of them encourage GPs to include pulse checks in their NHS Health Checks. NHS Health Checks are aimed at adults in England aged between 40 and 74 to help lower the risk of developing four common diseases: heart disease, stroke, diabetes and kidney disease. However, the 2011 survey also found that 26 per cent of NHS Health Checks did not include pulse checks. The report to the all-parliamentary committee on AF also cited best practice examples of NHS trusts providing education on AF to their personnel or recruiting dedicated AF consultants who could contribute to the screening, for instance during flu vaccination campaigns (AFA 2011).

The ‘Know Your Pulse’ campaign was jointly launched by the AFA and Arrhythmia Alliance in 2009 and organises yearly awareness-raising campaigns on the risks of AF and stroke as well as offering guidance on pulse self-check.²⁶ In the UK, Public Health England runs a stroke awareness campaign, Act FAST, although this does not presently include a focus on AF.²⁷

²⁵ See the Paciente Experto Anticoagulado Campaign website (as of 19 March 2015): <http://pacienteexpertoanticoagulado.com/>

²⁶ See the Know Your Pulse website (as of 19 March 2015): <http://www.knowyourpulse.org/>

²⁷ See the F.A.S.T campaign website (as of 19 March 2015): <http://www.stroke.org/understand-stroke/recognizing-stroke/act-fast>

Annex C Interview findings

To build on the evidence gathered through the rapid evidence assessment (REA) of the current landscape of atrial fibrillation (AF) and the use of anticoagulation for the prevention of AF-related stroke, we carried out key informant interviews (KII). Through these interviews, we sought to gain a better understanding of current issues and how they could develop in future. Overall, we found that countries broadly face the same issues, such as having a need to improve awareness and education about AF and cardiovascular health more generally, challenges in integrating primary and secondary care, and variability in the extent to which new management options are being adopted across the health system. However, differences arise in terms of, for example, how health systems are organised within each country and attitudes about the role of various actors (including nurses, patients and pharmacies) in care.

The KII were carried out in two phases, as described in Annex A. In the first phase, the interview protocol focused on the current landscape for AF-related anti-coagulation in each of six focus countries (Belgium, France, Germany, Italy, Spain and the UK). In the second phase, which covered the six focus countries and Europe in general, the focus was on discovering the drivers of change shaping the future of anticoagulation management in AF, with a particular emphasis on understanding political, economic, social, technological, legal and environmental (PESTLE) factors as well as relevant population trends. We present below an analysis of all 60 interviews, organised by PESTLE area. Additional detail on interviewee comments is provided in the PESTLE synthesis table in Annex E.²⁸

Political factors

Interviewees reported that policymaker awareness of AF was low, with the majority of countries viewing AF as more of a medical issue rather than a public health issue. However, some countries have seen an increase in awareness, either caused by lobbying by AF associations (the UK), or because the current Minister of Health is a doctor (Belgium). Increased awareness is desired to make AF a political priority; policymakers may then support specific public health policies aiming to reduce the cost of AF on society, such as publically funded awareness campaigns, or screening.

Lobbying from associations, cardiologists and the general public was a widely suggested mechanism of increasing policymaker awareness. This is already in progress to some extent. In the UK, the Atrial Fibrillation Association (AFA) and other patient groups are active in this area. In Belgium, policymakers are specifically targeted at AF awareness days. The main way suggested to increase political buy-in was to illustrate the economic consequences of AF (i.e. the cost of AF-related stroke) using evidence-based research and wide-ranging cost-effectiveness analysis. As well as the more direct costs of care, interviewees suggested cost-effectiveness analysis should include the cost of managing the complications of cardiovascular events, the cost of early retirement and the effect of the ageing population.

Population trends

As discussed in the REA (Annex B), the risk of suffering from AF increases with age, with 15 per cent of the population over 85 suffering.²⁹ Combining this with the

²⁸ The PESTLE synthesis table in Annex E presents KII responses alongside REA findings. Both sets of findings are organised by PESTLE factor and by whether they correspond to the current situation (and need for change), changes suggested, or changes expected or underway.

²⁹ Heeringa, et al. (2006).

facts that the elderly population in Europe is growing and that there is an increase in AF risk factors such as diabetes and obesity, an increased prevalence of AF is expected in the future. Interviewees from all countries mentioned that the elderly population can be challenging for healthcare practitioners (HCPs) to manage. Elderly-specific challenges cited included comorbidities and an elevated actual or perceived bleeding risk.

Interviewees thought that worries about the risks of anticoagulation can make GPs reluctant to provide anti-coagulants to the elderly, with one interviewee mentioning that there is a tendency for those with high stroke risk to be under-treated, whereas those with low stroke risk tend to be over-treated. One common worry was that it can be difficult to explain treatment and ensure compliance with the elderly population, although this was disputed, with some interviewees saying that elderly patients tend to have good compliance as they are used to taking medicines. Interviewees were asked about whether patients with renal dysfunction needed special attention; most interviewees felt that this comorbidity was rare enough not to be a big worry when thinking about the general care of patients with AF.

In general, interviewees saw a need for improved treatment for high-risk patients, including the elderly. One suggested route towards improved treatment was to encourage GPs to prescribe anticoagulants to the elderly, as per the guidelines, and monitor them carefully. This could be achieved through greater education for GPs, and also patients and families. Another suggested route was the development of new treatments such as safer anticoagulants for the elderly, anticoagulants which are not contraindicated for comorbidities such as renal dysfunction, and treatments that prevent thromboembolism or allow for better control of heart rhythm or rate. A further suggested avenue was to try and reduce the risk factors of AF. A better understanding of risk factors is particularly important, since though AF is seen as a disease of the elderly, it is also becoming more prevalent in the young.

Economic factors

Therapy for stroke prevention in AF patients was acknowledged to be expensive, regardless of the approach used. As discussed in the REA (Annex B), the main option for reducing the risk of stroke is oral

anticoagulants (OACs), of which there are two classes: vitamin K antagonists (VKAs) and non-VKA oral anti-coagulants (NOACs). VKAs, which have been in use for decades, are relatively cheap to prescribe but require regular INR monitoring to ensure patients remain in the target therapeutic range, whereas NOACs are much more expensive to prescribe but involve less follow-up care because they do not require regular INR monitoring.³⁰ The availability and extent of adoption of NOACs varies among and within countries. For instance, one Spanish interviewee felt that there is a need for availability to better match evidence of effectiveness, saying evidence indicates that in the long run NOACs are more effective than VKAs but are still unavailable in some regions in Spain. Interviewees from a range of countries mentioned that they would like cost-effectiveness analyses to be improved, potentially using real-world data, or focusing more on the long-term costs and the whole healthcare system rather than just the budget directly affected by the use of more expensive drugs. One interviewee suggested expanding cost-effectiveness even further to take into account effects beyond the healthcare system.

While interviewees reported that the cost of NOACs is a factor affecting the extent to which these drugs are adopted, there was variation across countries in terms of where in the health system that effect is felt. In France and Belgium, for example, interviewees reported that NOACs are fully reimbursed so the cost of particular treatments does not play a role in treatment decisions made by GPs. However, one Belgian interviewee reported that, despite full reimbursement for NOACs, guidelines recommend VKAs as the first choice drug for stroke prevention in patients with AF. The majority of interviewees thought that a reduction in cost would not affect use of NOACs, although there was some disagreement. In Germany, the UK, Spain and Italy the burden of cost is on GPs; there were some reports that, even if a specialist put a patient on NOACs, a GP may change the prescription to help balance their budget. In these countries, a reduction in cost is expected to increase use of NOACs. Across all countries, there was a consensus that, while cost is important in treatment decisions, it is not the only reason for low uptake of NOACs. Other reasons included lack of real-life data on the use of NOACs, fear of bleeding risks and conservatism.

In the UK there is an incentive scheme for GPs (the Quality Outcomes Framework, QOF) to encourage

³⁰ However, it should be noted that, as discussed elsewhere in this report, the French health authority has stated that there may be a need for monitoring in some patient groups when the NOAC dabigatran is used.

and reward good practice. Good management of AF is rewarded in the QOF,³¹ and interviewees from the UK felt that the QOF could also be used to encourage well-being checks, routine pulse checks, or to ensure effective NOAC use. This system is UK-specific, but Spanish and Italian interviewees felt that similar incentive schemes could work in their countries, whereas those from Belgium, France and Germany generally felt that incentive systems would not fit into their health systems. In interviews we introduced the idea of subsidies for diagnostic tools, or a NOAC antidote, to improve AF care. Again these were popular with UK, Spanish and Italian interviewees, with those in Belgium suggesting they could be useful but shouldn't be a priority, and those in France and Germany saying they would not be appropriate.

Social factors

There was general agreement that awareness and knowledge of AF is low in the general population and often, and possibly more importantly, lower than desired among HCPs as well. One suggested approach to increase awareness was public campaigns, which can help inform about what AF is, the risks, and why treatment is useful. To increase their worth they could be linked to existing campaigns, or be EU-wide. While many interviewees felt that campaigns would be useful, and might even help to reach policymakers, this was not a universal feeling, with some thinking that campaigns won't help those who are marginalised or who have asymptomatic AF and feel healthy. Interviewees from Spain, Italy and Belgium felt that public campaigns were unlikely, either due to the financial climate (Spain, Italy) or as public campaigns are uncommon (Belgium). However, in Belgium cardiologists have organised AF awareness programs with public funds, and in Belgium and France the pharmaceutical industry has supported awareness and education programs for HCPs. Some interviewees felt that the pharmaceutical industry can and should play more of a part in raising awareness and linking patients, GPs and cardiologists. In Belgium, the UK and Spain, patient associations are also starting to raise awareness.

Many interviewees felt that the level of GP (and other HCP) knowledge of AF was too low, and that education was needed to improve care. Concerns were raised that doctors often transmit fear of bleeds to patients,

rather than promoting the need to take anticoagulants to prevent strokes. Education on AF symptoms, the use and side-effects of NOACs and risk stratification is desired to help assuage fears of bleeding risks, and improve diagnosis rates so that cases aren't missed. In Italy this was seen as being very important as GPs will soon be able to prescribe NOACs. Interviewees mentioned that GPs face the challenge that they have many diseases to deal with and often do not have time to read all the guidelines; introduction of continuous GP training was suggested to help improve care. Many countries were reported to be already working on improving HCP education: in Belgium cardiologists organise GP training with public funds, and are developing an expertise centre allowing GPs to consult with specialists; in France pharmaceutical companies are organising training on NOAC use; and in Germany they have set up a programme with a pharmaceutical company where nurses are trained in anticoagulants, and then themselves give 90-minute group training to patients prescribed anticoagulants.

Interviewees also felt that improved patient education is needed to increase compliance, help empower patients and ensure that they get accurate information, which they may not get online. For some AF patients, interviewees felt that it may also be important to educate families so that they can act as a support system. A suggested alternative would be to have support groups for patients on anticoagulants. Improved patient education was reported to have already been instigated in Italy, Spain and the UK, through expert information days where patients can ask questions of cardiologists. In Spain, it was proposed that insurance providers could be encouraged to run education for patients.

One reason interviewees gave for the need for increased education is to improve patient compliance. Non-compliance is a general problem for reasons that are unclear. Within anticoagulation for stroke prevention in AF, it is believed that the lack of monitoring of NOACs compared to VKAs leads to worse compliance as patients are not regularly seen and reminded of the need to take their medication. However, there is also a chance that, as NOACs have fewer food restrictions and do not require finding the time to go for regular monitoring, compliance may be improved when they are used. Interviewees hoped that there would be more research to better understand non-compliance, better education for HCPs to help encourage compliance and

³¹ A summary of QOF indicators is available at (as of 19 March 2015):
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/213226/Summary-of-QOF-indicators.pdf

better education of patients on the importance of compliance. It was also suggested that follow-up checks for NOACs, or electronic checks or reminders about compliance, might help.

AF was reported to be an under-diagnosed condition, as many people suffering from it are asymptomatic, and are only diagnosed when they have a stroke. For many of these patients it would have been possible, and preferable, to diagnose and treat them before this happened. One suggested way to increase diagnosis rates would be to introduce routine screening, which is currently not carried out in any country. There was a consensus that screening would enable earlier diagnosis and treatment, but that it would be better to target elderly and at-risk groups rather than the general population, or to do it opportunistically when a patient visits the doctor for another reason. At the moment it is unclear who should be screened and how it should be carried out; research is desired to help inform these decisions. A few screening initiatives were reported, such as UK pulse check week, and screening for those with hereditary risk in the UK and Belgium.

Technological factors

As discussed in the REA (Annex B), the most common drugs used in the management of AF are VKAs and NOACs. Whilst anti-arrhythmic drugs are also available, an interviewer from France reported that as they are difficult to use they are becoming less popular. VKAs have been around for a long time and are relatively inexpensive. They require regular monitoring, for which many countries have set up specific systems and infrastructure, but which also can be a burden on the patient. NOACs are more recent, and availability and use of them varies between, and sometimes within, countries. They do not require regular monitoring; however, there were reports of reluctance to use them as they are more expensive, there is a lack of real-life studies about optimal dosages, NOAC safety and cost-effectiveness, and there is currently no antidote. Improvements on these issues were desired by interviewees, and were expected to increase NOAC use. Interviewees are also hoping that NOACs will be improved so that complication risks are reduced and they can be used on patients for whom they are currently contra-indicated (e.g. those with renal dysfunction and valvular AF). These changes are expected to cause use of NOACs to increase, possibly causing alternatives to disappear from the market. Interviewees from all countries expressed a hope that in the future NOACs will be used more effectively.

Surgical interventions can also be used to treat AF. The two that were referred to directly in interview protocols were ablation, a technique which removes small parts of the heart which are causing rapid and irregular heartbeats, and left atrial appendage occlusion (LAAO), where the left atrial appendage, the prominent site of thrombus formation, is closed (for more information, see Annex B). These two interventions were selected with input from the Steering Committee on the basis that both are seen, at least by some experts, as having potential to significantly impact when and how anticoagulation will be used in AF patients in future.

Interviewees reported that both of these interventions, ablation and LAAO, are currently performed relatively rarely and often reserved for younger patients who are severely suffering. As ablation removes bits of the heart causing an irregular heartbeat, there is hope that it could possibly cure AF. However, interviewees reported that it is currently unclear who it is appropriate for, how effective it is, and whether anticoagulants are still needed after it. Interviewees hoped or expected that in the future these concerns will be addressed, and that better techniques, possibly using robotics and/or ultrasound, will be developed. If ablation becomes more effective and frequent then countries will also need to develop more extensive training and infrastructure. Currently Italy, Spain, Germany and Belgium were reported to have sufficient numbers of skilled HCPs and centres for ablation (although the demand may currently be low in some countries), whereas interviewees from France and the UK felt that, particularly when looking to the future, they may not have sufficient numbers of trained doctors. In the near future most interviewees felt that ablation would not have a big impact on the use of oral anticoagulants, although in the much longer term it could mean that they were unnecessary. It is unclear how effective ablation will turn out to be and what proportion of the population it will be applicable for, so more evidence is desired to determine its value.

Technological advances are also expected to be very useful for diagnostics and disease management. Diagnosis of AF, particularly of asymptomatic patients, can be difficult. Portable devices and mobile technologies may make this easier. One example given was the iWatch, which can measure its wearer's pulse and hence detect AF; it will be released later this year. For disease management, portable devices are expected to enable a shift to community care as individuals may be able to self-monitor and then use telemedicine to submit results to the GP or nurse managing them. These devices or apps need to be designed with the

elderly in mind, or so that relatives can assist in their use. In the UK there has been a trial of AliveCor, a device which can read an electrocardiogram (ECG) and diagnose AF, and CoaguChek devices, which allow for home INR monitoring, are also being introduced in some areas.

Currently there is little knowledge of the cause or pathogenesis of AF; research into this was seen as important for improving AF treatment. An understanding of the molecular mechanisms of atrial thrombogenesis, or of why AF develops, may allow for diagnostics to be developed which enable early diagnosis and prevention. Biomarkers or ways to identify AF patients with high risk of thrombosis would also be useful, particularly if more is known about prevention. These advances could potentially allow for AF to be prevented, and possibly cured, reducing stroke risk greatly.

Legal factors

AF treatment guidelines vary throughout Europe, both in their recommendations and in how formal they are (see Annex B). There was a general consensus that, although guidelines can be useful, they often do not reflect reality well, since they do not capture real-life situations. This problem was discussed by interviewees from most countries, indicating that guidelines are not followed in all cases. Some interviewees reported current work towards making guidelines more useful: in France, for example, in addition to guidelines there are consensus documents which supplement the guidelines with short case studies that better represent clinical practice; in the UK, where guidelines can be very long, A4 sheets of the main points are being made for AF treatments. One UK interviewee suggested that specialist nurses may be more inclined to read the guidelines than non-specialist HCPs, and that much of the care could be moved to specialist nurses.

As mentioned above, devices for screening or monitoring, which can be used in the home and/or by the patient, may impact AF management. One example is CoaguChek, an INR tester for home use. One interviewee reported that it is currently being trialled in some regions in the UK, along with a web-based health platform, to allow patients to monitor themselves at home, communicate their readings to their HCPs, and potentially for dosages to be changed without the patient having to visit a clinic. Whilst these devices could have a big impact on AF treatment, it is not clear who is liable if there is a problem with a device; regulations for devices could make it easier for devices to be adopted.

Environmental factors

AF diagnosis was reported as usually occurring after a cardiovascular event or by chance by a GP during a visit for another reason. The next steps after diagnosis vary between and within countries, but often consist of an appointment with a cardiologist, followed by management of the disease either by the cardiologist, by GPs or by specialist nurses. This process, including which drugs are prescribed, is area specific, with interviewees from Italy, Spain and the UK reporting variability in treatment access. Whilst there are political efforts underway to homogenise care across Italy, in Spain the lack of availability of NOACs in some regions has led to 'health expats' who go to a different region to access treatment. There were widespread reports that some sections of society find it more difficult to access good care, including those in remote areas, those from lower-income groups (France) and those with low mobility (Germany, Italy). There was also a worry that, as many people with AF are asymptomatic and do not realise they have the condition, they do not receive care. The number of asymptomatic patients could be lowered by GPs focussing on prevention through increased diagnosis and monitoring of relevant risk factors; cheap, quick diagnostic tools could help with this. An alternative suggestion for increasing diagnosis rates in the UK, France and Italy, was to allow pharmacies to play a larger role, either through communicating information to GPs and cardiologists, or through screening. While detection falls within the remit of GPs, interviewees were worried that it may be difficult for GPs to keep up with the knowledge required, and for them to find the time in appointments to do opportunistic screening. In the UK, it was reported that GP appointments are only 10 minutes long, making it difficult to find the time even to answer patient's treatment questions.

AF management varies between countries, with many countries reported to be moving to more GP-managed care, facilitated by improved interactions between GPs and specialists. Interviewees reported that in Belgium they are developing an expertise centre which GPs can consult, and in Spain ICT systems are being developed for this purpose. Not all individuals are keen on this system, with one German interviewee saying that GPs are unwilling, and a UK interviewee suggesting that more referrals to specialists are needed, not fewer. As well as more GP involvement, Germany, the UK, France and Spain have implemented more nurse involvement. In the UK, some regions now have an arrhythmia service consisting of specialist nurses

who do outpatient clinics at GP surgeries, and refer only complicated cases to cardiologists. It is hoped that having more specialist nurses involved in the UK will help relieve the pressure on GPs in the NHS. Pharmacies were also mentioned by interviewees from the UK, France and Italy as an alternative or additional service provider that could become more involved in AF diagnosis and management. The shift towards community care is expected to be further enabled by telemedicine and data-sharing. There was widespread hope that home-based INR monitoring will improve care delivery and enable more patient autonomy and empowerment. One interviewee suggested this could be taken even further, with a pre-primary care model, where the first consultation would be online, and the patient would only see a doctor and have a referral if it was required.

Annex D Three future scenarios

Introduction

While we cannot predict with certainty what will happen in the future, we can use our understanding of the present to think about what might occur. By constructing scenarios – logical and consistent pictures of the future – we can explore the implications of decisions made today. Scenarios help us to provide insight into potential developments and how they might impact AF prevention, treatment and management. While the scenarios as described may be exaggerated versions of possible developments, the real future is likely to contain elements from each scenario. By thinking through these changes, we can explore the implications of today's choices – in terms of both risks and opportunities – and prepare for the future.

To inform the scenarios below, we analysed evidence from both the rapid evidence assessment (REA) and key informant interviews using a PESTLE framework,³² as described in Annex A. The scenarios were discussed in a one-day workshop with the project Steering Committee and were revised from their initial form on the basis of those discussions. Participants discussed the key developments that would need to occur for each scenario to be reached, and the risks and opportunities associated with each scenario.

The PESTLE framework allowed us to identify the important trends and drivers for AF diagnosis and care across the data and, to some extent, to gauge the apparent impact and likelihood of particular developments. We identified a number of factors through the REA and interviews that are considered to be highly likely to emerge or continue across all country contexts (Table D.1). We have taken these factors as the background context for all scenarios, which are placed approximately ten years in the future.

Table D.1: Trends present across all scenarios

Population trends	AF prevalence has increased due to population ageing, increased longevity of AF patients and rises in other risk factors
Economic context	Europe has continued to face financial constraints and healthcare systems have to do more with less
Use of NOACs	NOACs have nearly replaced VKAs for AF. The cost of NOACs is significantly less due to the expiration of patents
NOAC antidote	Antidotes have been developed for all NOACs
Data trends	There is increased data on the use of NOACs in different scenarios and patient groups

Overleaf we describe each scenario with a brief overview, and a table highlighting relevant aspects of the current landscape in each focus country and across Europe, where appropriate. We then set out the scenario in more detail, describing developments within each PESTLE category in turn, and then we present the risks and opportunities that were associated with each scenario.

³² The Political, Economic, Social, Technological, Legal and Environmental (PESTLE) framework is used to categorise the diverse factors that may be relevant for change with regards to a given issue and/or context. The analysis also included factors related to population trends.

Year 2025

Scenario one: Advancing a patient-centric approach through awareness and education

Large public campaigns mean everyone is aware of AF and many perform regular pulse checks on themselves. This is reinforced through the school curriculum, innovations to help individuals check their pulse and messages in community care centres and pharmacies. Primary care is mainly responsible for managing AF patients and primary care practitioners are struggling to cope with the increase in AF cases.

Political factor: Policymakers are aware of AF and invest in large public health campaigns to raise awareness among the general population

Lobbying and advocacy activities through patient groups such as the Atrial Fibrillation Association, charities and active parliamentary groups have led to increased policy awareness of AF and its association with stroke. The cost of stroke as well as increasing pressure on hospital resources has prompted policymakers to take a different approach. There is large investment in awareness campaigns for the general population and individuals are encouraged to check their own pulse on a regular basis. This includes the introduction of pulse checking and information on AF into school curriculums – starting at a young age.

The rationale for this approach is that individuals will be empowered to identify AF in themselves, reducing the need for systematic screening and ultimately reducing the number of strokes. In the long term it is hoped that this will cut AF-related mortalities and reduce pressure on hospital resources.

Population trend: The number of individuals identified with AF increases substantially, creating a burden on resources in the short term

Due to individual testing, there is a significant increase in the number of patients diagnosed with AF. This places increased pressure on primary care as all patients need a management and treatment plan. Despite a growing number of specialist GPs and nurses, primary care is struggling to cope.

Developments within each country taking place in 2015

	Patient associations are starting to raise awareness in Belgium, although public campaigns are uncommon and not thought to be likely for AF specifically. Nevertheless cardiologists have organised education programmes with public funds and the pharma industry has supported awareness/education programmes targeting HCPs
	In France there is agreement that patient and public education is needed, although it is thought to be unlikely that policymakers will invest in awareness and public health campaigns in the short-term. Several interviewees noted there is scope for GPs, nurses and pharmacists to get more involved in AF management and care
	In Germany there is far less emphasis on primary care in dealing with AF patients. However, there is a programme with a pharmaceutical company to train nurses in GP surgeries in anticoagulation. Pharmacies are primarily responsible for dispensing over-the-counter drugs and so interviewees did not generally expect that pharmacies would play a more significant role in healthcare
	Public investment is not expected in Italy due to the economic climate. However, there are information days/programmes for patients and there is a growing role for primary care in managing AF. Soon GPs will be able to prescribe NOACs
	In Spain patient associations are starting to raise awareness and there are expert information programmes for patients to ask questions of cardiologists – although public investment is not expected due to the economic climate and the reluctance to make AF a policy priority. There is also a shift underway from specialists to GPs for anticoagulant monitoring
	This scenario could result from current UK activities. There is an all-party parliamentary group to raise awareness, a pulse check week, patient associations are active, there are expert information days for patients and primary care is already responsible for AF patients. Nurses are becoming more involved and specialist nurses do outpatient clinics in GP surgeries

Economic factor: There is significant investment in awareness campaigns and large research studies, although the sustainability of this investment is unclear

In taking a long-term view of reducing the costs of treating AF-related stroke, money is made available for large awareness campaigns. In addition, many believe that understanding the cause of AF is increasingly important and will play a key role in prevention. As a result, there is also large investment into research to identify the cause of AF. However, the future of this funding is less certain. Despite the fact that in order to successfully identify the role of biomarkers, large longitudinal studies are likely to be needed, it may be the case that research funding is withdrawn if there are not promising results in the short-term – particularly due to short political cycles.

Social factor: Everyone is aware of AF and patients are empowered to assess themselves. The issue of patient compliance is reduced due to the education of patients

Education is of central importance to this scenario and as a result everyone is aware of AF – from policymakers to GPs, nurses, cardiologists and the general population – including children. This is reinforced in popular culture, with characters in television programmes suffering from AF. Children are taught about the importance of pulse checking at school and everyone is familiar with innovations to aid individuals to check their pulse and identify AF – such as smart phone apps, iWatches and small purpose-made devices. Due to increased awareness across the board the family unit becomes important in helping individuals check their pulse if unable to do so on their own. Families are encouraged to check the pulse of others on a regular basis. Indeed, the importance of the family features in awareness campaigns.

When patients have been diagnosed with AF, they are managed by their GP. Where NOACs are used, increased awareness among the population and patients means that issues associated with patient compliance are reduced. Patients are fully aware of their treatment options and of the role of NOACs in reducing the risk of stroke. They are also aware of the consequences of missed doses. As a result, compliance is high.

Technological factor: There are innovations in aiding the general public to check their pulse and these contribute to increasing awareness

The role of new innovations plays a key role in this scenario. The development of smart phone apps – and other smart technology such as iWatches – which help individuals to check their pulse play an important role in raising awareness. Advertising and marketing campaigns around these products and their potential role in healthcare reinforce policy messages about pulse checking. There are also purpose-built devices that aid individuals to check their pulse and identify AF. These are mass-produced and sold very cheaply. Again, the marketing campaigns for these devices heighten awareness and the products are ideal for those who do not own smart technology.

Legal factor: The role of innovations in enabling patients to check their own pulse raises questions of accountability if there are any errors.

Patients are now empowered to check their own pulse. However, there are concerns that an over-reliance on devices or apps to identify AF through pulse checks may lead to missed diagnoses. There have been legal battles between the manufacturers of devices and individuals who have experienced AF-related stroke after testing negative for AF using a device. It is unclear who should be accountable for effective diagnosis, and whether GPs or those in community care should bear any responsibility for missed diagnoses. This has stifled ongoing innovation in the area and the resolution of this problem remains unclear.

Environmental factor: Care and diagnosis is the responsibility of primary and community care

Due to individual empowerment, the management of AF takes place in primary and community care. Pharmacies play a significant role in reinforcing policy campaigns through continued education of the community. They also help individuals with pulse checks who cannot manage on their own. GPs diagnose and manage the vast majority of AF patients. There is an increase in specialist GPs and nurses although general healthcare professionals also have a good knowledge of AF and how it should be treated/managed. GPs refer patients for AF treatments such as ablation where appropriate.

Due to the increase in patients diagnosed with AF, primary care is struggling to cope. There is an expanding knowledge base in the area which GPs struggle to keep abreast of. There is growing concern that specialist GPs are losing their expertise in other areas, and struggling to cope with complicated cases such as patients with many comorbidities. There are nurse-led teams who deal with patients within surgeries, although they have had limited success due to the large number of patient complications. On the other hand, however, a reduction in the use of hospital resources is expected in the long term and there is growing evidence this is starting to occur.

Opportunities

Awareness and education:

- More education leads to more compliance
- Greater awareness can push policy change
- Quality online resources would benefit AF patients and their families
- Reduced dependence on 'Dr Google' – patients being misled about their condition or care options by unreliable information found online
- More awareness of comorbidities and general cardiovascular health
- Increased adherence to AF clinical guidelines
- Greater family involvement

Environmental issues and patient pathway:

- Moving towards NOACs could reduce pressure on primary care
- Local patient groups (partnerships of HCPs and patients) could provide support for patients (this could potentially replace the support that patients felt they received via monitoring)
- Potential for increased role for pharmacies
- More and earlier AF detection

Risks

Awareness and education:

- An increase in 'worried well' patients (concerned patients who may seek care that is not needed)
- Some HCPs may not like 'empowered' patients telling them how to be treated, so there may be some resistance about education, particularly in primary care
- Difficulty of placing AF as an issue on the wider agenda
- Lack of public knowledge of and popular impetus for AF as a disease area

Devices:

- Potential for confusion if there are multiple devices available for diagnosis or monitoring
- Possibility for devices giving false positives/negatives or false sense of security
- May require widespread availability of technology such as continuous long-term ECG monitoring that may not be feasible to provide due to other, more urgent health needs

Economic effects:

- Better health and fewer strokes could still carry a financial risk and high associated cost
- Primary care focus could result in inadequate investment for secondary care
- Reduced innovation and general progress if there is less involvement from secondary and tertiary care, as a result of academic complacency
- Scenarios require a shift towards making economic decisions based on maximising patient care and prevention measures, and this shift is not currently likely

Environmental issues and patient pathway:

- Interest from industry could be reduced if focus is entirely on primary care
- Potential for primary care being unable to cope with increased workload and pressure on the system
- Some patients would still not be diagnosed (and may have strokes or heart failure)
- Under-treatment of AF as a result of reduced secondary/tertiary involvement
- Obstacles in shifting from secondary to primary care

Monitoring:

- In the move to NOACs, some patients will miss having the regular checks that come with monitoring

Year 2025

Scenario two: Accelerating treatment through technology and innovation

To relieve pressure on primary care and ensure a high standard of care for AF, responsibility for AF patients is shifted almost entirely to specialists. Routine screening is implemented for those either over 65 or with relevant risk factors to ensure early detection. Significant advances in surgical interventions and new drugs mean the risk of stroke related to AF can be more dramatically and permanently reduced in a range of patients, including the elderly.

Political factor: Optimism about cost savings and the effectiveness of technology

Policymakers have acknowledged the importance of addressing AF. They have approved and invested in a routine systematic screening programme. They have also supported research to enhance and implement surgical intervention techniques on a wider scale, in the hope that the number of patients on life-long medication, such as OACs, would be reduced. Political buy-in centres on the idea that early intervention for AF is cost-effective in the long-term; it has been shown to reduce stroke rates and keep people fit to work for longer.

Population trend: Systematic screening caused a sudden increase in the number of patients diagnosed with AF

Screening by GPs takes place routinely every year for those aged 65 or over. Individuals also enter the screening programme if they are identified as having additional risk factors – although this does not take place systematically and additional risk factors are identified by chance through other medical appointments. The introduction of screening resulted in identification of a large number of previously undiagnosed patients, including many who were asymptomatic and otherwise healthy. Once screening became established, annual increases were much less dramatic, but population ageing and lifestyle factors continue to cause increases in prevalence.

Developments within each country taking place in 2015

	Techniques for one type of intervention, ablation, are likely to improve. From a patient perspective, ablation is improving as it is less aggressive and has positive effects. However, it is currently unclear which patients ablation is appropriate for and the extent to which patients require OACs after ablation. We also need better information about the risks of thrombosis after ablation. Nevertheless, improvements in heart imaging could facilitate ablation and it may be applicable to more and more people in the future
	In Belgium, some clinicians have resisted the shift towards increased use of surgical interventions, which they felt were unnecessary – although it was suggested that younger cardiologists are more willing to perform ablation
	Researchers in France have contributed to developments in ablation, but interviewees reported the technique is used rarely and mainly only in younger patients. However, one interviewee stated that ablation was an area that could contribute significantly to treatment advances
	In Germany, centres provide ablation treatment and interviewees reported that the country has enough skilled specialists to carry out these procedures (although it is not offered by all cardiologists). Multiple interviewees said they expected developments to continue improving the intervention. LAAO is also performed on a small number of patients
	In Italy, interviewees reported that skills and equipment were available for performing interventions such as ablation
	In Spain, a number of interviewees questioned the impact ablation could have on OAC use because they are only used on a small fraction of patients. However, they said that there were adequate skills and equipment for performing ablation and the procedures were done well
	UK interviewees reported that the country does not have enough specialists skilled in carrying out ablation to meet demand, but that developments underway in robotics could help automate the procedure and reduce the level of skill required. Interviewees said that LAAO is available at a small number of locations

Economic factor: There is significant investment in prevention, as well as in research and innovation

An emphasis on the longer-term savings in AF care that result from early intervention has enabled a strong case to be made for increased spending on AF screening and treatment. At the same time, the costs of specialised interventions have decreased substantially, particularly due to increased automation of the interventions, reducing the need for specialist skills. These two factors led to funds being made available for the systematic screening, specialist centres and specialised treatments, despite their large up-front costs.

Social factor: Limited education and awareness

Education and public awareness are not prioritised, and many patients avoid going for screening. The general public remains largely unaware of AF and how lifestyle factors can contribute to AF risks. In regions most dominated by specialised treatments, there is less support and information available for the patients who are still taking oral anticoagulants.

Technology factor: Research and innovation has made treatment better, faster and cheaper

The focus on specialist care has driven a number of advances in technology related to AF detection and treatment, and enabled comprehensive stratification of AF patients. Advances in robotics and heart imaging have had a significant impact on AF treatment. For instance, robotics advances have enabled ablation to be largely automated, so that a greater number of interventions can now be performed more cheaply. Heart imaging technology has made multiple treatments safer and more effective, and it has also enabled significant progress to be made in research.

Findings from research into biomarkers for AF have enabled significant advances in stratified medicine approaches. Advances in surgical interventions and basic research have led many to believe that interventions to dramatically and permanently reduce the stroke risk from AF are possible; this is a key focus for many researchers and clinicians.

Legal factor: Clinical guidelines recommend ablation, LAAO and other interventions

Guidelines have been updated to reflect the preference for specialised interventions over oral anticoagulants. They contain information about which patients should receive which interventions and what sort of follow-up is required. However, the majority of GPs are relatively unfamiliar with the information in the guidelines as they do not often need to manage AF patients.

Environmental factor: Specialists dominate

The majority of AF cases are detected when patients go for systematic screening. Patients are then immediately referred to specialist cardiologists, who assess whether they should receive ablation or another procedure. The procedures are usually carried out in specialised cardiology centres.

Only a minority of patients are cared for by GPs: those who do not qualify for a specialist intervention and those for whom the procedure is unsuccessful. In those cases the cardiologist recommends a management plan which the GP implements. GPs are encouraged to contact the centres of excellence for support if there are complications or if they are unsure of the appropriate action to take.

Opportunities	Risks
<p>Progress in understanding of AF and in technology:</p> <ul style="list-style-type: none"> Potential for effective therapies for cure – more patients cured as a result Better diagnosis and therapy via improved techniques and treatments More individualised care Avoidance of ‘unnecessary anticoagulation’ because there would be improved understanding of when anticoagulation is required) Fewer patients would require long-term anticoagulation Technological progress <p>Awareness and education:</p> <ul style="list-style-type: none"> Curative technology could generate media and public interest because technological advances are ‘sexy’ and curative medicine is well-received by the public <p>Economic:</p> <ul style="list-style-type: none"> Increased support and funding for secondary care <p>Environmental:</p> <ul style="list-style-type: none"> High level of academic engagement Reduced pressure on primary care, which can concentrate on other matters <p>Promise of new therapeutic devices for AF:</p> <ul style="list-style-type: none"> Economically appealing to have early intervention and treatment (provided treatment could be developed) Introduction of screening programmes and stratification of risk groups We are already seeing more ablation procedures across Europe 	<p>Progress in understanding of AF and in technology:</p> <ul style="list-style-type: none"> Ablation has not yet been shown to reduce stroke risk Major policy change would be needed and this may be hard to achieve <p>Awareness and education:</p> <ul style="list-style-type: none"> GPs’ skills related to AF would not improve and may decline Lack of public awareness for general population if GPs are not involved in treatment Patients underestimate their own risk Promise of a therapy may result in a false sense of security <p>Economic:</p> <ul style="list-style-type: none"> This is a costly approach and may overload the healthcare system (a high spend for a small patient population) <p>Environmental:</p> <ul style="list-style-type: none"> Many specialists needed (it is possible that secondary care could not cope) Isolation of primary care Less holistic approach Specialists are generally less interested in simpler cases This approach may be more aggressive than needed for relatively simple cases <p>Promise of new therapeutic devices for AF:</p> <ul style="list-style-type: none"> Long approval process for drug or surgical procedure cures before screening happens Proof of cost-effectiveness would be needed Problem of variations in interventional surgeries across EU ‘Worried well’ problem that comes with screening There is a concern that there is not currently enough emphasis on the benefits and outcomes of procedures

Year 2025

Scenario three: Maximising specialist care through knowledge exchange

Since 2015, little has changed in the management and identification of AF. However, healthcare delivery has changed substantially: electronic health records, a broader evidence base and data sharing systems have enabled effective care and management across different health settings.

Political factor: AF is not a policy priority; however, policymakers acknowledge that a reorganisation of care through cardiology centres may improve patient outcomes

AF is not a policy priority and there remains an overall lack of awareness about AF among the general population. Despite activity from advocacy and patient groups, most people are unaware of what AF is or its connection with stroke. However, people are aware of new cardiology centres which have been introduced to deal with the treatment and management of a range of cardiac problems, including AF. On a broader level, there is investment in interoperable electronic health records and data sharing.

Population trends: The number of people with AF has continued to increase, although a lack of routine screening means there are many more that have not been identified

Although routine systematic screening is not in place, the abundance of data has contributed to the identification of at-risk individuals. Data is collected at an individual level through a diverse range of sources and those with associated conditions such as hypertension – as well as risk factors such as obesity and alcohol intake – are identifiable to GPs and those working in cardiology centres. GPs and others make judgements about whether certain at-risk individuals should be called into cardiology centres for diagnostic tests on an ongoing basis.

Developments within each country taking place in 2015

	<p>There is likely to be a trend towards electronic health records (EHRs) and data sharing. However there are concerns that if this happens as a 'top-down initiative' – i.e. EHRs are implemented by large multinational companies, innovation will be stifled. There are already organisations which are focused on the sharing and utilisation of data – e.g. sending the results of self-INR checks directly to GPs</p>
	<p>Belgium is developing an expertise centre, where GPs can consult with specialists on AF management. This facility reduces the need for patients to visit hospitals to receive specialist care</p>
	<p>Some interviewees felt there is potential for more to be done to fully integrate the patients' journey and involve all relevant actors. For example, nurses are not extensively involved in AF treatment and management at present</p>
	<p>Cardiology centres already exist in Germany and studies show that patients treated by a cardiologist are usually on a better treatment regime than those treated by a GP. There is an ongoing programme where different specialties from care and stroke prevention work together although GPs are generally unwilling to engage in this. Two interviewees noted specialist AF centres would be desirable</p>
	<p>In Italy differences across regions cause difficulties in regard to access to care and how various medicines (including NOACs) are prescribed. A number of interviewees noted the importance of support at the regional level as well as the need to facilitate training and knowledge-sharing in non-hospital facilities</p>
	<p>Healthcare delivery is varied across autonomous regions, although collaboration is already facilitated by e-solutions to communicate a patient's characteristics</p>
	<p>In the UK management of AF is patchy. While it is primarily the responsibility of GPs, many struggle to keep abreast of guidelines. Specialist support for GPs would be welcome</p>

Economic factor: There has been a considerable reduction in the cost of NOACs due to patent expirations

There has been a considerable reduction in NOAC costs due to the expiration of patents and the introduction of generic drugs on the market. However, there has been no significant investment in AF – either in diagnosis, treatment or management. Nevertheless, the management of AF has improved due to broader trends in the use of data.

Social factor: There is not widespread awareness of AF in the general population; there is greater awareness and education among HCPs and the relationship between specialist nurses and patients has increased patient compliance

The general population is still not aware of AF and the challenges it brings. However, there is greater knowledge and understanding of AF in the healthcare professional community. There are specialist GPs and nurses and they work with general healthcare providers to educate them regarding issues related to AF. There is a strong role for nurses in working with patients to ensure they understand AF and their treatment options. Through the relationship patients are educated and there is a higher level of compliance (in comparison with 2015). However, there are still challenges in this regard and nurses still report that it is hard to know whether patients have taken NOACs as intended.

In the preceding ten years there has been significant monitoring of patients taking NOACs (despite initial speculation that NOACs would reduce the amount of INR and patient monitoring). As a result there is a wealth of data about how NOACs work in different scenarios and in different patient types. This data is accessible to a range of actors and healthcare settings including GPs, nurses and cardiologists. This has improved the effective use of NOACs (including dosage decisions). Now only a few difficult cases are monitored and there are a reduced number of adverse events associated with NOACs (such as bleeds).

Technological factor: Knowledge transfer and patient management across healthcare settings is facilitated through shared data

There are breakthroughs in implementing electronic health records across Europe which are interoperable and can be shared across healthcare settings. Patient information is shared across cardiology centres,

hospitals and GP surgeries enabling a seamless experience for patients and knowledge transfer across settings.

In addition real-world data is used significantly in healthcare. There are databases detailing patient profiles, medical interventions and outcomes which can be used to aid healthcare professionals in making decisions. Data is also collected on individual lifestyles and risk factors through surveys and other means.

Legal factor: The use of data requires complex legal frameworks

Many individuals are concerned about their data being passed on and used by third parties such as commercial organisations. As a result there are stringent regulatory frameworks on how data can be used which also apply to healthcare settings.

A number of individuals object to their data being used and this has resulted in the need to ‘opt in’ to the sharing of individual data. This means that individuals who do not opt in do not benefit from being identified as ‘at risk’ – and therefore a number of individuals are missed in diagnosis.

Environmental factor: Care is delivered through cardiology centres which fuse primary and secondary care; these centres also go out into the community in more remote areas and facilitate outreach

There are cardiology centres which draw upon primary and secondary care. They consist of cardiologists as well as specialist GPs and nurses. Most work there part-time and spend the rest of their time in hospitals or GP surgeries. This facilitates knowledge transfer and general GPs and nurses become more knowledgeable about AF. In turn, NOACs are used effectively and there is a high level of guideline adherence in appropriate cases. Cardiology centres form part of wider GP networks and polyclinics which are already beginning to emerge in the UK.

These centres also go into the community to existing GP surgeries to offer their expertise to HCPs and patients. The mobility of HCPs across health settings in part reduces the strain on specialist GPs and nurses due to knowledge transfer. However there is a shortage of skills overall and several of these centres are under-staffed.

Opportunities	Risks
<p>Political:</p> <ul style="list-style-type: none"> Opportunity to get more real-time data on outcomes. This information could then be used to influence political decisions <p>Education and awareness:</p> <ul style="list-style-type: none"> Concentrating resources could increase disease awareness <p>Economic:</p> <ul style="list-style-type: none"> Sustainable costs over longer-term timeframe <p>Technology:</p> <ul style="list-style-type: none"> Developing large datasets for research, etc. Chip technology can identify high-risk patients (avoiding the 'worried well') Automatic identification of risk factors and therefore creating better stratification <p>Environment:</p> <ul style="list-style-type: none"> Creation of a well-networked healthcare system and more 'holistic' patient approach <p>Knowledge exchange:</p> <ul style="list-style-type: none"> Would be beneficial and popular with GPs Little resistance from new generation of 'tech savvy' HCPs <p>Long-term cost saving:</p> <ul style="list-style-type: none"> Move to outcome-based decisionmaking and valuing long-term cost effectiveness Disease areas viewed as 'high priority' like Hepatitis C merit investment 	<p>Education and awareness:</p> <ul style="list-style-type: none"> Lower media awareness because the media are more interested in new treatments – less 'sexy' <p>Economic:</p> <ul style="list-style-type: none"> High upfront cost <p>Social:</p> <ul style="list-style-type: none"> E-data safety and data privacy concerns Patients could be missing from a programme or excluded; difficult access for general population Resistance to change (by public or HCPs) <p>Environment:</p> <ul style="list-style-type: none"> Barriers to inter-professional exchange (may be country-specific) Patients may feel that they are being treated 'by robots' Need incentives for the outreach to happen More arrhythmias directed to specialists Patients may receive sub-optimal care if the approach was not fully adopted <p>Knowledge exchange:</p> <ul style="list-style-type: none"> Difficult for specialists to find time to engage in knowledge exchange schemes Challenge for human resources to create time for this to happen <p>Long-term cost saving:</p> <ul style="list-style-type: none"> AF not seen as a high priority Difficulties for budget managers in balancing delivery of long-term cost-effectiveness, good outcomes and affordable treatment

Summary

Table D.2 compares the scenarios based on the degree of change that takes place in each one across different PESTLE areas. No one scenario is intended to represent a ‘perfect’ world or a prediction of the future, and each comes with its own risks and opportunities. However,

the scenarios can be used to help policymakers and other stakeholders focus on the implications of each area of change for the future. Each factor is exaggerated to some extent in order to provide a range of future concepts and understand how each factor impacts on others.

Table D.2: Comparison of scenarios based on degree of change in key areas

		Scenario one	Scenario two	Scenario three
Policy	Policy awareness	High	High	Low
	AF as a political priority	High	High	Low
Economic	Cost-effectiveness in decisionmaking	Medium	High	Low
	Key investment area	Awareness and education	Technology and specialist care	Data sharing and reorganisation of health services
Social	Public awareness	High	Low	Low
	Patient education/compliance	High	Low	High
	HCP education	High (but GPs struggle to cope with demands)	Variable (lower among GPs)	High
	Patient empowerment	High	Low	Medium
Technology	Technology for identification	High	High	Medium
	Technology for treatment	Low	High	Low
	Developments in electronic patient data and software for health services	Low	Low	High
	Technology for AF patient monitoring	Low	High	High
Legal/guidelines	Guidelines adherence	Medium	Variable (lower in primary care)	High
Environment	Primary care involvement	High	Low	High
	Secondary care involvement	Low	High	High
	New models of care	Low	High	High

Annex E PESTLE factor synthesis

The table in this annex presents a synthesis of findings from the key informant interviews (white rows) and rapid evidence assessment (blue rows). The key informant interview findings are summarised in Annex C, while the rapid evidence assessment findings are presented in Annex B. Methods for carrying out the interviews, evidence assessment and PESTLE analysis are described in Annex A.

The findings are organised by:

1. PESTLE area: political, population trends, economic, social, technological, legal and environmental
2. Aspect of change: needed, suggested, expected

Where findings or comments are country-specific, the country/countries are indicated using standard abbreviations.

Political factors

Issue	Current situation and views on a need for change	Changes suggested	Changes expected or currently underway
Policymaker awareness	Awareness generally low Need to better understand if AF is a disability. This affects employers/employment (UK)	Increased lobbying from AF associations and/or general public Target policymakers via awareness days (BE) National or EU-wide awareness campaigns	Lobbying is impacting awareness in UK (from All-party AF group, AFA)
			High economic burden of AF may drive policymaker engagement
AF as policy priority	AF needs to be a political priority to get publicly funded awareness campaigns, run screening programmes, etc.	Build evidence base including cost-effectiveness analysis (early retirement, high cost of AF complications and cardiovascular events, illustrate AF impacts and contribution to heart failure)	

Population trends

Issue	Current situation and views on a need for change	Changes suggested	Changes expected or currently underway
Issues specific to elderly	<p>Elderly population can be difficult to manage due to:</p> <ul style="list-style-type: none"> • Comorbidities, polypharmacy • Frailness • Difficulty explaining treatment and ensuring compliance (disputed) • higher risks on anticoagulation medicines <p>There is some reluctance to provide anticoagulation for the elderly and some treatments may have age restrictions (UK and ES have limits on ablation)</p>	<p>Put elderly on anticoagulants and monitor carefully</p> <p>Try to reduce risk factors</p> <p>Increased surveillance as part of routine care</p> <p>Treatments:</p> <ul style="list-style-type: none"> • Safer anticoagulants • Methods to prevent thromboembolism • Methods to better control heart rhythm/ rate • NOAC antidotes <p>Education for GPs on treating elderly, and for patients and family</p>	<p>Europe-wide increase in elderly population will lead to increased prevalence of AF</p> <p>More people of working age with AF (as people work longer)</p>
	<p>AF prevalence increases exponentially with age (affects <0.5% of people aged <40 and 18% of people aged >85) (Fumagalli et al. 2012)</p> <p>Elderly have been underrepresented in OAC trials, and patients excluded from trials are generally at higher risk of bleeding, which reduces applicability (real or perceived) of results to real-world cases (van Walraven et al. 2009)</p>		
Ageing population	In Europe, 5.1% of people are aged >80 (Eurostat 2014)		In Europe, people aged >80 will be 7% of the population in 2030 and 11% in 2050 (Eurostat 2014)
Issues specific to groups with renal dysfunction	<p>NOACs contraindicated for renal dysfunction</p> <p>Patients often have comorbidities and are hard to manage</p>	<p>NOACs which can be used on patients with renal dysfunction</p> <p>GP education</p>	
	There are limitations on use of NOACs in patients with renal dysfunction (Gheorghiade et al. 2013)		
Issues specific to young people			Increasing AF prevalence, possibly from intense exercise
Prevalence	Current prevalence in the European population is 2% (Zoni-Berisso et al. 2014)		<p>Projected prevalence in Europe in 2050 (based on age demographics alone) is 3%</p> <p>Prevalence expected to rise due to ageing population and other factors (Chugh et al. 2014)</p> <p>IT: If all individuals with AF were identified, patient number would double (ALFA 2014)</p>

Economic factors

Issue	Current situation and views on a need for change	Changes suggested	Changes expected or currently underway
Costs, cost-effectiveness	Cost-benefit analyses help decide whether a drug should be used, but currently most do not consider the whole health system; instead different parts of the system are viewed as 'silos'	More 'holistic' cost-effectiveness studies (as in Sweden) Cost-effectiveness assessments could use real-world data on, e.g., NOACs vs warfarin	Improved ability to use new drugs that are only cost-effective in the long term (like NOACs)
	The economic burden of AF is high (Stewart 2004; Wodchis et al. 2012)		
NOAC cost	While the cost is generally seen as high, it is seen to have mixed effects on prescription decisions, depending on how directly affected doctors are by budget restrictions. In some health systems, cost considerations can cause GPs to change from a drug a specialist has prescribed Although cost is seen as an issue in NOACs uptake, conservatism, fear and lack of education are also important BE and FR: <ul style="list-style-type: none">• NOACs are fully reimbursed so cost not taken into account by prescriber• However, NOACs are not first choice drug• Disagreement over whether NOAC price drop would increase uptake• Low uptake may be due to fear and lack of knowledge about side effects DE, IT, UK and ES: <ul style="list-style-type: none">• NOAC cost taken into account by prescriber• Price drop expected to increase uptake	Reduction in NOAC cost up front (25%, 50% or to level of warfarin) EU authorities impose universal drug prices In countries with regional variation, government should impose one national price	Increase in use of NOACs
	NOACs have been proven to be more cost-effective (in QALY terms) than the alternatives (Harrington et al. 2013; Canestaro et al. 2013)		

Issue	Current situation and views on a need for change	Changes suggested	Changes expected or currently underway
Incentives	UK: the Quality and Outcomes Framework rewards GPs for certain tasks, including AF management FR: has introduced a bonus for doctors who fulfil a certain number of public health objectives ES: gives incentives to doctors to get them to control spending	Introduce incentives for: <ul style="list-style-type: none">• Spending more time with patients• Monitoring patients on anticoagulants• Well-being checks• Routine pulse checks• Effective use of NOACs (by % of AF population)• Including other players, such as pharmacies• Training	UK, ES, IT: incentives concept welcomed, expected to improve service BE, FR, DE (in DE, doctors are paid a fixed amount per patient): most agreed incentives would not fit with their health systems
Subsidies	Subsidies for certain tools or treatments (e.g. NOAC antidote, screening devices) could increase their uptake and use, leading to better care	Subsidies for: <ul style="list-style-type: none">• Telemedicine for screening• Devices for pulse monitoring• Cost of antidote for NOACs (10–20% subsidy) Subsidies provided by industry instead of/as well as government Industry can help with subsidies for diagnostic or monitoring tools	ES, IT, UK: concept welcomed in certain areas BE: acceptable but shouldn't be a priority. Some diagnostic tools already subsidised by government FR, DE: not supported (not appropriate or necessary)

Social factors

Issue	Current situation and views on a need for change	Changes suggested	Changes expected or currently underway
Awareness of public, HCPs	Awareness campaigns could help inform public about what AF is and risks, and why treatment useful (most interviewees agree but not all) GP/healthcare professional (HCP) awareness important (some say more important than public awareness) Awareness campaigns can reach policymakers (BE) Campaigns won't help people who are marginalised or feel healthy/asymptomatic	Link AF to existing campaigns, e.g. for stroke, cardio health Pharma industry can/should play role in awareness raising and help link patients, GPs, cardiologists EU-wide awareness raising	Patient associations starting to raise awareness (UK, ES, BE) No public investment expected due to econ climate, other diseases higher priority (ES, IT) Public campaigns uncommon, unlikely for AF but cardiologists have organised programmes with public funds (BE) Pharma industry has supported awareness/education programmes targeting HCPs (BE, FR)
			DE: annual awareness-raising tour by BI highlighting AF as a risk factor for stroke (Vorhofflimern 2013) FR: campaigns from Bayer and BI to raise awareness and increase diagnosis (Davy 2014)

Issue	Current situation and views on a need for change	Changes suggested	Changes expected or currently underway
Education of HCPs	<p>GPs need education in particular (and pharmacists in UK), especially on use and side-effects of NOACs, and risk stratification</p> <p>GP challenge: many diseases to deal with, cannot read all guidelines</p> <p>Education needed so more HCPs (GPs, emergency room doctors, nurses) can better recognise AF symptoms and detect irregular pulse – so cases aren't missed</p> <p>General need for more continuous training of GPs</p> <p>GPs fears about bleeding risk can be addressed through training</p> <p>IT: GPs will soon be able to prescribe NOACs so education key</p> <p>GPs may fear bleed, but patients fear stroke</p> <p>High level of industry involvement may reduce trust among some HCPs and discourage their engagement with AF and use of NOACs</p>	Clinical champions across country to reinforce guidance, evidence	<p>Cardiologists organising GP training with public funds (BE)</p> <p>BE: developing an expertise centre with heart specialists who GP can consult; avoids patient visits to hospital</p> <p>Pharma companies organise training on NOAC use (FR)</p> <p>DE: programme with pharma company where nurses in GP surgeries trained in anticoagulation. Patients get 90-minute group training when prescribed anticoagulants (800 nurses trained last year; very successful)</p>
			Low guideline adherence leading to campaigns for informing physicians about anticoagulation treatment options (e.g. ES, FR – see details under legal factors section)
Education of public/ patients	<p>General agreement on need for more/better patient education, which some interviewees said could also include patients' families</p> <p>Patient education can improve compliance</p> <p>Patient/public education about symptoms and risks can help in earlier detection of AF (not all symptomatic patients go to doctor, but also some are asymptomatic)</p> <p>Some symptoms difficult to identify but self-pulse-checking may be good</p> <p>Some patients get misinformation online</p> <p>Patients need support to take more responsibility for their health, condition – more empowerment</p> <p>Patients need to know treatment options and be encouraged to ask questions</p>	Accurate information for patients online (for some patients) Support systems, groups for patients on anticoagulants	<p>ES: exploring possibility of having insurance providers run education for patients</p> <p>Expert information days/programmes being run in where patients can ask questions to cardiologists and others (IT, ES, UK)</p>

Issue	Current situation and views on a need for change	Changes suggested	Changes expected or currently underway
Patient preference, engagement	<p>Patient engagement varies by country, region and doctor (e.g. low in France, higher in UK, varies in Italy and Spain)</p> <p>Greater patient empowerment can reduce burden on doctors</p> <p>Some say patient preference important due to high cost of non-compliance</p> <p>Some say patients prefer occlusion (to avoid years of drugs), others say oral drugs, NOACs due to simplicity</p>		
Patient compliance	<p>Reasons for non-compliance unclear/disputed; also unclear which groups more compliant (e.g. old vs young)</p> <p>Patient education and trust of physician are key for compliance</p> <p>Monitoring in VKAs leads to better compliance; lack of monitoring is an issue with NOACs</p> <p>However, cardiologists offered option of monitoring NOAC patients have not used it (BE)</p> <p>Unclear whether reduced burden of NOAC vs VKA will improve compliance</p> <p>Compliance is a general problem, not particular to AF or OACs</p> <p>Good compliance is desirable (especially in NOACs due to shorter half-life)</p> <p>Doctors often transmit fear of bleed to patients more than security about stroke prevention</p>	<p>More research to better understand non-compliance</p> <p>Educate HCPs and pharmacists on how to encourage compliance</p> <p>Introduce follow-up checks for NOACs</p> <p>Better education of patients on importance of compliance</p> <p>Electronic check/reminder about compliance or pill-on-chip (both mentioned, neither widely supported)</p> <p>More data on NOAC use under different conditions (i.e. real world data) to make patients more comfortable using NOACs</p>	

Issue	Current situation and views on a need for change	Changes suggested	Changes expected or currently underway
	<p>Patient compliance in taking warfarin has historically been a problem due to concerns about adverse effects on quality of life (Ingelgard et al. 2006)</p> <p>Factors influencing compliance include inconvenience of:</p> <ul style="list-style-type: none"> • Taking regular medication • Frequent monitoring and clinic visits • Dietary and alcohol restrictions (Kneeland & Fang 2010) <p>Patients tend to place a higher disutility on stroke than non-fatal bleeding and treatment burden (MacLean et al. 2012)</p>		<p>The convenience of NOACs compared to VKAs in relation to monitoring may increase uptake and remove a reason for under-use of anticoagulants</p>
Screening	<p>Currently no routine screening in any country</p> <p>Screening enables earlier diagnosis and treatment (consensus)</p> <p>Diagnoses occur by chance or after stroke; should happen earlier</p> <p>Asymptomatic patients – specific challenge in AF</p> <p>Need for more public awareness of AF and symptoms</p> <p>Evidence needed to justify introducing screening and understand who to screen, pulse check vs ECG</p>	<p>Routine screening should target elderly and at-risk groups (not general population)</p> <p>Opportunistic screening supported (when patient sees doctor for another reason)</p>	<p>A few initiatives exist (e.g. UK pulse check week, Belgium sports centres screenings, some screening for those with hereditary risk) (UK, BE)</p> <p>UK: National Screening Committee to review decision not to support AF screen in 2018 (or sooner)</p>
		<p>IT: Pulse checks and routine screening recommended for patients presenting with chest pain, dyspnoea and palpitation (Battigelli et al. 2013)</p> <p>Systematic population screening not recommended (UK)</p> <p>DE: Advocacy for screening for high-risk groups (Kompetenznetz Vorhofflimmern 2014)</p>	<p>BE: Annual mass screening events organised by Belgium Heart Rhythm Association, with BU and Sanofi (Claes et al. 2012)</p> <p>UK: GPs being encouraged to include pulse checks in NHS health checks</p>

Technological factors

Issue	Current situation and views on a need for change	Changes suggested	Changes expected or currently underway
Oral anticoagulants and other drugs	<p>Availability and use of NOACs varies between, and sometimes within, countries</p> <p>Some drugs, such as warfarin, are a heavy burden on patients as they have to have regular blood tests and check-ups. Removing this burden would be beneficial</p> <p>Lack of antidote for NOACs can make doctors reluctant to use them (but some say there is not an ideal antidote for VKAs either)</p> <p>Lack of real-life experience of NOACs can lead to a reluctance to use them</p> <p>Individuals from all countries hope there will be more effective NOAC use</p> <p>There are existing systems and infrastructure set up for VKAs</p> <p>Anti-arrhythmic drugs less popular as they are hard to use (FR)</p>	<p>Possible improvements to NOACs:</p> <ul style="list-style-type: none"> • Lower risks of complications • Usable on patients with renal dysfunction • Usable on patients with valvular AF • More knowledge of optimal dosage • Antidote available • A treatment that facilitates better compliance • Needed only weekly <p>More evidence on cost-effectiveness and safety</p> <p>With multiple NOACs available, it will be important to understand which are most appropriate in different circumstances (better if HCPs have fewer options to think about)</p>	<p>Use of NOACs will increase, possibly causing alternatives to disappear from the market</p> <p>A big market for warfarin still expected in future (ES)</p> <p>New antiarrhythmic drugs possible</p>
	<p>Lack of NOAC antidote may impact patient preference and (to a lesser extent) physician willingness to prescribe (Kornej et al. 2013; Schneider 2014)</p> <p>Lethargy in transitioning from VKAs (more pronounced in DE, ES) (Luger et al. 2014)</p>		<p>A NOAC antidote may be found in coming years (Kornej et al. 2013; Schneider 2014)</p>

Issue	Current situation and views on a need for change	Changes suggested	Changes expected or currently underway
Non-pharmacological interventions (ablation, LAAO)	<p>Ablation is rare, commonly reserved for young patients with serious AF (FR)</p> <p>FR: ablation currently applied to 5% of AF population</p> <p>From a patient point of view, ablation is improving – less aggressive and has positive effects</p> <p>Currently unclear:</p> <ul style="list-style-type: none"> • Which patients ablation is appropriate for • Whether patients need anticoagulants after ablation • Ablation can need repeating and guidelines for this can be vague (UK) <p>Reported efficacy of ablation varied (low to 80%)</p> <p>IT, ES, DE, BE: sufficient skills and centres for ablation reported</p> <p>FR, UK: mixed views about whether there are enough trained doctors, particularly looking to the future</p> <p>LAAO performed only on a small number of patients (UK, DE)</p>	<p>Possible improvements to ablation:</p> <ul style="list-style-type: none"> • Better techniques • Knowledge of who ablation is appropriate for • Infrastructure and training for ablation • Clarity on need for OACs after ablation • Knowledge about risks of thrombosis or recurrence after ablation • Ability to use ablation as cure • Robotic technologies for ablation • Using ablation earlier, not just as a last resort <p>More evidence on the value of ablation</p> <p>Increased use of LAAO for stroke prevention</p>	<p>Ablation not expected to have an impact on use of OACs due to rarity and lack of clarity over needs on anticoagulation after ablation (IT, DE, ES, UK)</p> <p>Robotics under development to facilitate ablation</p> <p>If ablation were improved so it could be used as a cure, it could become more frequent and replace anticoagulants</p> <p>Even with expected improvements, ablation will still be a long and complex process, only useful for 20% of the population (FR)</p> <p>Improved heart imaging to facilitate ablation</p>
			<p>Developments in LAAO and other interventions may increase their use (but this is unlikely to directly impact anticoagulant use) (Han et al. 2012)</p>
Devices and tools	<p>Diagnosing patients, particularly asymptomatic patients, can be difficult</p> <p>Portable medical devices and mobile technologies are becoming more sophisticated and may allow for home diagnosis and home monitoring</p> <p>Portable devices may enable shift to community care</p> <p>Portable devices need data collection, security, and analysis to be well designed</p>	<p>Many portable devices mentioned:</p> <ul style="list-style-type: none"> • iWatch – measures pulse and can detect AF • Mobile devices designed for the elderly • Telediagnosis/ telemedicine • Devices which allow for home blood testing for patients on warfarin (such as CoaguChek) • Devices which can diagnose silent or asymptomatic AF <p>Involving relatives as well as the patient to help with home devices</p> <p>Better use of ECG and ultrasonography to improve diagnosis</p> <p>Mobile devices allowing home or self-controlled therapy</p>	<p>Holter-ECG often used (FR)</p> <p>UK: Tried Alivecore device which can read an ECG and diagnose AF. Thousands of devices were given away to patients, and some people were diagnosed in hospitals and surgeries as a result</p> <p>A company specialising in having a secure web system (for storing all of your medical records, activity and other notes) is working with CoaguChek devices to help improve efficiency of warfarin use (UK)</p> <p>In long term, there may be implantable bio-monitoring chips or chip-in-pill</p>

Issue	Current situation and views on a need for change	Changes suggested	Changes expected or currently underway
			New screening methods emerging: hand-held ECGs, blood pressure machines and finger-probe instruments (Lowres et al. 2013)
Research developments	<p>We do not know why AF occurs, how it develops, or the relationship between AF and strokes. Better understanding could allow for early diagnosis and prevention, and could make anticoagulants unnecessary</p> <p>Genomic sequencing, particularly with aims of personalised medicine, is becoming more available. Unclear how this will impact on AF</p>	<p>Understand why AF develops and how it can be prevented</p> <p>Understand molecular mechanisms of atrial thrombogenesis; more knowledge of AF-stroke relationship</p> <p>Discover biomarkers for AF (widely suggested, but also noted that without methods of prevention biomarkers may not help)</p> <p>Improve ability to identify AF patients with high risk of thrombosis</p> <p>A better knowledge of the pathology of AF and consequences in the population</p> <p>Diagnostics that enable treatment before any changes in heart atrium occur</p> <p>Non-invasive and easy-to-use diagnostic techniques to help prevent AF</p> <p>Improved ability to treat arrhythmia; restore sinus rhythm</p>	<p>Improved knowledge of AF and better treatments could lead to:</p> <ul style="list-style-type: none"> • Cure • Prevention • No need for anticoagulants • Much reduced stroke risk <p>Understanding of biomarker and risk factors could lead to prevention through primary care looking at risk factors</p>
			<p>Possible trend towards personalised therapy. Imaging techniques and genetic risk factors could inform anticoagulants prescription decisions (Shenasa et al. 2012; Helms et al. 2014)</p> <p>Possible shift towards upstream therapies to prevent AF substrate development or reverse AF pathophysiology (Shenasa et al. 2012; Woods & Ogin 2014)</p> <p>Developments in diagnostic techniques such as using prediction with biomarkers may be important in early intervention/prevention and subsequent management of AF (Woods & Ogin 2014)</p>

Legal factors

Issue	Current situation and views on a need for change	Changes suggested	Changes expected or currently underway
Guidelines	<p>All countries have recommendations on drug use; there are variations in how formal they are</p> <p>Guidelines often believed not to represent reality well, as they do not capture the complexity of real-life situations</p> <p>Guidelines are long, numerous – may not be read by GPs who have many other guidelines to read (UK, DE)</p> <p>Aspirin use continues; GPs cautious to try new things, so they stick with warfarin, aspirin (UK), despite guidelines</p>	<p>More formalised guidelines (BE)</p> <p>Single A4 sheets with salient guidelines on them</p> <p>Move to more care by nurses, who may be more inclined to read guidelines</p>	In UK, A4 info sheets for NOACs are being introduced
Guidelines adherence	<p>Studies have found anticoagulation therapy is under prescribed in practice (BE, DE, IT, ES) (Dores et al. 2011; Gorin et al. 2011; Diez-Manglano et al. 2014; Ogilvie et al. 2010, De Bruecker et al. 2010, Denoël et al. 2014, Lotze et al. 2010, Ohlmeier et al. 2013, Monte et al. 2006, Martín Martínez et al. 2013)</p> <p>There is evidence of overtreatment with OACs, e.g. PREFER-AF study findings (Kirchhof et al. 2014)</p> <p>Reasons for deviation from guidelines include:</p> <ul style="list-style-type: none"> • Lack of physician knowledge of guidelines (Fay & Montana 2012) • Contraindications, polypharmacy and fear of falls. Significant physician judgement is often required in making decisions to treat due to interpretation of risk factors and contraindications (Pechlaner 2011) • Patient preference and compliance (particularly in relation to VKAs) (Zarraga & Kron 2013; Lip & Lane 2013; Kneeland & Fang 2010) • Risk factors for stroke and bleeding complicate OAC prescription. Patients may be more stroke averse and less bleed-risk averse than physicians (MacLean et al. 2012) <p>Studies have found NOACs are effective at reducing stroke risk in the elderly (>75) and have found the benefits outweighed the bleeding risks (Sardar et al. 2014; Barco et al. 2013) but this is not a clear picture</p>	<p>More sophisticated frameworks to prescribe anticoagulants may be required (O'Brien et al. 2013)</p>	<p>Spanish Society of Cardiology campaign to raise awareness of benefits of anticoagulation therapy across GP practices</p> <p>FR: training on NOAC treatment organised in >100,000 GP practices since summer 2013.</p> <p>National Health Authority making an effort to put up-to-date info on AF treatments online</p>
Other	<p>Currently unclear who is liable if something goes wrong with a monitoring device. Is it the:</p> <ul style="list-style-type: none"> • Device provider? • Service providers? • GP? • Patient? 	Regulations for monitoring devices	

Environmental factors

Issue	Current situation and views on a need for change	Changes suggested	Changes expected or currently underway
Patient pathway	<p>Patients usually diagnosed when they have a cardiovascular event or by chance by GP (some in awareness events). Need systematic approach to diagnosis</p> <p>Key actors are cardiologists, GPs (sometimes nurses)</p> <p>There is evidence that patients treated by cardiologists usually on better regime than those treated by GPs (DE)</p> <p>Large regional variability in terms of access to specialised care and certain drugs (ES, IT) – ‘health expats’ in Spain seek therapies in other provinces</p> <p>Patients expect full work-up including ECG, which is more accessible in DE than elsewhere (DE)</p> <p>NOAC use widespread (BE) but GPs less open to NOACs than cardiologists</p> <p>GP appointments are 10 minutes – too short for patients’ treatment questions; need for more joined-up care (UK)</p>	<p>Pharmacies could play larger role (e.g. communicating info to GPs and cardiologists (FR), doing screening (UK, IT))</p> <p>GPs could do more diagnosis (but lack cheap, quick tools and time)</p> <p>GP remit is prevention so they should do stroke risk assessment and intervention (but maybe difficult to keep up with knowledge)</p> <p>Home-based INR monitoring could help (if reliable)</p> <p>Approaches enabling more patient autonomy (if safe)</p> <p>GPs should refer more patients to specialists (UK)</p> <p>Clarify if AF is under primary or secondary care (UK)</p>	<p>Belgium developing an expertise centre GPs can consult, reducing hospital visits (BE)</p> <p>Effort ongoing to integrate care and stroke prevention (get specialists and GPs working together) but GPs unwilling (DE)</p> <p>Shift underway from specialists to GPs for anticoagulant monitoring (ES)</p> <p>GP/specialist collaboration facilitated by ICT tools (ES)</p> <p>In Italy, soon GPs will be able to prescribe NOACs</p>

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Patient pathway	<p>Lack of consensus regarding method of screening</p> <p>Elderly patients often diagnosed by chance in other health assessments (Sankaranarayanan et al. 2013)</p> <p>Identification through single time-point screening:</p> <ol style="list-style-type: none"> 1. Opportunistic screening: <ul style="list-style-type: none"> • Peripheral pulse check on 65+ (Dobrea et al. 2013) • Checks in other health checks (Dewar & Lip 2007) 2. Systematic screening: <ul style="list-style-type: none"> • More costly (Lowres et al. 2013) <p>Remote monitoring can lead to earlier detection (Lorenzoni et al. 2014)</p> <p>Monitoring is useful to confirm diagnosis and document frequency of arrhythmia (Dewar & Lip 2007)</p> <p>ES: Risk factors to diagnosis include >75, male, prior chronic heart failure, rural environment (Clua-Espuny et al. 2014), difficulty interpreting ECG, no arrhythmia at time of test (ESC 2014)</p>		<p>New screening methods: hand-held ECGs, blood pressure machines and finger-probe instruments (Lowres et al. 2013)</p>

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Access to care	<p>Access reported as adequate (IT, ES, UK) to good (FR, DE). Regional variability in available treatments in IT, ES, UK</p> <p>Variability in access to NOACs occurs at regional level (ES) and doctor level (UK)</p> <p>Long waiting times for specialists (IT, ES)</p> <p>Care deteriorates in nursing homes; difficult logistics for patients to see physicians, get monitored when not mobile – many not given anticoagulants (DE). INR logistics a challenge (IT)</p> <p>Lower-income groups have lower access to care (FR)</p> <p>Access to care a problem for people who don't know they have AF</p> <p>Access to specialised care lower in remote areas</p> <p>Ablations and LAAO only available in certain centres (DE, UK). UK needs centralised information on what is available where</p>	<p>Apps and telemedicine could help with care delivery</p> <p>Special AF treatment centres could help deliver care, especially in larger cities</p> <p>ES: care needs to be more homogenised</p>	Political efforts underway to homogenise care across Italy
Access to care	<p>AF is often underdiagnosed (Fitzmaurice et al. 2007)</p> <p>AF often asymptomatic, particularly in elderly. One study found up to 40% of elderly hospital patients have asymptomatic AF. (Sankaranarayanan et al. 2013)</p>		
Community Care	<p>Pharmacies can play a role in UK, FR, IT (in DE they only dispense OTC drugs)</p> <p>Need for more points of care, e.g. for INR (IT)</p>	<p>Pharmacies could play large role in AF screening, treatment (UK, IT)</p> <p>Possible pre-primary care model: first online consultation, then see someone, then referral</p> <p>Would be good to have more specialist nurses in community getting involved in diagnosis and management to relieve pressure in NHS (UK)</p> <p>Empower patients and families more</p>	<p>Nurses becoming more involved (DE, UK, ES)</p> <p>General shift towards community care (can be enabled by telehealth, data-sharing; approaches still evolving)</p> <p>UK has arrhythmia service: eight specialised nurses who do outpatient clinics in GP surgeries. Specialist cardiologists only see complicated cases (rest are GPs/nurses); approach slowly building up</p>