A roadmap to improve the quality of atrial fibrillation management

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A roadmap to improve the quality of atrial fibrillation management:

Proceedings from the 5th AFNET/EHRA consensus conference

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Abstract

At least 30 million people worldwide carry a diagnosis of atrial fibrillation (AF), and many more suffer from undiagnosed, subclinical or "silent" AF. AF-related cardiovascular mortality and morbidity, including cardiovascular deaths, heart failure, stroke, and hospitalizations, remain unacceptably high, even when evidence-based therapies such as anticoagulation and rate control are used. Furthermore, it is still necessary to define how best to prevent AF, largely due to a lack of clinical measures that would allow identification of treatable causes of AF in any given patient. Hence, there are important unmet clinical and research needs in the evaluation and management of AF patients.

The ensuing needs and opportunities for improving the quality of AF care were discussed during the 5th Atrial Fibrillation Network (AFNET)/European Heart Rhythm Association (EHRA) consensus conference in Nice on 22nd and 23rd January 2015. Here, we report the outcome of this conference, with a focus on:

1. Learning from our "neighbours" to improve AF care
2. Patient centred approaches to AF management
3. Structured care of AF patients
4. Improving the quality of AF treatment
5. Personalization of AF management

This report ends with a list of priorities for research in AF patients.

Key words

Atrial fibrillation, outcomes, quality of care, research, rate control, antiarrhythmic drugs, catheter ablation, anticoagulation, cardiovascular risk, bleeding, research priorities

Introduction

At least 30 million people worldwide carry a diagnosis of atrial fibrillation (AF) [1], and many more suffer from undiagnosed or "silent" AF. Oral anticoagulation can prevent the majority of AF-related strokes [2], but does only partially mitigate the burden of AF that affects patients, their families, and society [3]: AF-related cardiovascular mortality and morbidity, including cardiovascular deaths, heart failure, stroke, and hospitalizations, remain unacceptably high. [3, 4] The prevalence of diagnosed AF has increased in Europe in recent years [5, 6], due to better awareness of AF, earlier and systematic diagnosis of AF, and an increase in the conditions that predispose to developing AF. [7] In fact, we have to expect that 2% or even 3% of the populations in Europe and in other parts of the world suffer from atrial fibrillation [1, 8], including those with silent AF [1, 8-10]: Clearly, this alarming increase calls for better ways to prevent AF: We are not able to prevent AF, largely due to a lack of clinical measures that would allow identification of treatable causes of AF in any given patient. Hence, there are important unmet needs in the evaluation and management of AF patients.

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1. Learning from our neighbours.

Health care systems, like political systems, develop and "grow" into different shapes in different jurisdictions. Some developments are well suited for patient-centred care and/or may be more efficient compared to others. Controlled trials comparing different ways to deliver AF patient care [11, 12] and regional differences in AF management highlight opportunities to improve outcomes in AF patients. [13, 14] Systematic comparisons of health care systems are a useful tool to inform change in health care systems. [15] In addition, informal exchange of health care organisation can benefit health care professionals and patients. Despite differences in background risk, complications of AF and treatment strategies, the goals of care remain the same: stroke prevention, reduction in cardiovascular complications and amelioration of symptoms. Universally, these issues can be addressed by thoughtful consideration and administration of anticoagulant therapy, rate control and rhythm control therapy, and appropriate management of concomitant cardiovascular conditions.

Each country has a unique variety of regional or local organizations that deliver health care. In some countries, healthcare plans (e.g. Medicare in the US) are in place for some populations but not for others, whilst in other countries almost universal healthcare coverage provides equal access to specialist and generalist care (e.g. Austria, Belgium, Germany, the Netherlands, Scandinavia, the UK, and others). Private purchase of medications and healthcare services is the only means to access health care in some other areas of the world. In some jurisdictions, health care is organized centrally or even directly by state agencies, in others it is managed by regional authorities or offered by units that compete for patients and payment. In addition, the care of AF patients differs markedly, as reflected by simple indicators such as the responsible health care professional (Table 1).

Observational studies suggest that the prevalence of AF may be higher in Caucasians than in persons of African or Asian ethnicity. [16] Similarly, differences in stroke risk in patients with diagnosed AF have been found, e.g. higher stroke rates in China compared to Europe in patients at similar stroke risk based on scoring systems. [17, 18] Such disparity likely reflects differences in the definition of cardiovascular diseases, access to diagnostic procedures, and differences in the management of cardiovascular diseases including antihypertensive treatment, heart failure management, anticoagulation, [13] or rhythm control interventions.[14] Differences in "customary" treatment patterns and different organisation of health care systems can furthermore explain the variation in use of evidence-based AF therapies such as oral anticoagulants, [19] in the quality of INR control or in the use of catheter ablation. Such differences are not compatible with the principle of equal access to evidence-based AF management for all patients and may lead to increased cost in the long-term.

In summary, the care offered to AF patients is different in different countries and regions, at times resulting in variations in quality of care. There is a huge opportunity to improve AF care by exposing these differences and identifying the factors that drive high quality diagnosis and treatment of AF. International organisations such as the European Society of Cardiology (ESC) should contribute to the identification of these differences, and coordinate the discussions that are needed to improve diagnostic and therapeutic pathways by learning from our neighbours.

We recommend a continued professional dialogue about the optimal infrastructure and type of AF care, based on comparable data on type of AF care, outcomes, and resource use in different health care settings to allow improvement of existing AF services.

We recommend a policy of identifying role models of excellent AF care for wider

implementation.

2. Patient centred approaches to atrial fibrillation management

Shared decision making with informed patients. Shared decision making and active involvement of patients in chronic care is a principle that should guide most relations between patients and physicians. It seems very suitable for the management of AF. Recent clinical guidelines have stressed the importance of integrating patient preferences into AF management. [20-23] This reflects a broader move in society to educate and inform patients and communities, thus empowering them to contribute actively to decisions about their care. The 2012 ESC AF guidelines have already emphasized the need for shared decision making in the management of AF. [24]

As stated by Seaburg *et al* [25], "*the goal of shared decision making [in the management of patients with AF] is to increase the likelihood that patients will receive the care that they need in a manner consistent with the best available research evidence and their values and preferences*". It requires a change away from traditional "paternalistic" models of treatment decisions to a model integrating medical facts into an open discussion with the patient who contributes his or her own values and preferences. As a result, patients will be appropriately informed about their disease, its potential progression and complications, and the various treatment options. AF seems ideally suited to shared decision making given the range of alternative diagnostic and treatment options that are available. This is particularly true when there is clinical equipoise relating to a decision affecting the patient in markedly different ways, such as the choice between antiarrhythmic drugs or catheter ablation for initial rhythm control of AF. The main aim is to empower the patients to be appropriately informed about all aspects of their health, wellness and disease state,

ultimately improving the outcome of care. Active participation of patients is needed to make life style changes that will improve outcomes and quality of life in AF patients (Table 2A) and to ensure adherence to therapy. However, it is important to gauge the patient's desire for their degree of involvement in treatment decisions as some patients may prefer the doctor to make treatment recommendations while other prefer shared decision-making**.**

Patient reported outcomes. Patient reported outcomes (PRO) are defined as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else". [26] PROs include assessment of health-related quality of life and symptoms. PROs may be used in a number of applications [27] to provide the patient voice within AF care. In a routine clinical setting, quality of life or symptom questionnaires may be used to provide a standardized estimation of a patient´s well-being to health-care providers. Although most instruments have been validated as paper questionnaires, completed by the patient or with the help of a health care professional, they are suitable for digital, semi-automated or remote assessment of patients. [28] In the future these data may be used at an individual level to identify patients with deteriorating symptoms or aggregated to provide a quality measure, Although the use of PRO instruments in AF patients is in its infancy, these data are likely to evolve further and may develop into a quality measure in the future. [29-31]

Shared decision making in the care of AF patients. Once AF is diagnosed, individual assessment should identify the modifiable risk factors (e.g., arterial hypertension, diabetes mellitus, alcohol consumption, obesity, smoking, sleep apnoea

and concomitant cardiovascular diseases) which are found in approximately 60% of populations with AF. [32] Such precipitating factors may be modified by changes in lifestyle [33, 34], while an inherited predisposition to AF cannot be modified. Since AF is a heterogeneous disease with respect to its aetiology, pathophysiology, mechanisms, clinical presentation, natural history [35, 36] and outcomes, patients are entitled to comprehensive information on the causes, manifestations, and complications of AF. The concept of different types of AF reflecting the main pathophysiological drivers of the arrhythmia seems suitable for this conversation [7] and needs to be supplemented by information on the complex interaction of disease-related factors in the shared decision making process. Patients with AF need adequate and understandable information about the main complications, such as stroke, cognitive impairment, heart failure and sudden death. They should recognize signs of stroke (new-onset neurological deficit) and heart failure (shortness of breath) and the need for immediate medical attention when such symptoms develop or quickly worsen. Information technology can provide such information in a tailored way via interactive electronic educational material (e.g. www.afibmatters.org or http://www.atrial-fibrillation-network.eu/en/home or www.afassociation.org.uk). This will require time and a willingness to explain the information in a language that the patient understands. These resources seems well invested to enable the patient to understand and execute the agreed management plan.

We recommend the involvement of all AF patients in the major decisions about their care, and to enhance the publicly available information on AF, its complications, and the therapeutic options.

3. Structured care of AF patients

Evidence-based management of AF patients. Many aspects of AF management are informed by clear evidence, which is reflected in largely overlapping (but with some worrying differences) international guidelines on treatment of underlying cardiovascular conditions, anticoagulation, rate control, and rhythm control. [20, 21] There are multiple treatment modalities, but also many causes of AF, drivers of AF-related complications, and reasons for impaired patient well-being. The profile and treatment needs of AF patients change over time, and frequently require in-patient hospital care when managed in current approaches. [37, 38] Hence, adequate management of AF patients is complex. It requires a structured approach. [39, 40] Such AF care should ensure that evidence-based therapy is offered to all AF patients, and that follow up and repeated evaluation are sufficient to maintain adherence to agreed management principles. Integrated, multidisciplinary care of AF patients, supported by information technology and patient education, can help to avoid AF-related complications and hospital stays according to recent randomized trials, thereby reducing the burden of AF to patients and decreasing the cost of care. [41] The organization of care will differ locally (see section 1) and local solutions will need to be developed to define a good model of care.

We suggest the development of structured, patient-centred care plans for all AF patients, based on structured initial evaluation and guided by risk profiling and symptom assessment (Table 2). [39] *Interdisciplinary, dedicated AF services which also incorporate lifestyle interventions are likely to facilitate such a structured, risk-based, patient-centred care model.* [41]

We recommend the development of integrated and structured approaches to AF care led by interdisciplinary teams to improve the quality of AF care.

3. Improving the quality of AF treatment

Patients are entitled to high quality care that is safe, effective, and accessible. While the medical literature has traditionally focussed on the best way of caring for patients, it is important to define minimal standards of good care for AF patients. Such standards would ideally be developed and endorsed with wide input from global stakeholders.

We recommend that quality standards are defined and monitored in AF care. EHRA, AFNET and similar organisations in other parts of the world should play a central role in the further definition and dissemination of such criteria, and in linking these to outcomes. The following sections (4.1 - 4.4) outline quality criteria, which are summarized in Table 3.1-3.3.

4.1 Timely diagnosis of atrial fibrillation

Many people, especially those who are older and have concomitant cardiovascular conditions, suffer from undiagnosed, "silent" AF. The prognosis of untreated asymptomatic atrial fibrillation is characterized by a high risk of stroke and death which can be reduced by appropriate oral anticoagulation. [42] Screening for unknown AF and initiation of anticoagulation has the potential to prevent strokes in patients with undiagnosed AF, but has so far mainly been evaluated in physician offices, where pulse palpation followed by 12-lead ECG recording seem cost effective for AF screening.[43, 44] A recent systematic review [45] demonstrated that unknown AF would be detected in 1.4% of the population aged ≥65 on a single screening whether in a clinical or community setting. Pulse palpation is universally available to an educated population. Novel technologies which allow easy cardiac rhythm assessment by lay persons and patients, either by pulse irregularity (oscillometry [46] or smart phone

camera [47]) or by analysis of an ECG rhythm strip [48-51], are now readily available and offer better, less costly methods for more effective and more broadly-based AF screening. A number of studies have explored population or clinic screening using hand-held single-lead ECG devices. [48-50] An economic analysis showed that if an AF screen with these devices at a single time point was extended to the population aged 65-84 years, it would be cost-effective for stroke prevention. [49] Community pilot screening studies suggest that the criteria for widespread screening over age 65 are now met, [52] but the precise implementation method would need to fit with the country-specific health care system.

Silent AF first presenting with ischaemic stroke accounts for at least 10% of all ischaemic strokes. [53-56], and widespread screening could substantially reduce this figure. A systematic review found that an additional 11.5% of survivors will have paroxysmal AF which remains undetected by current ECG monitoring practices, but may be detected by prolonged non-invasive or invasive ECG monitoring, although the available studies are heterogeneous. [57] More recently, two randomised trials of either 30 day external monitors [10] or 1- 3 years of implantable cardiac monitors [58] demonstrated an even higher detection rate of AF, albeit in a subgroup of stroke survivors with "cryptogenic" stroke. Some form of prolonged monitoring after ischaemic stroke should now become the standard of care [59], and offered by a high quality AF service. Ongoing randomized multicentre studies such as MonDAFIS (NCT02204267) will determine whether the detection of "silent" AF after acute ischemic stroke will change long term management in stroke survivors.

We recommend the establishment of more widespread screening programmes for persistent and paroxysmal AF in those over age 65, and in populations at risk, particularly survivors of ischaemic stroke.

4.2 Defining and improving the quality of stroke prevention

The majority of ischaemic strokes in AF patients are caused by AF, and a substantial proportion of those "cardio-embolic" strokes can be prevented by oral anticoagulation. Aspirin is not effective in preventing strokes in AF. Nonetheless, underuse or premature termination of therapy with oral anticoagulants is still common. [60-65] Although non-vitamin K antagonist oral anticoagulants (NOAC) are easy to handle and offer the promise of improved efficacy and safety compared to vitamin K antagonist (VKA) treatment [2, 66], there is still a substantial underuse of oral anticoagulation in AF patients in the "NOAC era". [67, 68] While anticoagulation therapy needs to be paused when patients actively bleed, absolute contraindications to long-term anticoagulant treatment in AF patients are rare, e.g. severe bleeding *without treatable underlying cause in critical organs*. The bleeding risk of anticoagulant use in elderly patients, in patients with cognitive dysfunction, or in those with frequent falls or frailty is often overestimated and should usually not preclude the use of anticoagulants. [69, 70]

Oral anticoagulants need to be taken consistently. The best evidence for this stems from analyses of the time of patients treated with VKA within and below the therapeutic range [71], but it seems reasonable to suggest that regular intake of relatively short half-life NOACs is even more important for successful stroke prevention. [65, 72] Although adherence to therapy is currently not measured systematically in clinical practice, the outcomes of recent observational data-sets replicate the findings in phase III trials of NOACs . [66, 73] Dedicated interventions to enhance adherence to therapy are currently being evaluated e.g. AEGEAN (NCT01184350). [74, 75] Permanent withdrawal of anticoagulation therapy is associated with cardiovascular complications. Re-initiation of anticoagulation after a bleeding event is often possible and clinically justified. Difficult decisions, including the discontinuation of anticoagulation, should

be taken by multidisciplinary teams involving AF, anticoagulation, stroke specialists as well as the patients to adequately balance the risks and benefits of continued anticoagulation.

Limited reimbursement of NOACs is an important driver of inequality in care of patients with AF. [68] This group advocates access to NOACs for all AF patients in need for oral anticoagulation as an initial therapy option. [66, 73, 76, 77] When this is not deemed feasible, clinical estimates for the likelihood to achieve good anticoagulation with VKA could be considered to identify patients who can be treated with VKA. [73, 78]

We recommend the following steps to improve stroke prevention in AF patients

1. *All AF patients in need of oral anticoagulation should have access to NOAC therapy, or to VKA therapy, if NOACs therapy is not feasible.*
2. *We recommend a structured follow-up for all anticoagulated AF patients to remind the patient of the need for AF treatment and to increase adherence and persistence to therapy.* [40, 79]
3. *AF patients who suffer a stroke should be acutely managed in specialized stroke units.* [80]

4.3 What is effective rate control?

The goal of rate control therapy of AF is to reduce patient symptoms and prevent a tachycardia-related reduction in myocardial function. While these treatment goals can be achieved with a lenient rate control approach in some patients [81], others may require stricter rate control, such as those with heart failure or persistent symptoms. [21, 22] The effectiveness of rate control therapy should be assessed at regular intervals in AF patients as part of integrated AF management. Adjustments to rate control

medication seem necessary in many patients [60, 82], and all AF patients need systematic follow-up to allow such adjustments over time. Such assessment will require analysis of a conventional 12-lead ECG, Holter consideration of patient symptoms and preferences, and repeated assessment of left ventricular function (especially when symptoms worsen). The optimal therapy for achieving rate control requires further research. [83, 84] Until the results of such research are available, it will be difficult to define quality indicators for effective rate control therapy in addition to the simple statement that resting heart rate should be < 110 bpm. In patients who remain symptomatic on such a lenient rate control therapy, it may be worthwhile to control rate during exercise, and/or to aim for a lower resting heart rate.

4.4 Improving quality of rhythm control therapy

Defining quality in AF ablation. The evidence underpinning the use of catheter ablation to maintain sinus rhythm in symptomatic AF patients has mainly been generated in recognized regional, national, or international centres of electrophysiological excellence. As AF ablation is being offered to more patients, and hence AF ablation services are established in more and more centres, recruiting and training of electrophysiologists and maintaining a high quality of AF ablation procedures develops into a key issue. It is recognized that there is a need to define and measure quality, both in terms of AF ablation operators and institutions offering AF ablation. Catheter ablation of AF, especially isolation of the pulmonary veins, is now a standardized procedure that has become part of routine clinical care. [24, 85, 86]. Thus, a set of variables to define both a qualified operator and a quality AF ablation centre is proposed (Table 3.3). Using these criteria, systematic assessment of the AF ablation operators and of AF ablation centres can be undertaken to ensure their quality, and to

study the validity and the clinical usefulness of these criteria. This process should be led by professional organisations such as EHRA or Heart Rhythm Society (HRS).

Hybrid rhythm control therapy. It is well recognized that catheter ablation will not completely eliminate AF in many patients. [87, 88] It is in this context that we discuss the concept of "hybrid therapy" for AF (ablation plus antiarrhythmic drugs). Hybrid therapy, defined as the use of antiarrhythmic drug therapy more than 3 months following an ablation to reduce symptoms and/or episodes of AF, is a common therapeutic concept in AF patients. [89, 90] While it is common practice to stop antiarrhythmic drugs a few weeks or months after restoration of sinus rhythm by catheter ablation [91] or cardioversion [92], the result is an excess in AF recurrences compared to continued antiarrhythmic drug therapy [91, 92] Hence, some patients may be advised and/or may prefer to continue antiarrhythmic drug therapy after ablation of AF, especially when the therapy is well tolerated, integrating patient preferences, the perceived risk of recurrence, and the risk of therapy. [93]

Repeat ablation or antiarrhythmic drug therapy after AF ablation? Many patients who undergo an initial AF ablation will continue to experience symptomatic AF once antiarrhythmic drugs have been discontinued. [85, 89] Decisions to perform a repeat ablation should only be done once recurrence of AF has been documented and follow the same process used to decide on the initial AF ablation. This process involves shared decision making based on a consideration of safety and efficacy of repeat ablation, discussion of all treatment options including antiarrhythmic drug therapy and acceptance of AF ("rate control only"), and should integrate patient preferences. Hereby, the patient has a better appreciation of what the procedure

involves, and the electrophysiologist has more knowledge about the procedural details, including risk and the potential extent of re-ablation. Atrial tachycardias may be better amenable to re-ablation than AF. Some patients will prefer a trial of antiarrhythmic drugs rather than repeat ablation.

We recommend systematic collection of information on centre and operator quality, based on simple quality indicators and procedural complications (Table 3.3), from all AF ablation centres.

We recommend further research into the best rhythm control therapy in patients with recurrent AF after AF ablation.

5. Beyond the present state of the art: Personalized AF management

A broad range of different cellular and molecular mechanisms underlie AF and are modified by environmental factors. [94-96] Thus, the manifestation, progression and outcome of disease will vary between these subtypes of AF, consistent with clinical observations.[7] Furthermore, the clinical differentiation between "paroxysmal" and "persistent" AF may be poor, suggesting that this differentiation is not reflecting different biology. [97] Clinical conditions that are associated with AF and AF-related complications may vary substantially by AF aetiology, but will overlap. To investigate the development of mechanism-oriented therapy of AF, prior consensus conferences suggested a pathophysiological classification of AF types. [7] The precise identification of AF mechanisms would ideally involve assessment of atrial tissue. As this is inherently difficult to obtain, blood (or possibly imaging) markers that correlate with atrial pathophysiology, could indicate whether major molecular mechanisms of AF are present in a given patient. Cardiac imaging modalities such as echocardiography, CT, or magnetic resonance imaging give a relatively detailed view of atrial size and to some

extent of atrial structure. They usually require specialised equipment and expertise for interpretation, and have been discussed in a recent review [7]. The existing biomarkers for AF were therefore reviewed with a view to utilising them for the classification of AF patients into different types.

Unfortunately, many biomarkers that have been evaluated in AF patients identify abnormal cardiac or inflammatory states, rather than reflecting atrial pathology.

Natriuretic peptides, in particular B-type natriuretic peptide (BNP), cannot differentiate between underlying or concomitant cardiovascular conditions and comorbidities. Elevated BNP is associated with incident AF, and BNP is correlated with disease burden, e.g. frequency and duration of AF episodes and overall cardiac abnormality.[98] Its predictive ability for new onset AF in community cohorts is strong, but improvement in C-statistic and reclassification remain modest. [99, 100] N-terminal pro-BNP is also strongly and independently associated with stroke and mortality in patients with AF. [101]

C-reactive protein may be considered for general cardiovascular risk assessment when treatment decisions based on conventional risk scoring are uncertain. [102] Although modification of C-reactive protein concentrations, e.g. by statin treatment may alter AF risk [103] , Mendelian randomization, i.e. a correlation of genetic determinants of CRP levels and their association with AF, suggests that it is unlikely that C-reactive protein *per se* causes AF. [104] Consequently, the power of CRP to identify patients with AF is low. [99, 100]

Similarly, markers of impaired kidney and bone marrow function such as *glomerular filtration rate, cystatin C, or low hemoglobin* have been associated with many aspects of AF pathophysiology. [105] They represent aging, general health status and comorbid conditions that affect AF incidence and prognosis rather than intrinsic AF

mechanisms. While the combination of these markers of disease can slightly improve the prediction of incident AF [99, 100] , or complications of therapy (e.g. bleeding on anticoagulants), the value of such general biomarkers for personalized management of AF needs to be established. It seems unlikely that these markers can discriminate different subtypes of AF in the near future.

Common genetic variants. Genetic variation is fairly stable over a life course, independent of environmental changes and may help to define AF subtypes. In rare monogenic AF, a single mutation determines the disease phenotype (e.g. long QT syndrome or an inherited cardiomyopathy, but also in familial AF [106, 107]). Common genetic polymorphisms correlate with the risk of AF development and risk of stroke, and predispose to recurrences of AF on antiarrhythmic drugs [108] or ablation success. [109] About a third of all AF patients carry common gene variants that predispose to AF. [110, 111] In general, every single nucleotide polymorphism (SNP) only carries a small relative risk, but they can be combined to generate more precise information. [111, 112] Genetically determined subtypes of AF in the community have not yet been formulated. Future in-depth analysis of genetic information collected in large consortia will provide additional information on the genetic underpinnings of AF, including very many SNPs. Furthermore, the molecular mechanisms conveying AF risk in carriers of the AF-related genetic variants may unveil novel “atrial specific” disease pathways and biomarkers, including altered epigenetic or microRNA related pathways. [113-118] The practical consequences of these findings need to be determined and tested in controlled trials.

The search for atrial-specific biomarkers. The increasingly broad availability of

novel “big data” technologies will provide access to blood and tissue for largely unbiased “omics” interrogation. Omics data including genome transcriptome, proteome and metabolome information will reveal intermediate phenotypes and disease patterns in AF. These analyses have the potential to identify promising new AF biomarkers. The information derived from different clinical and molecular sources then needs to be combined to identify new biomarkers or marker signatures of clinical relevance.[119]

Novel biomarkers will need to be able to identify a group of AF patients (or populations at risk for AF) who respond well to a given therapy and/or who show a distinct course of disease, e.g. in terms of AF progression or for complications of AF. Subsequently, proof of concept and prospective controlled testing need to demonstrate feasibility and cost effectiveness.

The overall success of future biomarker studies will rely crucially on two interrelated issues: the establishment of distinct AF phenotypes and rigorous validation of biomarkers e.g, as recently suggested by the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) investigators. [120] Current biomarker studies are limited by the crude AF phenotype definition that impairs specific associations. On the other hand, biomarkers and biomarker signatures may largely enhance the differentiation of AF subtypes and their optimal management. Existing and emerging biomarkers and AF subtypes will then need rigorous validation and prospective testing.

ECG parameters. The ECG is a widely available diagnostic test in many health care settings. Furthermore, emerging technology will give patients and citizens unsupervised access to ECG recordings. Several ECG parameters can be used to detect

patients at risk for AF. The PR interval has a clear genetic trait [121, 122] and a prolonged PR interval is associated with an increased the risk of prevalent AF in populations. [123-125] Direct electrocardiographic contact mapping studies in patients undergoing open-chest surgery have indeed demonstrated that a progressive structural remodeling process is reflected in more complex atrial activation patterns [126, 127] which may promote recurrent AF [128-130]. The complexity of the AF activation pattern may be indirectly measured by time domain (F-wave analysis, principal component analysis, sample entropy) and frequency domain (dominant frequency, organization index of power spectrum, spectral entropy) parameters. [131] Such quantifiable parameters of "AF complexity" have been evaluated as markers for recurrent AF in patients receiving rhythm control therapy (cardioversion, antiarrhythmic drug therapy, or catheter ablation). [132, 133] Sufficiently powered studies using standardized technology are needed to determine the clinical value of ECG analyses during AF to differentiate different types of AF. [132]

We recommend performing properly powered genomic, genetic and biochemical analyses in controlled trials.

We recommend using existing large biosample collections to identify atrial-specific biomarkers.

We recommend research into clinical parameters that can differentiate different "aetiologic types" of AF.

6. Research priorities in the next five years

Based on the challenges in understanding and eliminating the inequalities and barriers that prevent optimal care of AF described above, we have outlined the priority research needs:

1. Prospective studies evaluating the prognostic value of modern rhythm control therapy are fortunately underway and should be completed as soon as possible.
2. Prospective studies are needed to determine the most effective strategy for AF detection in populations and in patients at risk for AF and stroke, including the methods of detection, implementation and cost effectiveness.
3. Evaluation of integrated and structured care approaches compared to current care models has immense potential to improve quality of AF patient care and is essential to make these useful in clinical practice.
4. Definition of the optimal patient reported outcomes to capture AF-related symptoms and patients' experiences of AF, and the development and adoption of methods to ensure optimal PRO assessment and reporting from AF trials.
5. Evaluation of new parameters (e.g. blood biomarkers, ECG parameters, etc.) to refine anticoagulation decisions in patients with an intermediate or low risk for stroke.
6. Strategies to minimize interruption or discontinuation of anticoagulant therapy should be systematically evaluated, including different in-person or remote follow-up patterns and interventions geared at empowering patients.
7. Interdisciplinary therapeutic strategies for "therapy failures" on oral anticoagulation, e.g. patients with an ischaemic stroke on adequate anticoagulation or those with severe bleeds, should be developed and evaluated.
8. Controlled trials of anticoagulation strategies in AF patients with advanced kidney disease (MDRD stages IV-V) are urgently needed.

9. We recommend high quality research projects on the research on timing of recommencing oral anticoagulants after bleeding. [134]

10. The best use of left atrial appendage occlusion devices in clinical practice is not well established.[135] Evaluation of this technology in patient groups with the potentially highest benefit and optimization of post-interventional antithrombotic treatment is needed.

11. Controlled studies on heart rate control comparing beta adrenoceptor-blockers, digoxin, and non-dihydropyridine calcium channel blockers as well as heart rate targets and their effects on quality of life, cardiac function, and cardiovascular outcomes are urgently needed.

12. Prospective studies evaluating the success of hybrid rhythm control therapy combining antiarrhythmic drugs and ablation compared to catheter ablation alone seem warranted. Follow-up after catheter ablation for AF should be standardized to enable comparison of research results. Evaluation of novel markers for different "types" of AF should be integrated into such projects.

13. Databases of existing trials and cohort studies should be used to propose clinical subtypes of AF, e.g. based on imaging, ECG or on blood biomarkers (including genetic markers).

14. Genetic risk variants or genetic risk scores for AF should be examined to see if they can help to identify AF or stroke risk prediction, the subtypes of AF, response to therapies, or clinical outcomes.

15. Since clinical trials of AF represent unique research opportunities, we encourage the systematic collection of AF covariate data and samples to enable future studies on biomarkers and "types of AF".

16. Patients should be actively involved in clinical AF research projects. Patients

can for example advise on patient information sheets, lay summaries and consent forms and help to optimize recruitment strategies, but also contribute to practical design aspects. [136] To ensure effective patient involvement, all parties should be clear of the role of patient involvement. More information can be found (http://www.nets.nihr.ac.uk/ppi; and http://www.invo.org.uk/).

17. Mechanistic research should be conducted to link genetic variants to AF mechanisms, and to reveal novel therapeutic targets.

18. Long-term research funding is critically necessary to address each of these challenges and to ensure the optimal treatment of AF.

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Table 1: Examples of existing care models for the care of AF patients

Care model	Advantages	Disadvantages
General practitioner	Easy access for patients; possibility to perform initial tests (history, ECG, blood sample)	Limited initial evaluation; limited management options; lower adherence to guidelines[137]
Cardiologist/ AF subspecialist	Experience; comprehensive evaluation; full range of treatment options	Resource demanding; initially expensive
Integrated care of general practitioner and internal medicine specialist	More complete assessment and management of co-morbidities	Limited cardiology-specific evaluation and management options
Integrated care of general practitioner and cardiologist	More tailored management approach using full range of treatment options; distribution of care across healthcare system	Limited cardiology-specific follow-up
Cardiologist led integrated care including nurses, allied professionals/lifestyle specialists	Full assessment and range of treatments; tailored follow-up; structured care	Costs (but possibly cost-effective)
Nurse led integrated care	Patient-centred care approach; efficient and possibly cost-effective[138]	Education, training and monitoring of staff

Table 2A: Life style changes that can improve AF management by either improving outcomes, reducing the risk of complications, rendering recurrent AF less likely, or improving quality of life.

Life style change	**Effect on**	
	Outcomes and complications	**recurrent AF and quality of life**
Regular physical activity	X	not known
Weight reduction	not known	X
Low sodium, low fat diet	X (by reducing blood pressure)	not known
Smoking cessation	X	not known

Table 2B. Structured initial care of AF patients

A. Components of initial care:
ECG – confirmation of AF[139]
Detailed medical history
mEHRA symptom assessment [140]
CHA_2DS_2-VASc stroke risk assessment [141]
Assessment and correction of modifiable bleeding risk factors (e.g. by HASBLED score) [142]
Physical examination including blood pressure and body mass index
Risk factors and comorbidities assessment including heart failure, chronic airways disease, dementia, sleep apnoea, renal disease, diabetes, thyroid disease and coronary artery disease – requires cardiac imaging (usually echocardiogram) and blood sampling [86]
B. Tailored additional evaluation according to the patient:
Additional diagnostic tests
Correction of risk factors
C. Initial management plan
According to ESC guidelines Defined by an AF team representing all relevant expertise Advice on life style changes affecting outcomes and AF
D. Follow-up
Regular, scheduled follow-ups according to the model of care (see Table 1) Assessment of symptoms and patient-reported outcomes (see Section 2, Table 4) Heart rate targets (see Section 4) Adherence and response to treatment Complications of treatment and complications of AF Assessment of quality metric targets (see Tables 3 and 4) Informed decision on adjustment of therapy

Table 3: Quality criteria for management components of atrial fibrillation

Table 3.1: Quality criteria for anticoagulant therapy

Individual risk assessment
▪ Assess stroke risk with CHA_2DS_2-VASc score ▪ Assess bleeding risk and minimize bleeding risk factors - Control blood pressure - Discontinue treatment with non-essential antiplatelet(s)/NSAIDs - Counsel patient to reduce alcohol consumption if excessive ▪ Check renal function and estimate creatinine clearance prior to deciding on anticoagulation therapy
Guideline adherent OAC prescription
▪ CHA_2DS_2-VASc score ≥2, OAC recommended ▪ Documented decision in patients with CHA_2DS_2-VASc score = 1 ▪ If patient is on VKA, achieve high time in therapeutic range (TTR, e.g. > 65%)
Decision-making
Individualized approach to decision making ▪ Gauge and follow patient's desire for involvement in making OAC treatment decision (e.g. following input from patient, doctor, or relative)
Support of anticoagulation therapy
▪ OAC-specific information (verbally, pictorially, written)[40, 146] ▪ Check patient understanding of key elements: dose, frequency, with/without food, bleeding side effects; result of non-adherence (stroke) ▪ check and reinforce knowledge on TIA/stroke alarm symptoms e.g. by "FAST" (face, arm, speech, time) and explain need for emergency transfer to stroke unit when such symptoms occur ▪ Provide written information to reinforce verbal information ▪ All information tailored to the patient's ability to understand and desire for information
Providers of care (see table 2, one option should be available)
▪ Physician, nurse, pharmacist, other healthcare professional, 'expert' patient, combination ▪ Nurse led supported by consultant expertise[40] ▪ Supported with software to aid clinical decisions (algorithms)[144] ▪ Intervention for VKA initiation[145]

Table 3.2 Quality criteria for antiarrhythmic drug therapy in AF patients.

Individual assessment
▪ Quantify AF related symptoms (mEHRA score) [147] ▪ Assess the need for rhythm control on the background of adequate rate control ▪ Assess concomitant cardiovascular diseases and prior attempts of rhythm control to inform choice of AAD ▪ Assess 12-lead ECG for signs of conduction or repolarization disturbances ▪ Document baseline QT interval, QTc, QRS duration, and QRS abnormalities ▪ Check baseline blood levels as needed (thyroid and liver function for amiodarone, liver function and creatinine for dronedarone, creatinine and estimated creatinine clearance for sotalol, flecainide, and propafenone)
Guideline adherent prescription and therapy initiation
▪ Choose antiarrhythmic drug according to ESC guidelines ▪ Prescribe effective dose ▪ Monitor ECG during therapy initiation (days 1-3 for flecainide, propafenone, and sotalol, week 1 and 2 for dronedarone, week 1 and 4 for amiodarone) ▪ Monitor blood levels as needed
Dedicated patient education[143]
Provide information on: ▪ The main aims of rhythm control therapy (reducing symptoms) ▪ The possible need for further procedures (cardioversion, catheter ablation) ▪ Possible side effects including proarrhythmia ▪ All information tailored to the patient's ability to understand and desire for information
Once antiarrhythmic drug treatment decision is made
▪ Provide clear information on duration of therapy (pill in the pocket, short-term, long-term) and drug interactions (e.g. anticoagulants) ▪ Check patient understanding of key elements: dose, frequency, with/without food, result of non-adherence (recurrence of AF) ▪ Provide written information to reinforce verbal information

Table 3.3 Quality indicators for AF ablation.[85]

A. Quality indicators for care in AF ablation centres
Structured and documented assessment of indications for AF ablation - Symptoms (mEHRA score) Prior rhythm control attempts - Other therapeutic options (antiarrhythmic drugs, no further rhythm control therapy, combination therapy) - Likelihood of recurrent AF
Required infrastructure for AF ablation centres in addition to the general quality criteria (See Tables 3.1 and 3.2) - Dedicated, adequately equipped electrophysiology laboratory - Minimum number of AF ablation procedures per year (over 50) - Availability of backup open heart surgery capable of managing complications of AF ablation, especially pericardial tamponade - Availability of backup anaesthetic support. - Data base to track complications over time - Regular structured complication conference - Standardized patient follow-up program
B. Quality indicators for AF ablation operators
Adequately trained and qualified electrophysiologists
Operators should perform a minimum of 25 AF ablation procedures per year.
Rate of major complications: defined as complications that prolong hospital stay or require intervention. The rate of cardiac tamponade is an important subset of the complication rate that should be separately monitored.
Although efficacy is also important, this parameter is difficult to define as it depends on the type and complexity of the patient's AF, the extent of post-ablation monitoring, the definition of success, and the duration of follow-up. We encourage operators to track the recurrence rate of AF, rate of re-ablation, and to assess quality of life before and after ablation using dedicated PRO instruments.

Table 4 (on line): Relevant biomarkers that have been evaluated to identify AF patients at risk for complications. Most markers identify general cardiovascular risk and cardiovascular diseases, with the exception of genetic variants that are relatively specific for AF. Biomarkers that are specific for AF or for AF-related complications seem most promising for further evaluation.

Biomarker	Occurrence/Recurrence	Complications		
		Death	Stroke	Bleeding
Cardiovascular stress and cell damage				
Elevated hs-Troponin	↑ [148] ↑ (postoperative) [149, 150]	↑ [151-153]	↑ [151-153]	↑ [152, 153]
Elevated BNP	↑ [99, 100, 154-159] ↑ (postoperative) [160, 161]	↑ [151, 162]	↑ [151, 163-166]	X [151]
Inflammation and oxidative stress				
Elevated CRP	↑ [99, 100, 104, 157, 167-171] ↑ (recurrence after ablation) [171-175] ↑ (recurrence after cardioversion) [176] X (recurrence after cardioversion) [177]	↑ [178]	↑ [179] ↑ (echo markers of thrombus) [180]	
Elevated GDF-15	X [148]	↑ [181]	↑ [181]	↑ [181]
Kidney function				
High creatinine / low eGFR	↑ (recurrence after ablation) [182]	↑ [183]	↑ [183-187]	↑ [183, 184, 186]
Cystatin C	↑ [105, 188, 189] X [190]	↑ [183]	↑ [183]	↑ [183]
Coagulation state				
D-dimer	X [99]	↑ [191-193]	↑ [191, 192, 194-196] ↑ (LAA thrombus) [197]	↑ [192]
Anaemia	↑ [189] ↑ (postoperative) [198]	↑ [199]		↑ [187, 200-203]
Common genetic variation				
Chromosome 4q25 locus, SCN10A, SCN5A, KCNE1	↑ [110, 111, 119, 204-210]		↑ [111, 211-214] X (postoperative) [210] X (Han Chinese) [215]	
ECG parameters				
PR interval	↑			
P-wave and F-wave information	↑ stroke ↑ recurrence after ablation			

↑ = positive association, X = no association ; hs = high-sensitivity.

Figure legends

Figure 1: Roadmap to improve quality of AF services. Shown is a virtuous circle relying on four major pillars to improve the quality of AF services for patients. Shared decision making, quantifiable quality measures, integration of AF services across health care sectors, and the use of stratified approaches to therapy can improve AF service quality. They will require continuous evaluation of quality.

Figure 2: Biomarkers may help to define AF subtypes. They can comprise blood and tissue based markers as well as electrocardiographic or further objectively determined characteristics (e.g. atrial imaging). Both, biomarkers and existing and novel AF phenotypes need rigorous validation.

References

1. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, Gillum RF, Kim YH, McAnulty JH, Jr., Zheng ZJ, Forouzanfar MH, Naghavi M, Mensah GA, Ezzati M, Murray CJ. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation*. 2014;**129**:837-847

2. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, Yamashita T, Antman EM. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet*. 2014;**383**:955-962

3. Marijon E, Le Heuzey JY, Connolly S, Yang S, Pogue J, Brueckmann M, Eikelboom JW, Themeles E, Ezekowitz MD, Wallentin L, Yusuf S. Causes of Death and Influencing Factors in Patients with Atrial Fibrillation: A Competing Risk Analysis from the Randomized Evaluation of Long-Term Anticoagulant Therapy Study. *Circulation*. 2013;**128**:2192-2201

4. Kirchhof P, Breithardt G, Camm AJ, Crijns HJ, Kuck KH, Vardas P, Wegscheider K. Improving outcomes in patients with atrial fibrillation: rationale and design of the Early treatment of Atrial fibrillation for Stroke prevention Trial. *Am Heart J*. 2013;**166**:442-448

5. Wilke T, Groth A, Mueller S, Pfannkuche M, Verheyen F, Linder R, Maywald U, Bauersachs R, Breithardt G. Incidence and prevalence of atrial fibrillation: an analysis based on 8.3 million patients. *Europace*. 2013;**15**:486-493

6. Lip GY, Brechin CM, Lane DA. The global burden of atrial fibrillation and stroke: a systematic review of the epidemiology of atrial fibrillation in regions outside North America and Europe. *Chest*. 2012;**142**:1489-1498

7. Kirchhof P, Breithardt G, Aliot E, Al Khatib S, Apostolakis S, Auricchio A, Bailleul C, Bax J, Benninger G, Blomstrom-Lundqvist C, Boersma L, Boriani G, Brandes A, Brown H, Brueckmann M, Calkins H, Casadei B, Clemens A, Crijns H, Derwand R, Dobrev D, Ezekowitz M, Fetsch T, Gerth A, Gillis A, Gulizia M, Hack G, Haegeli L, Hatem S, Georg Hausler K, Heidbuchel H, Hernandez-Brichis J, Jais P, Kappenberger L, Kautzner J, Kim S, Kuck KH, Lane D, Leute A, Lewalter T, Meyer R, Mont L, Moses G, Mueller M, Munzel F, Nabauer M, Nielsen JC, Oeff M, Oto A, Pieske B, Pisters R, Potpara T, Rasmussen L, Ravens U, Reiffel J, Richard-Lordereau I, Schafer H, Schotten U, Stegink W, Stein K, Steinbeck G, Szumowski L, Tavazzi L, Themistoclakis S, Thomitzek K, Van Gelder IC, von Stritzky B, Vincent A, Werring D, Willems S, Lip GY, Camm AJ. Personalized management of atrial fibrillation: Proceedings from the fourth Atrial Fibrillation competence NETwork/European Heart Rhythm Association consensus conference. *Europace*. 2013;**15**:1540-1556

8. Svennberg E, Engdahl J, Al-Khalili F, Friberg L, Frykman V, Rosenqvist M. Mass Screening for

Untreated Atrial Fibrillation: The STROKESTOP Study. *Circulation*. 2015;10.1161/CIRCULATIONAHA.114.014343

9. Grond M, Jauss M, Hamann G, Stark E, Veltkamp R, Nabavi D, Horn M, Weimar C, Kohrmann M, Wachter R, Rosin L, Kirchhof P. Improved detection of silent atrial fibrillation using 72-hour Holter ECG in patients with ischemic stroke: a prospective multicenter cohort study. *Stroke*. 2013;**44**:3357-3364

10. Gladstone DJ, Spring M, Dorian P, Panzov V, Thorpe KE, Hall J, Vaid H, O'Donnell M, Laupacis A, Cote R, Sharma M, Blakely JA, Shuaib A, Hachinski V, Coutts SB, Sahlas DJ, Teal P, Yip S, Spence JD, Buck B, Verreault S, Casaubon LK, Penn A, Selchen D, Jin A, Howse D, Mehdiratta M, Boyle K, Aviv R, Kapral MK, Mamdani M, Investigators E, Coordinators. Atrial fibrillation in patients with cryptogenic stroke. *N Engl J Med*. 2014;**370**:2467-2477

11. Hendriks JM, de Wit R, Crijns HJ, Vrijhoef HJ, Prins MH, Pisters R, Pison LA, Blaauw Y, Tieleman RG. Nurse-led care vs. usual care for patients with atrial fibrillation: results of a randomized trial of integrated chronic care vs. routine clinical care in ambulatory patients with atrial fibrillation. *Eur Heart J*. 2012;ehs071 [pii]
10.1093/eurheartj/ehs071

12. Stewart S, Ball J, Horowitz JD, Marwick TH, Mahadevan G, Wong C, Abhayaratna WP, Chan YK, Esterman A, Thompson DR, Scuffham PA, Carrington MJ. Standard versus atrial fibrillation-specific management strategy (SAFETY) to reduce recurrent admission and prolong survival: pragmatic, multicentre, randomised controlled trial. *Lancet*. 2015;**385**:775-784

13. Oldgren J, Healey JS, Ezekowitz M, Commerford P, Avezum A, Pais P, Zhu J, Jansky P, Sigamani A, Morillo CA, Liu L, Damasceno A, Grinvalds A, Nakamya J, Reilly PA, Keltai K, Van Gelder IC, Yusufali AH, Watanabe E, Wallentin L, Connolly SJ, Yusuf S, Investigators R-LAFR. Variations in cause and management of atrial fibrillation in a prospective registry of 15,400 emergency department patients in 46 countries: the RE-LY Atrial Fibrillation Registry. *Circulation*. 2014;**129**:1568-1576

14. Piccini JP, Stevens SR, Lokhnygina Y, Patel MR, Halperin JL, Singer DE, Hankey GJ, Hacke W, Becker RC, Nessel CC, Mahaffey KW, Fox KA, Califf RM, Breithardt G, Committee RAS, Investigators. Outcomes after cardioversion and atrial fibrillation ablation in patients treated with rivaroxaban and warfarin in the ROCKET AF trial. *J Am Coll Cardiol*. 2013;**61**:1998-2006

15. OECD. Health at a Glance: Europe 2014. *Health Consumer Powerhouse, Euro Health Consumer Index. 2014 Report.* 2014

16. Dewland TA, Olgin JE, Vittinghoff E, Marcus GM. Incident atrial fibrillation among Asians, Hispanics, blacks, and whites. *Circulation*. 2013;**128**:2470-2477

17. Chang KC, Wang YC, Ko PY, Wu HP, Chen YW, Muo CH, Sung FC, Li TC, Hsu CY. Increased risk of first-ever stroke in younger patients with atrial fibrillation not recommended for antithrombotic therapy by current guidelines: a population-based study in an East Asian cohort of 22 million people. *Mayo Clin Proc*. 2014;**89**:1487-1497

18. Siu CW, Lip GY, Lam KF, Tse HF. Risk of stroke and intracranial hemorrhage in 9727 Chinese with atrial fibrillation in Hong Kong. *Heart Rhythm*. 2014;**11**:1401-1408

19. Olesen JB, Sorensen R, Hansen ML, Lamberts M, Weeke P, Mikkelsen AP, Kober L, Gislason GH, Torp-Pedersen C, Fosbol EL. Non-vitamin K antagonist oral anticoagulation agents in anticoagulant naive atrial fibrillation patients: Danish nationwide descriptive data 2011-2013. *Europace*. 2015;**17**:187-193

20. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J*. 2010;**31**:2369-2429

21. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P, E. S. C. Committee for Practice Guidelines. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J*. 2012;**33**:2719-2747

22. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2014;**64**:1-1

23. Excellence NIfC. Atrial fibrillation: Patient decision aid. 2014;2015

24. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation--developed with the special contribution of the European Heart Rhythm Association. *Europace*. 2012;**14**:1385-1413

25. Seaburg L, Hess EP, Coylewright M, Ting HH, McLeod CJ, Montori VM. Shared decision making in atrial fibrillation: where we are and where we should be going. *Circulation*. 2014;**129**:704-710

26. US Department of Health and Human Services Food and Drug Administration. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims. *www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf*. 2009

27. Basch E. New frontiers in patient-reported outcomes: adverse event reporting, comparative effectiveness, and quality assessment. *Annu Rev Med*. 2014;**65**:307-317

28. Calvert M, Thwaites R, Kyte D, Devlin N. Putting patient-reported outcomes on the 'Big Data Road Map'. *J R Soc Med*. 2015;10.1177/0141076815579896

29. Anker SD, Agewall S, Borggrefe M, Calvert M, Jaime Caro J, Cowie MR, Ford I, Paty JA, Riley JP, Swedberg K, Tavazzi L, Wiklund I, Kirchhof P. The importance of patient-reported outcomes: a call for their comprehensive integration in cardiovascular clinical trials. *Eur Heart J*. 2014;10.1093/eurheartj/ehu205

30. Calvert M, Blazeby J, Altman DG, Revicki DA, Moher D, Brundage MD, Group CP. Reporting of patient-reported outcomes in randomized trials: the CONSORT PRO extension. *JAMA*. 2013;**309**:814-822

31. ISOQOL. User' s guide to implementing patient-reported outcomes assessment in clinical pracice. 2015;2015:http://www.isoqol.org/UserFiles/2015UsersGuide-Version2012.pdf

32. Huxley RR, Lopez FL, Folsom AR, Agarwal SK, Loehr LR, Soliman EZ, Maclehose R, Konety S, Alonso A. Absolute and attributable risks of atrial fibrillation in relation to optimal and borderline risk factors: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation*. 2011;**123**:1501-1508

33. Pathak RK, Middeldorp ME, Lau DH, Mehta AB, Mahajan R, Twomey D, Alasady M, Hanley L, Antic NA, McEvoy RD, Kalman JM, Abhayaratna WP, Sanders P. Aggressive Risk Factor Reduction Study for Atrial Fibrillation and Implications for the Outcome of Ablation: The ARREST-AF Cohort Study. *J Am Coll Cardiol*. 2014;**64**:2222-2231

34. Abed HS, Wittert GA, Leong DP, Shirazi MG, Bahrami B, Middeldorp ME, Lorimer MF, Lau DH, Antic NA, Brooks AG, Abhayaratna WP, Kalman JM, Sanders P. Effect of weight reduction and cardiometabolic risk factor management on symptom burden and severity in patients with atrial fibrillation: a randomized clinical trial. *JAMA*. 2013;**310**:2050-2060

35. de Vos CB, Pisters R, Nieuwlaat R, Prins MH, Tieleman RG, Coelen RJ, van den Heijkant AC, Allessie MA, Crijns HJ. Progression from paroxysmal to persistent atrial fibrillation clinical correlates and prognosis. *J Am Coll Cardiol*. 2010;**55**:725-731

36. De Vos CB, Breithardt G, Camm AJ, Dorian P, Kowey PR, Le Heuzey JY, Naditch-Brule L, Prystowsky

EN, Schwartz PJ, Torp-Pedersen C, Weintraub WS, Crijns HJ. Progression of atrial fibrillation in the REgistry on Cardiac rhythm disORDers assessing the control of Atrial Fibrillation cohort: Clinical correlates and the effect of rhythm-control therapy. *Am Heart J*. 2012;**163**:887-893

37. Friberg J, Buch P, Scharling H, Gadsbphioll N, Jensen GB. Rising rates of hospital admissions for atrial fibrillation. *Epidemiology*. 2003;**14**:666-672

38. Friberg L, Rosenqvist M. Cardiovascular hospitalization as a surrogate endpoint for mortality in studies of atrial fibrillation: report from the Stockholm Cohort Study of Atrial Fibrillation. *Europace*. 2011;**13**:626-633

39. National-Institute-for-Health-and-Care-Excellence. Atrial fibrillation: the management of atrial fibrillation. (Clinical guideline 180.) 2014. http://guidance.nice.org.uk/CG180. 2014:http://guidance.nice.org.uk/CG180.

40. Hendriks JM, de Wit R, Crijns HJ, Vrijhoef HJ, Prins MH, Pisters R, Pison LA, Blaauw Y, Tieleman RG. Nurse-led care vs. usual care for patients with atrial fibrillation: results of a randomized trial of integrated chronic care vs. routine clinical care in ambulatory patients with atrial fibrillation. *Eur Heart J*. 2012;**33**:2692-2699

41. Berti D, Hendriks JM, Brandes A, Deaton C, Crijns HJ, Camm AJ, Hindricks G, Moons P, Heidbuchel H. A proposal for interdisciplinary, nurse-coordinated atrial fibrillation expert programmes as a way to structure daily practice. *Eur Heart J*. 2013;**34**:2725-2730

42. Martinez C, Katholing A, Freedman SB. Adverse prognosis of incidentally detected ambulatory atrial fibrillation. A cohort study. *Thromb Haemost*. 2014;**112**:276-286

43. Hobbs FDR, Fitzmaurice DA, Mant J, Murray E, Jowett S, Bryan S, Raftery J, Davies M, Lip G. A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study. *Health Technology Assessment (Winchester, England)*. 2005;**9**:iii-iv, ix-x, 1-74

44. Camm AJ, Lip GYH, Caterina RD, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation. An update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *European Heart Journal*. 2012;**33**:2719-2747

45. Lowres N, Neubeck L, Redfern J, Freedman SB. Screening to identify unknown atrial fibrillation. A systematic review. *Thrombosis and Haemostasis*. 2013;**110**:213-222

46. Wiesel J, Arbesfeld B, Schechter D. Comparison of the Microlife blood pressure monitor with the Omron blood pressure monitor for detecting atrial fibrillation. *Am J Cardiol*. 2014;**114**:1046-1048

47. McManus DD, Lee J, Maitas O, Esa N, Pidikiti R, Carlucci A, Harrington J, Mick E, Chon KH. A novel application for the detection of an irregular pulse using an iPhone 4S in patients with atrial fibrillation. *Heart Rhythm*. 2013;**10**:315-319

48. Engdahl J, Andersson L, Mirskaya M, Rosenqvist M. Stepwise screening of atrial fibrillation in a 75-year-old population: implications for stroke prevention. *Circulation*. 2013;**127**:930-937

49. Lowres N, Neubeck L, Salkeld G, Krass I, McLachlan AJ, Redfern J, Bennett AA, Briffa T, Bauman A, Martinez C, Wallenhorst C, Lau JK, Brieger DB, Sy RW, Freedman SB. Feasibility and cost effectiveness of stroke prevention through community screening for atrial fibrillation using iPhone ECG in pharmacies. The SEARCH-AF study. *Thromb Haemost*. 2014;**111**

50. Tieleman RG, Plantinga Y, Rinkes D, Bartels GL, Posma JL, Cator R, Hofman C, Houben RP. Validation and clinical use of a novel diagnostic device for screening of atrial fibrillation. *Europace*. 2014;**16**:1291-1295

51. Kaleschke G, Hoffmann B, Drewitz I, Steinbeck G, Naebauer M, Goette A, Breithardt G, Kirchhof P. Prospective, multicentre validation of a simple, patient-operated electrocardiographic system for the detection of arrhythmias and electrocardiographic changes. *Europace*. 2009;**11**:1362-1368

52. Wilson JM, Jungner G. Principles and Practice of Screening for Disease *World Health Organization, Geneva, Switzerland*. 1968

53. Leyden JM, Kleinig TJ, Newbury J, Castle S, Cranefield J, Anderson CS, Crotty M, Whitford D, Jannes J, Lee A, Greenhill J. Adelaide stroke incidence study: declining stroke rates but many preventable cardioembolic strokes. *Stroke*. 2013;**44**:1226-1231

54. Hannon N, Sheehan O, Kelly L, Marnane M, Merwick A, Moore A, Kyne L, Duggan J, Moroney J, McCormack PME, Daly L, Fitz-Simon N, Harris D, Horgan G, Williams EB, Furie KL, Kelly PJ. Stroke associated with atrial fibrillation – incidence and early outcomes in the North Dublin population stroke study. *Cerebrovascular Diseases*. 2010;**29**:43-49

55. Friberg L, Rosenqvist M, Lindgren A, Terent A, Norrving B, Asplund K. High prevalence of atrial fibrillation among patients with ischemic stroke. *Stroke*. 2014;**45**:2599-2605

56. Sposato LA, Cipriano LE, Saposnik G, Vargas ER, Riccio PM, Hachinski V. Diagnosis of atrial fibrillation after stroke and transient ischaemic attack: a systematic review and meta-analysis. *Lancet Neurol*. 2015;**14**:377-387

57. Kishore A, Vail A, Majid A, Dawson J, Lees KR, Tyrrell PJ, Smith CJ. Detection of atrial fibrillation after ischemic stroke or transient ischemic attack: a systematic review and meta-analysis. *Stroke*. 2014;**45**:520-526

58. Sanna T, Diener HC, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA, Rymer MM, Thijs V, Rogers T, Beckers F, Lindborg K, Brachmann J, Investigators CA. Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med*. 2014;**370**:2478-2486

59. Kamel H. Heart-rhythm monitoring for evaluation of cryptogenic stroke. *N Engl J Med*. 2014;**370**:2532-2533

60. Kirchhof P, Ammentorp B, Darius H, De Caterina R, Le Heuzey JY, Schilling RJ, Schmitt J, Zamorano JL. Management of atrial fibrillation in seven European countries after the publication of the 2010 ESC Guidelines on atrial fibrillation: primary results of the PREvention oF thromboemolic events--European Registry in Atrial Fibrillation (PREFER in AF). *Europace*. 2014;**16**:6-14

61. Lip GY, Laroche C, Ioachim PM, Rasmussen LH, Vitali-Serdoz L, Petrescu L, Darabantiu D, Crijns HJ, Kirchhof P, Vardas P, Tavazzi L, Maggioni AP, Boriani G. Prognosis and treatment of atrial fibrillation patients by European cardiologists: One Year Follow-up of the EURObservational Research Programme-Atrial Fibrillation General Registry Pilot Phase (EORP-AF Pilot registry). *Eur Heart J*. 2014;10.1093/eurheartj/ehu374

62. Lip GY, Al-Khatib SM, Cosio FG, Banerjee A, Savelieva I, Ruskin J, Blendea D, Nattel S, De Bono J, Conroy JM, Hess PL, Guasch E, Halperin JL, Kirchhof P, MD GC, Camm AJ. Contemporary management of atrial fibrillation: what can clinical registries tell us about stroke prevention and current therapeutic approaches? *J Am Heart Assoc*. 2014;**3**

63. Nabauer M, Gerth A, Limbourg T, Schneider S, Oeff M, Kirchhof P, Goette A, Lewalter T, Ravens U, Meinertz T, Breithardt G, Steinbeck G. The Registry of the German Competence NETwork on Atrial Fibrillation: Patient characteristics and initial management. *Europace*. 2009;**11**:423-434

64. Kirchhof P, Nabauer M, Gerth A, Limbourg T, Lewalter T, Goette A, Wegscheider K, Treszl A, Meinertz T, Oeff M, Ravens U, Breithardt G, Steinbeck G. Impact of the type of centre on management of AF patients: surprising evidence for differences in antithrombotic therapy decisions. *Thromb Haemost*. 2011;**105**:1010-1023

65. Gorst-Rasmussen A, Skjoth F, Larsen TB, Rasmussen LH, Lip GY, Lane DA. Dabigatran adherence in atrial fibrillation patients during the first year after diagnosis: a nationwide cohort study. *J Thromb Haemost*. 2015;10.1111/jth.12845

66. Graham DJ, Reichman ME, Wernecke M, Zhang R, Southworth MR, Levenson M, Sheu TC, Mott K, Goulding MR, Houstoun M, MaCurdy TE, Worrall C, Kelman JA. Cardiovascular, bleeding, and mortality risks in elderly medicare patients treated with dabigatran or warfarin for nonvalvular atrial fibrillation. *Circulation*. 2015;**131**:157-164

67. Lip GY, Laroche C, Dan GA, Santini M, Kalarus Z, Rasmussen LH, Oliveira MM, Mairesse G, Crijns HJ, Simantirakis E, Atar D, Kirchhof P, Vardas P, Tavazzi L, Maggioni AP. A prospective survey in European Society of Cardiology member countries of atrial fibrillation management: baseline results of EURObservational Research Programme Atrial Fibrillation (EORP-AF) Pilot General Registry. *Europace*. 2014;**16**:308-319

68. Le Heuzey JY, Ammentorp B, Darius H, De Caterina R, Schilling RJ, Schmitt J, Zamorano JL, Kirchhof P. Differences among western European countries in anticoagulation management of atrial fibrillation. Data from the PREFER IN AF Registry. *Thromb Haemost*. 2014;**111**:833-841

69. Donze J, Clair C, Hug B, Rodondi N, Waeber G, Cornuz J, Aujesky D. Risk of falls and major bleeds in patients on oral anticoagulation therapy. *Am J Med*. 2012;**125**:773-778

70. Man-Son-Hing M, Nichol G, Lau A, Laupacis A. Choosing antithrombotic therapy for elderly patients with atrial fibrillation who are at risk for falls. *Arch Intern Med*. 1999;**159**:677-685

71. Wallentin L, Yusuf S, Ezekowitz MD, Alings M, Flather M, Franzosi MG, Pais P, Dans A, Eikelboom J, Oldgren J, Pogue J, Reilly PA, Yang S, Connolly SJ. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. *Lancet*. 2010;**376**:975-983

72. Shore S, Carey EP, Turakhia MP, Jackevicius CA, Cunningham F, Pilote L, Bradley SM, Maddox TM, Grunwald GK, Baron AE, Rumsfeld JS, Varosy PD, Schneider PM, Marzec LN, Ho PM. Adherence to dabigatran therapy and longitudinal patient outcomes: insights from the veterans health administration. *Am Heart J*. 2014;**167**:810-817

73. Ho CW, Ho MH, Chan PH, Hai JJ, Cheung E, Yeung CY, Lau KK, Chan KH, Lau CP, Lip GY, Leung GK, Tse HF, Siu CW. Ischemic stroke and intracranial hemorrhage with aspirin, dabigatran, and warfarin: impact of quality of anticoagulation control. *Stroke*. 2015;**46**:23-30

74. Gallego P, Roldan V, Marin F, Romera M, Valdes M, Vicente V, Lip GY. Cessation of oral anticoagulation in relation to mortality and the risk of thrombotic events in patients with atrial fibrillation. *Thromb Haemost*. 2013;**110**:1189-1198

75. Smith DE, Xuereb CB, Pattison HM, Lip GY, Lane DA. TRial of an Educational intervention on patients' knowledge of Atrial fibrillation and anticoagulant therapy, INR control, and outcome of Treatment with warfarin (TREAT). *BMC Cardiovasc Disord*. 2010;**10**:21

76. De Caterina R, Husted S, Wallentin L, Andreotti F, Arnesen H, Bachmann F, Baigent C, Huber K, Jespersen J, Kristensen SD, Lip GY, Morais J, Rasmussen LH, Siegbahn A, Verheugt FW, Weitz JI. Vitamin K antagonists in heart disease: current status and perspectives (Section III). Position paper of the

ESC Working Group on Thrombosis--Task Force on Anticoagulants in Heart Disease. *Thromb Haemost*. 2013;**110**:1087-1107

77. Gallego P, Roldan V, Marin F, Galvez J, Valdes M, Vicente V, Lip GY. SAMe-TT2R2 score, time in therapeutic range, and outcomes in anticoagulated patients with atrial fibrillation. *Am J Med*. 2014;**127**:1083-1088

78. Apostolakis S, Sullivan RM, Olshansky B, Lip GY. Factors affecting quality of anticoagulation control among patients with atrial fibrillation on warfarin: the SAMe-TT(2)R(2) score. *Chest*. 2013;**144**:1555-1563

79. Heidbuchel H, Verhamme P, Alings M, Antz M, Hacke W, Oldgren J, Sinnaeve P, Camm AJ, Kirchhof P. EHRA practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary. *Eur Heart J*. 2013;**34**:2094-2106

80. Stroke Unit Trialists Collaboration. Organised inpatient (stroke unit) care for stroke. *Cochrane Database Syst Rev*. 2013;**9**:CD000197

81. Van Gelder IC, Groenveld HF, Crijns HJ, Tuininga YS, Tijssen JG, Alings AM, Hillege HL, Bergsma-Kadijk JA, Cornel JH, Kamp O, Tukkie R, Bosker HA, Van Veldhuisen DJ, Van den Berg MP. Lenient versus strict rate control in patients with atrial fibrillation. *N Engl J Med*. 2010;**362**:1363-1373

82. Camm AJ, Breithardt G, Crijns H, Dorian P, Kowey P, Le Heuzey JY, Merioua I, Pedrazzini L, Prystowsky EN, Schwartz PJ, Torp-Pedersen C, Weintraub W. Real-life observations of clinical outcomes with rhythm- and rate-control therapies for atrial fibrillation RECORDAF (Registry on Cardiac Rhythm Disorders Assessing the Control of Atrial Fibrillation). *J Am Coll Cardiol*. 2011;**58**:493-501

83. Kotecha D, Holmes J, Krum H, Altman DG, Manzano L, Cleland JG, Lip GY, Coats AJ, Andersson B, Kirchhof P, von Lueder TG, Wedel H, Rosano G, Shibata MC, Rigby A, Flather MD, Beta-Blockers in Heart Failure Collaborative Group. Efficacy of beta blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. *Lancet*. 2014;**384**:2235-2243

84. Kotecha D, Kirchhof P. Rate and rhythm control have comparable effects on mortality and stroke in atrial fibrillation but better data are needed. *Evid Based Med*. 2014;**19**:222-223

85. Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA, Crijns HJ, Damiano RJ, Jr., Davies DW, DiMarco J, Edgerton J, Ellenbogen K, Ezekowitz MD, Haines DE, Haissaguerre M, Hindricks G, Iesaka Y, Jackman W, Jalife J, Jais P, Kalman J, Keane D, Kim YH, Kirchhof P, Klein G, Kottkamp H, Kumagai K, Lindsay BD, Mansour M, Marchlinski FE, McCarthy PM, Mont JL, Morady F, Nademanee K, Nakagawa H, Natale A, Nattel S, Packer DL, Pappone C, Prystowsky E, Raviele A, Reddy V, Ruskin JN, Shemin RJ, Tsao HM, Wilber D. 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter

and Surgical Ablation of Atrial Fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. *Europace*. 2012;**14**:528-606

86. January CT, Wann LS, Alpert JS, Calkins H, Cleveland JC, Jr., Cigarroa JE, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2014;10.1161/CIR.0000000000000041

87. Cosedis Nielsen J, Johannessen A, Raatikainen P, Hindricks G, Walfridsson H, Kongstad O, Pehrson S, Englund A, Hartikainen J, Mortensen LS, Hansen PS. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. *N Engl J Med*. 2012;**367**:1587-1595

88. Wilber DJ, Pappone C, Neuzil P, De Paola A, Marchlinski F, Natale A, Macle L, Daoud EG, Calkins H, Hall B, Reddy V, Augello G, Reynolds MR, Vinekar C, Liu CY, Berry SM, Berry DA, ThermoCool AFTI. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. *JAMA*. 2010;**303**:333-340

89. Arbelo E, Brugada J, Hindricks G, Maggioni AP, Tavazzi L, Vardas P, Laroche C, Anselme F, Inama G, Jais P, Kalarus Z, Kautzner J, Lewalter T, Mairesse GH, Perez-Villacastin J, Riahi S, Taborsky M, Theodorakis G, Trines SA, Atrial Fibrillation Ablation Pilot Study I. The atrial fibrillation ablation pilot study: a European Survey on Methodology and results of catheter ablation for atrial fibrillation conducted by the European Heart Rhythm Association. *Eur Heart J*. 2014;**35**:1466-1478

90. Cappato R, Calkins H, Chen SA, Davies W, Iesaka Y, Kalman J, Kim YH, Klein G, Natale A, Packer D, Skanes A, Ambrogi F, Biganzoli E. Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2010;**3**:32-38

91. Darkner S, Chen X, Hansen J, Pehrson S, Johannessen A, Nielsen JB, Svendsen JH. Recurrence of arrhythmia following short-term oral AMIOdarone after CATheter ablation for atrial fibrillation: a double-blind, randomized, placebo-controlled study (AMIO-CAT trial). *Eur Heart J*. 2014;**35**:3356-3364

92. Kirchhof P, Andresen D, Bosch R, Borggrefe M, Meinertz T, Parade U, Ravens U, Samol A, Steinbeck G, Treszl A, Wegscheider K, Breithardt G. Short-term versus long-term antiarrhythmic drug treatment after cardioversion of atrial fibrillation (Flec-SL): a prospective, randomised, open-label, blinded endpoint assessment trial. *Lancet*. 2012;**380**:238-246

93. Kirchhof P, Sipido KR, Cowie MR, Eschenhagen T, Fox KA, Katus H, Schroeder S, Schunkert H, Priori S. The continuum of personalized cardiovascular medicine: a position paper of the European Society of Cardiology. *Eur Heart J*. 2014;10.1093/eurheartj/ehu312

94. Schotten U, Verheule S, Kirchhof P, Goette A. Pathophysiological mechanisms of atrial fibrillation: a translational appraisal. *Physiol Rev*. 2011;**91**:265-325

95. Wakili R, Voigt N, Kaab S, Dobrev D, Nattel S. Recent advances in the molecular pathophysiology of atrial fibrillation. *J Clin Invest*. 2011;**121**:2955-2968

96. Nattel S, Guasch E, Savelieva I, Cosio FG, Valverde I, Halperin JL, Conroy JM, Al-Khatib SM, Hess PL, Kirchhof P, De Bono J, Lip GY, Banerjee A, Ruskin J, Blendea D, Camm AJ. Early management of atrial fibrillation to prevent cardiovascular complications. *Eur Heart J*. 2014;10.1093/eurheartj/ehu028

97. Charitos EI, Purerfellner H, Glotzer TV, Ziegler PD. Clinical classifications of atrial fibrillation poorly reflect its temporal persistence: insights from 1,195 patients continuously monitored with implantable devices. *J Am Coll Cardiol*. 2014;**63**:2840-2848

98. Plitt DC, Chung EH, Mounsey JP, Schwartz JD, Pursell IW, Gehi AK. Relation of atrial fibrillation burden and N-terminal pro-brain natriuretic peptide. *Am J Cardiol*. 2013;**111**:1315-1318

99. Schnabel RB, Larson MG, Yamamoto JF, Sullivan LM, Pencina MJ, Meigs JB, Tofler GH, Selhub J, Jacques PF, Wolf PA, Magnani JW, Ellinor PT, Wang TJ, Levy D, Vasan RS, Benjamin EJ. Relations of biomarkers of distinct pathophysiological pathways and atrial fibrillation incidence in the community. *Circulation*. 2010;**121**:200-207

100. Sinner MF, Stepas KA, Moser CB, Krijthe BP, Aspelund T, Sotoodehnia N, Fontes JD, Janssens AC, Kronmal RA, Magnani JW, Witteman JC, Chamberlain AM, Lubitz SA, Schnabel RB, Vasan RS, Wang TJ, Agarwal SK, McManus DD, Franco OH, Yin X, Larson MG, Burke GL, Launer LJ, Hofman A, Levy D, Gottdiener JS, Kaab S, Couper D, Harris TB, Astor BC, Ballantyne CM, Hoogeveen RC, Arai AE, Soliman EZ, Ellinor PT, Stricker BH, Gudnason V, Heckbert SR, Pencina MJ, Benjamin EJ, Alonso A. B-type natriuretic peptide and C-reactive protein in the prediction of atrial fibrillation risk: the CHARGE-AF Consortium of community-based cohort studies. *Europace*. 2014;**16**:1426-1433

101. Hijazi Z, Wallentin L, Siegbahn A, Andersson U, Christersson C, Ezekowitz J, Gersh BJ, Hanna M, Hohnloser S, Horowitz J, Huber K, Hylek EM, Lopes RD, McMurray JJ, Granger CB. NT-proBNP for Risk Assessment in Patients with Atrial Fibrillation: Insights from the ARISTOTLE trial. *J Am Coll Cardiol*. 2013;S0735-1097(13)01299-0 [pii]
10.1016/j.jacc.2012.11.082

102. Goff DC, Jr., Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Sr., Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC, Jr., Sorlie P, Stone NJ, Wilson PW, American College of Cardiology/American Heart Association Task Force on Practice G. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll*

Cardiol. 2014;**63**:2935-2959

103. Pena JM, MacFadyen J, Glynn RJ, Ridker PM. High-sensitivity C-reactive protein, statin therapy, and risks of atrial fibrillation: an exploratory analysis of the JUPITER trial. *Eur Heart J*. 2012;**33**:531-537

104. Marott SC, Nordestgaard BG, Zacho J, Friberg J, Jensen GB, Tybjaerg-Hansen A, Benn M. Does elevated C-reactive protein increase atrial fibrillation risk? A Mendelian randomization of 47,000 individuals from the general population. *J Am Coll Cardiol*. 2010;**56**:789-795

105. Alonso A, Lopez FL, Matsushita K, Loehr LR, Agarwal SK, Chen LY, Soliman EZ, Astor BC, Coresh J. Chronic kidney disease is associated with the incidence of atrial fibrillation: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation*. 2011;**123**:2946-2953

106. Brugada R, Tapscott T, Czernuszewicz GZ, Marian AJ, Iglesias A, Mont L, Brugada J, Girona J, Domingo A, Bachinski LL, Roberts R. Identification of a genetic locus for familial atrial fibrillation. *N Engl J Med*. 1997;**336**:905-911

107. Hodgson-Zingman DM, Karst ML, Zingman LV, Heublein DM, Darbar D, Herron KJ, Ballew JD, de Andrade M, Burnett JC, Jr., Olson TM. Atrial natriuretic peptide frameshift mutation in familial atrial fibrillation. *N Engl J Med*. 2008;**359**:158-165

108. Parvez B, Vaglio J, Rowan S, Muhammad R, Kucera G, Stubblefield T, Carter S, Roden D, Darbar D. Symptomatic response to antiarrhythmic drug therapy is modulated by a common single nucleotide polymorphism in atrial fibrillation. *J Am Coll Cardiol*. 2012;**60**:539-545

109. Husser D, Adams V, Piorkowski C, Hindricks G, Bollmann A. Chromosome 4q25 variants and atrial fibrillation recurrence after catheter ablation. *J Am Coll Cardiol*. 2010;**55**:747-753

110. Lubitz SA, Lunetta KL, Lin H, Arking DE, Trompet S, Li G, Krijthe BP, Chasman DI, Barnard J, Kleber ME, Dorr M, Ozaki K, Smith AV, Muller-Nurasyid M, Walter S, Agarwal SK, Bis JC, Brody JA, Chen LY, Everett BM, Ford I, Franco OH, Harris TB, Hofman A, Kaab S, Mahida S, Kathiresan S, Kubo M, Launer LJ, Macfarlane PW, Magnani JW, McKnight B, McManus DD, Peters A, Psaty BM, Rose LM, Rotter JI, Silbernagel G, Smith JD, Sotoodehnia N, Stott DJ, Taylor KD, Tomaschitz A, Tsunoda T, Uitterlinden AG, Van Wagoner DR, Volker U, Volzke H, Murabito JM, Sinner MF, Gudnason V, Felix SB, Marz W, Chung M, Albert CM, Stricker BH, Tanaka T, Heckbert SR, Jukema JW, Alonso A, Benjamin EJ, Ellinor PT. Novel genetic markers associate with atrial fibrillation risk in europeans and Japanese. *J Am Coll Cardiol*. 2014;**63**:1200-1210

111. Tada H, Shiffman D, Smith JG, Sjogren M, Lubitz SA, Ellinor PT, Louie JZ, Catanese JJ, Engstrom G, Devlin JJ, Kathiresan S, Melander O. Twelve-single nucleotide polymorphism genetic risk score identifies individuals at increased risk for future atrial fibrillation and stroke. *Stroke*. 2014;**45**:2856-2862

112. Everett BM, Cook NR, Conen D, Chasman DI, Ridker PM, Albert CM. Novel genetic markers improve measures of atrial fibrillation risk prediction. *Eur Heart J*. 2013;**34**:2243-2251

113. Wang J, Bai Y, Li N, Ye W, Zhang M, Greene SB, Tao Y, Chen Y, Wehrens XH, Martin JF. Pitx2-microRNA pathway that delimits sinoatrial node development and inhibits predisposition to atrial fibrillation. *Proc Natl Acad Sci U S A*. 2014;10.1073/pnas.1405411111

114. Nattel S, Harada M. Atrial remodeling and atrial fibrillation: recent advances and translational perspectives. *J Am Coll Cardiol*. 2014;**63**:2335-2345

115. McManus DD, Lin H, Tanriverdi K, Quercio M, Yin X, Larson MG, Ellinor PT, Levy D, Freedman JE, Benjamin EJ. Relations between circulating microRNAs and atrial fibrillation: Data from the Framingham Offspring Study. *Heart Rhythm*. 2014;**11**:663-669

116. Luo X, Pan Z, Shan H, Xiao J, Sun X, Wang N, Lin H, Xiao L, Maguy A, Qi XY, Li Y, Gao X, Dong D, Zhang Y, Bai Y, Ai J, Sun L, Lu H, Luo XY, Wang Z, Lu Y, Yang B, Nattel S. MicroRNA-26 governs profibrillatory inward-rectifier potassium current changes in atrial fibrillation. *J Clin Invest*. 2013;**123**:1939-1951

117. Dawson K, Wakili R, Ordog B, Clauss S, Chen Y, Iwasaki Y, Voigt N, Qi XY, Sinner MF, Dobrev D, Kaab S, Nattel S. MicroRNA29: a mechanistic contributor and potential biomarker in atrial fibrillation. *Circulation*. 2013;**127**:1466-1475, 1475e1461-1428

118. Adam O, Lohfelm B, Thum T, Gupta SK, Puhl SL, Schafers HJ, Bohm M, Laufs U. Role of miR-21 in the pathogenesis of atrial fibrosis. *Basic Res Cardiol*. 2012;**107**:278

119. Sinner MF, Tucker NR, Lunetta KL, Ozaki K, Smith JG, Trompet S, Bis JC, Lin H, Chung MK, Nielsen JB, Lubitz SA, Krijthe BP, Magnani JW, Ye J, Gollob MH, Tsunoda T, Muller-Nurasyid M, Lichtner P, Peters A, Dolmatova E, Kubo M, Smith JD, Psaty BM, Smith NL, Jukema JW, Chasman DI, Albert CM, Ebana Y, Furukawa T, Macfarlane PW, Harris TB, Darbar D, Dorr M, Holst AG, Svendsen JH, Hofman A, Uitterlinden AG, Gudnason V, Isobe M, Malik R, Dichgans M, Rosand J, Van Wagoner DR, Benjamin EJ, Milan DJ, Melander O, Heckbert SR, Ford I, Liu Y, Barnard J, Olesen MS, Stricker BH, Tanaka T, Kaab S, Ellinor PT. Integrating genetic, transcriptional, and functional analyses to identify 5 novel genes for atrial fibrillation. *Circulation*. 2014;**130**:1225-1235

120. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. *BMJ*. 2015;**350**:g7594

121. Kolek MJ, Parvez B, Muhammad R, Shoemaker MB, Blair MA, Stubblefield T, Kucera GA, Denny JC, Roden DM, Darbar D. A common variant on chromosome 4q25 is associated with prolonged PR interval in subjects with and without atrial fibrillation. *Am J Cardiol*. 2014;**113**:309-313

122. Pfeufer A, van Noord C, Marciante KD, Arking DE, Larson MG, Smith AV, Tarasov KV, Muller M, Sotoodehnia N, Sinner MF, Verwoert GC, Li M, Kao WH, Kottgen A, Coresh J, Bis JC, Psaty BM, Rice K, Rotter JI, Rivadeneira F, Hofman A, Kors JA, Stricker BH, Uitterlinden AG, van Duijn CM, Beckmann BM, Sauter W, Gieger C, Lubitz SA, Newton-Cheh C, Wang TJ, Magnani JW, Schnabel RB, Chung MK, Barnard J, Smith JD, Van Wagoner DR, Vasan RS, Aspelund T, Eiriksdottir G, Harris TB, Launer LJ, Najjar SS, Lakatta E, Schlessinger D, Uda M, Abecasis GR, Muller-Myhsok B, Ehret GB, Boerwinkle E, Chakravarti A, Soliman EZ, Lunetta KL, Perz S, Wichmann HE, Meitinger T, Levy D, Gudnason V, Ellinor PT, Sanna S, Kaab S, Witteman JC, Alonso A, Benjamin EJ, Heckbert SR. Genome-wide association study of PR interval. *Nat Genet*. 2010;**42**:153-159

123. Schnabel RB, Aspelund T, Li G, Sullivan LM, Suchy-Dicey A, Harris TB, Pencina MJ, D'Agostino RB, Sr., Levy D, Kannel WB, Wang TJ, Kronmal RA, Wolf PA, Burke GL, Launer LJ, Vasan RS, Psaty BM, Benjamin EJ, Gudnason V, Heckbert SR. Validation of an atrial fibrillation risk algorithm in whites and African Americans. *Arch Intern Med*. 2010;**170**:1909-1917

124. Schnabel RB, Sullivan LM, Levy D, Pencina MJ, Massaro JM, D'Agostino RB, Sr., Newton-Cheh C, Yamamoto JF, Magnani JW, Tadros TM, Kannel WB, Wang TJ, Ellinor PT, Wolf PA, Vasan RS, Benjamin EJ. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. *Lancet*. 2009;**373**:739-745

125. Cheng S, Keyes MJ, Larson MG, McCabe EL, Newton-Cheh C, Levy D, Benjamin EJ, Vasan RS, Wang TJ. Long-term outcomes in individuals with prolonged PR interval or first-degree atrioventricular block. *JAMA*. 2009;**301**:2571-2577

126. de Groot NM, Houben RP, Smeets JL, Boersma E, Schotten U, Schalij MJ, Crijns H, Allessie MA. Electropathological Substrate of Longstanding Persistent Atrial Fibrillation in Patients With Structural Heart Disease. Epicardial Breakthrough. *Circulation*. 2010;CIRCULATIONAHA.109.910901 [pii]
10.1161/CIRCULATIONAHA.109.910901

127. Allessie MA, de Groot NM, Houben RP, Schotten U, Boersma E, Smeets JL, Crijns HJ. Electropathological substrate of long-standing persistent atrial fibrillation in patients with structural heart disease: longitudinal dissociation. *Circ Arrhythm Electrophysiol*. 2010;**3**:606-615

128. Eckstein J, Maesen B, Linz D, Zeemering S, van Hunnik A, Verheule S, Allessie M, Schotten U. Time course and mechanisms of endo-epicardial electrical dissociation during atrial fibrillation in the goat. *Cardiovasc Res*. 2011;**89**:816-824

129. Verheule S, Tuyls E, van Hunnik A, Kuiper M, Schotten U, Allessie M. Fibrillatory conduction in the atrial free walls of goats in persistent and permanent atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2010;**3**:590-599

130. Eckstein J, Verheule S, de Groot NM, Allessie M, Schotten U. Mechanisms of perpetuation of atrial fibrillation in chronically dilated atria. *Prog Biophys Mol Biol*. 2008;**97**:435-451

131. Lankveld TA, Zeemering S, Crijns HJ, Schotten U. The ECG as a tool to determine atrial fibrillation complexity. *Heart*. 2014;**100**:1077-1084

132. Schotten U, Maesen B, Zeemering S. The need for standardization of time- and frequency-domain analysis of body surface electrocardiograms for assessment of the atrial fibrillation substrate. *Europace*. 2012;**14**:1072-1075

133. Platonov PG, Corino VD, Seifert M, Holmqvist F, Sornmo L. Atrial fibrillatory rate in the clinical context: natural course and prediction of intervention outcome. *Europace*. 2014;**16 Suppl 4**:iv110-iv119

134. Kuramatsu JB, Gerner ST, Schellinger PD, Glahn J, Endres M, Sobesky J, Flechsenhar J, Neugebauer H, Juttler E, Grau A, Palm F, Rother J, Michels P, Hamann GF, Huwel J, Hagemann G, Barber B, Terborg C, Trostdorf F, Bazner H, Roth A, Wohrle J, Keller M, Schwarz M, Reimann G, Volkmann J, Mullges W, Kraft P, Classen J, Hobohm C, Horn M, Milewski A, Reichmann H, Schneider H, Schimmel E, Fink GR, Dohmen C, Stetefeld H, Witte O, Gunther A, Neumann-Haefelin T, Racs AE, Nueckel M, Erbguth F, Kloska SP, Dorfler A, Kohrmann M, Schwab S, Huttner HB. Anticoagulant reversal, blood pressure levels, and anticoagulant resumption in patients with anticoagulation-related intracerebral hemorrhage. *JAMA*. 2015;**313**:824-836

135. Lewalter T, Kanagaratnam P, Schmidt B, Rosenqvist M, Nielsen-Kudsk JE, Ibrahim R, Albers BA, Camm AJ. Ischaemic stroke prevention in patients with atrial fibrillation and high bleeding risk: opportunities and challenges for percutaneous left atrial appendage occlusion. *Europace*. 2014;**16**:626-630

136. INVOLVE. Briefing notes for researchers: involving the public in NHS, public health and social care research. *www.invo.org.uk/wp-content/uploads/2012/04/INVOLVEBriefingNotesApr2012.pdf*. 2012

137. Piccinocchi G, Laringe M, Guillaro B, Arpino G, Piccinocchi R, Nigro G, Calabro P. Diagnosis and management of atrial fibrillation by primary care physicians in Italy : a retrospective, observational analysis. *Clin Drug Investig*. 2012;**32**:771-777

138. Hendriks J, Tomini F, van Asselt T, Crijns H, Vrijhoef H. Cost-effectiveness of a specialized atrial fibrillation clinic vs. usual care in patients with atrial fibrillation. *Europace*. 2013;**15**:1128-1135

139. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH, European Heart Rhythm A, European Association for Cardio-Thoracic S, Guidelines ESCCfP.

Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Europace*. 2010;**12**:1360-1420

140. Wynn GJ, Todd DM, Webber M, Bonnett L, McShane J, Kirchhof P, Gupta D. The European Heart Rhythm Association symptom classification for atrial fibrillation: validation and improvement through a simple modification. *Europace*. 2014;**16**:965-972

141. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest*. 2010;**137**:263-272

142. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest*. 2010;**138**:1093-1100

143. Lane DA, Barker RV, Lip GY. Best practice for atrial fibrillation patient education. *Curr Pharm Des*. 2015;**21**:533-543

144. Hendriks JM, de Wit R, Vrijhoef HJ, Tieleman RG, Crijns HJ. An integrated chronic care program for patients with atrial fibrillation: study protocol and methodology for an ongoing prospective randomised controlled trial. *Int J Nurs Stud*. 2010;**47**:1310-1316

145. Clarkesmith DE, Pattison HM, Lip GY, Lane DA. Educational intervention improves anticoagulation control in atrial fibrillation patients: the TREAT randomised trial. *PLoS One*. 2013;**8**:e74037

146. Lane DA, Wood K. A patient's guide to the NOACs. *Circulation* 2015:in press

147. Wynn GJ, Todd D, Webber M, Bonnett L, McSHane J, Kirchhof P, Gupta D. The European Heart Rhythm Association Symptom Classification for Atrial Fibrillation: Validation and Improvement through a simple modification. *Europace*. 2014;**in press**

148. Rienstra M, Yin X, Larson MG, Fontes JD, Magnani JW, McManus DD, McCabe EL, Coglianese EE, Amponsah M, Ho JE, Januzzi JL, Jr., Wollert KC, Fradley MG, Vasan RS, Ellinor PT, Wang TJ, Benjamin EJ. Relation between soluble ST2, growth differentiation factor-15, and high-sensitivity troponin I and incident atrial fibrillation. *Am Heart J*. 2014;**167**:109-115 e102

149. Hernandez-Romero D, Vilchez JA, Lahoz A, Romero-Aniorte AI, Orenes-Pinero E, Caballero L, Jara-Rubio R, Arribas JM, Garcia-Alberola A, Valdes M, Lip GY, Marin F. High-sensitivity troponin T as a biomarker for the development of atrial fibrillation after cardiac surgery. *Eur J Cardiothorac Surg*. 2014;**45**:733-738

150. Koolen BB, Labout JA, Mulder PG, Gerritse BM, Rijpstra TA, Bentala M, Rosseel PM, van der Meer

NJ. Association of perioperative troponin and atrial fibrillation after coronary artery bypass grafting. *Interact Cardiovasc Thorac Surg*. 2013;**17**:608-614

151. Hijazi Z, Oldgren J, Andersson U, Connolly SJ, Ezekowitz MD, Hohnloser SH, Reilly PA, Vinereanu D, Siegbahn A, Yusuf S, Wallentin L. Cardiac biomarkers are associated with an increased risk of stroke and death in patients with atrial fibrillation: a Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) substudy. *Circulation*. 2012;**125**:1605-1616

152. Hijazi Z, Siegbahn A, Andersson U, Granger CB, Alexander JH, Atar D, Gersh BJ, Mohan P, Harjola VP, Horowitz J, Husted S, Hylek EM, Lopes RD, McMurray JJ, Wallentin L, Aristotle Investigators. High-sensitivity troponin I for risk assessment in patients with atrial fibrillation: insights from the Apixaban for Reduction in Stroke and other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial. *Circulation*. 2014;**129**:625-634

153. Roldan V, Marin F, Diaz J, Gallego P, Jover E, Romera M, Manzano-Fernandez S, Casas T, Valdes M, Vicente V, Lip GY. High sensitivity cardiac troponin T and interleukin-6 predict adverse cardiovascular events and mortality in anticoagulated patients with atrial fibrillation. *J Thromb Haemost*. 2012;**10**:1500-1507

154. Cushman M, Judd SE, Howard VJ, Kissela B, Gutierrez OM, Jenny NS, Ahmed A, Thacker EL, Zakai NA. N-terminal pro-B-type natriuretic peptide and stroke risk: the reasons for geographic and racial differences in stroke cohort. *Stroke*. 2014;**45**:1646-1650

155. Kara K, Geisel MH, Mohlenkamp S, Lehmann N, Kalsch H, Bauer M, Neumann T, Dragano N, Moebus S, Jockel KH, Erbel R, Mahabadi AA. B-type natriuretic peptide for incident atrial fibrillation-The Heinz Nixdorf Recall Study. *J Cardiol*. 2014;10.1016/j.jjcc.2014.08.003

156. Mandalenakis Z, Eriksson H, Welin L, Caidahl K, Dellborg M, Rosengren A, Lappas G, Hedner J, Johansson S, Svardsudd K, Hansson PO. Atrial natriuretic peptide as a predictor of atrial fibrillation in a male population study. The Study of Men Born in 1913 and 1923. *Int J Cardiol*. 2014;**171**:44-48

157. Parashar S, Kella D, Reid KJ, Spertus JA, Tang F, Langberg J, Vaccarino V, Kontos MC, Lopes RD, Lloyd MS. New-onset atrial fibrillation after acute myocardial infarction and its relation to admission biomarkers (from the TRIUMPH registry). *Am J Cardiol*. 2013;**112**:1390-1395

158. Patton KK, Ellinor PT, Heckbert SR, Christenson RH, DeFilippi C, Gottdiener JS, Kronmal RA. N-terminal pro-B-type natriuretic peptide is a major predictor of the development of atrial fibrillation: the Cardiovascular Health Study. *Circulation*. 2009;**120**:1768-1774

159. Patton KK, Heckbert SR, Alonso A, Bahrami H, Lima JA, Burke G, Kronmal RA. N-terminal pro-B-type natriuretic peptide as a predictor of incident atrial fibrillation in the Multi-Ethnic Study of

Atherosclerosis: the effects of age, sex and ethnicity. *Heart*. 2013;**99**:1832-1836

160. Kallel S, Jarrya A, Triki Z, Abdenadher M, Frikha J, Karoui A. The use of N-terminal pro-brain natriuretic peptide as a predictor of atrial fibrillation after cardiac surgery. *J Cardiovasc Surg (Torino)*. 2013;**54**:403-411

161. Matsuura K, Mogi K, Sakurai M, Kawamura T, Misue T, Hatakeyama I, Takahara Y. Preoperative high N-terminal pro-B-type natriuretic peptide level can predict the incidence of postoperative atrial fibrillation following off-pump coronary artery bypass grafting. *Ann Thorac Cardiovasc Surg*. 2013;**19**:375-381

162. Hijazi Z, Wallentin L, Siegbahn A, Andersson U, Christersson C, Ezekowitz J, Gersh BJ, Hanna M, Hohnloser S, Horowitz J, Huber K, Hylek EM, Lopes RD, McMurray JJ, Granger CB. N-terminal pro-B-type natriuretic peptide for risk assessment in patients with atrial fibrillation: insights from the ARISTOTLE Trial (Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation). *J Am Coll Cardiol*. 2013;**61**:2274-2284

163. Folsom AR, Nambi V, Bell EJ, Oluleye OW, Gottesman RF, Lutsey PL, Huxley RR, Ballantyne CM. Troponin T, N-terminal pro-B-type natriuretic peptide, and incidence of stroke: the atherosclerosis risk in communities study. *Stroke*. 2013;**44**:961-967

164. Nakamura M, Koeda Y, Tanaka F, Onoda T, Itai K, Ohsawa M, Tanno K, Sakata K, Omama S, Ishibashi Y, Makita S, Ohta M, Ogasawara K, Komatsu T, Okayama A. Plasma B-type natriuretic peptide as a predictor of cardiovascular events in subjects with atrial fibrillation: a community-based study. *PLoS ONE*. 2013;**8**:e81243

165. Roldan V, Vilchez JA, Manzano-Fernandez S, Jover E, Galvez J, Puche CM, Valdes M, Vicente V, Lip GY, Marin F. Usefulness of N-terminal pro-B-type natriuretic Peptide levels for stroke risk prediction in anticoagulated patients with atrial fibrillation. *Stroke*. 2014;**45**:696-701

166. Shimizu H, Murakami Y, Inoue S, Ohta Y, Nakamura K, Katoh H, Sakne T, Takahashi N, Ohata S, Sugamori T, Ishibashi Y, Shimada T. High plasma brain natriuretic polypeptide level as a marker of risk for thromboembolism in patients with nonvalvular atrial fibrillation. *Stroke*. 2002;**33**:1005-1010

167. Aviles RJ, Martin DO, Apperson-Hansen C, Houghtaling PL, Rautaharju P, Kronmal RA, Tracy RP, Van Wagoner DR, Psaty BM, Lauer MS, Chung MK. Inflammation as a risk factor for atrial fibrillation. *Circulation*. 2003;**108**:3006-3010

168. Dernellis J, Panaretou M. Effects of C-reactive protein and the third and fourth components of complement (C3 and C4) on incidence of atrial fibrillation. *Am J Cardiol*. 2006;**97**:245-248

169. Acevedo M, Corbalan R, Braun S, Pereira J, Gonzalez I, Navarrete C. Biochemical predictors of cardiac

rhythm at 1 year follow-up in patients with non-valvular atrial fibrillation. *J Thromb Haemost*. 2012;**33**:383-388

170. Makrygiannis SS, Margariti A, Rizikou D, Lampakis M, Vangelis S, Ampartzidou OS, Katsifa K, Tselioti P, Foussas SG, Prekates AA. Incidence and predictors of new-onset atrial fibrillation in noncardiac intensive care unit patients. *J Crit Care*. 2014;**29**:697 e691-695

171. Wu N, Xu B, Xiang Y, Wu L, Zhang Y, Ma X, Tong S, Shu M, Song Z, Li Y, Zhong L. Association of inflammatory factors with occurrence and recurrence of atrial fibrillation: a meta-analysis. *Int J Cardiol*. 2013;**169**:62-72

172. Lim HS, Schultz C, Dang J, Alasady M, Lau DH, Brooks AG, Wong CX, Roberts-Thomson KC, Young GD, Worthley MI, Sanders P, Willoughby SR. Time course of inflammation, myocardial injury, and prothrombotic response after radiofrequency catheter ablation for atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2014;**7**:83-89

173. Lin YJ, Tsao HM, Chang SL, Lo LW, Tuan TC, Hu YF, Udyavar AR, Tsai WC, Chang CJ, Tai CT, Lee PC, Suenari K, Huang SY, Nguyen HT, Chen SA. Prognostic implications of the high-sensitive C-reactive protein in the catheter ablation of atrial fibrillation. *Am J Cardiol*. 2010;**105**:495-501

174. Sasaki N, Okumura Y, Watanabe I, Mano H, Nagashima K, Sonoda K, Kogawa R, Ohkubo K, Nakai T, Hirayama A. Increased levels of inflammatory and extracellular matrix turnover biomarkers persist despite reverse atrial structural remodeling during the first year after atrial fibrillation ablation. *J Interv Card Electrophysiol*. 2014;**39**:241-249

175. Sotomi Y, Inoue K, Ito N, Kimura R, Toyoshima Y, Masuda M, Iwakura K, Fujii K. Incidence and risk factors for very late recurrence of atrial fibrillation after radiofrequency catheter ablation. *Europace*. 2013;**15**:1581-1586

176. Hoglund N, Andersson J, Almroth H, Tornvall P, Englund A, Rosenqvist M, Jensen SM, Boman K. The predictive value of C-reactive protein on recurrence of atrial fibrillation after cardioversion with or without treatment with atorvastatin. *Int J Cardiol*. 2013;**167**:2088-2091

177. Deftereos S, Giannopoulos G, Kossyvakis C, Raisakis K, Angelidis C, Efremidis M, Panagopoulou V, Kaoukis A, Theodorakis A, Toli K, Zavitsanakis P, Mantas I, Pyrgakis V, Stefanadis C, Cleman MW. Association of post-cardioversion transcardiac concentration gradient of soluble tumor necrosis factor-related apoptosis-inducing ligand (sTRAIL) and inflammatory biomarkers to atrial fibrillation recurrence. *Clin Biochem*. 2013;**46**:1020-1025

178. Hermida J, Lopez FL, Montes R, Matsushita K, Astor BC, Alonso A. Usefulness of high-sensitivity C-reactive protein to predict mortality in patients with atrial fibrillation (from the Atherosclerosis Risk In

Communities [ARIC] Study). *Am J Cardiol*. 2012;**109**:95-99

179. Lip GY, Patel JV, Hughes E, Hart RG. High-sensitivity C-reactive protein and soluble CD40 ligand as indices of inflammation and platelet activation in 880 patients with nonvalvular atrial fibrillation: relationship to stroke risk factors, stroke risk stratification schema, and prognosis. *Stroke*. 2007;**38**:1229-1237

180. Ederhy S, Di Angelantonio E, Dufaitre G, Meuleman C, Masliah J, Boyer-Chatenet L, Boccara F, Cohen A. C-reactive protein and transesophageal echocardiographic markers of thromboembolism in patients with atrial fibrillation. *Int J Cardiol*. 2012;**159**:40-46

181. Wallentin L, Hijazi Z, Andersson U, Alexander JH, De Caterina R, Hanna M, Horowitz JD, Hylek EM, Lopes RD, Asberg S, Granger CB, Siegbahn A, Aristotle Investigators. Growth differentiation factor 15, a marker of oxidative stress and inflammation, for risk assessment in patients with atrial fibrillation: insights from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial. *Circulation*. 2014;**130**:1847-1858

182. Berkowitsch A, Kuniss M, Greiss H, Wojcik M, Zaltsberg S, Lehinant S, Erkapic D, Pajitnev D, Pitschner HF, Hamm CW, Neumann T. Impact of impaired renal function and metabolic syndrome on the recurrence of atrial fibrillation after catheter ablation: a long term follow-up. *Pacing Clin Electrophysiol*. 2012;**35**:532-543

183. Hijazi Z, Hohnloser SH, Oldgren J, Andersson U, Connolly SJ, Eikelboom JW, Ezekowitz MD, Reilly PA, Siegbahn A, Yusuf S, Wallentin L. Efficacy and safety of dabigatran compared with warfarin in relation to baseline renal function in patients with atrial fibrillation: a RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy) trial analysis. *Circulation*. 2014;**129**:961-970

184. Eikelboom JW, Connolly SJ, Gao P, Paolasso E, De Caterina R, Husted S, O'Donnell M, Yusuf S, Hart RG. Stroke risk and efficacy of apixaban in atrial fibrillation patients with moderate chronic kidney disease. *J Stroke Cerebrovasc Dis*. 2012;**21**:429-435

185. Go AS, Fang MC, Udaltsova N, Chang Y, Pomernacki NK, Borowsky L, Singer DE, Atria Study Investigators. Impact of proteinuria and glomerular filtration rate on risk of thromboembolism in atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. *Circulation*. 2009;**119**:1363-1369

186. Hohnloser SH, Hijazi Z, Thomas L, Alexander JH, Amerena J, Hanna M, Keltai M, Lanas F, Lopes RD, Lopez-Sendon J, Granger CB, Wallentin L. Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial. *Eur Heart J*. 2012;**33**:2821-2830

187. Singer DE, Chang Y, Borowsky LH, Fang MC, Pomernacki NK, Udaltsova N, Reynolds K, Go AS. A new risk scheme to predict ischemic stroke and other thromboembolism in atrial fibrillation: the ATRIA study stroke risk score. *J Am Heart Assoc*. 2013;**2**:e000250

188. McManus DD, Corteville DC, Shlipak MG, Whooley MA, Ix JH. Relation of kidney function and albuminuria with atrial fibrillation (from the Heart and Soul Study). *Am J Cardiol*. 2009;**104**:1551-1555

189. Xu D, Murakoshi N, Sairenchi T, Irie F, Igarashi M, Nogami A, Tomizawa T, Yamaguchi I, Yamagishi K, Iso H, Ota H, Aonuma K. Anemia and Reduced Kidney Function as Risk Factors for New Onset of Atrial Fibrillation (from the Ibaraki Prefectural Health Study). *Am J Cardiol*. 2015;**115**:328-333

190. Deo R, Katz R, Kestenbaum B, Fried L, Sarnak MJ, Psaty BM, Siscovick DS, Shlipak MG. Impaired kidney function and atrial fibrillation in elderly subjects. *J Card Fail*. 2010;**16**:55-60

191. Sadanaga T, Sadanaga M, Ogawa S. Evidence that D-dimer levels predict subsequent thromboembolic and cardiovascular events in patients with atrial fibrillation during oral anticoagulant therapy. *J Am Coll Cardiol*. 2010;**55**:2225-2231

192. Christersson C, Wallentin L, Andersson U, Alexander JH, Ansell J, De CR, Gersh BJ, Granger CB, Hanna M, Horowitz JD, Huber K, Husted S, Hylek EM, Lopes RD, Siegbahn A. D-dimer and risk of thromboembolic and bleeding events in patients with atrial fibrillation--observations from the ARISTOTLE trial. *J Thromb Haemost*. 2014;**12**:1401-1412

193. Mahe I, Drouet L, Simoneau G, Minh-Muzeaux S, Caulin C, Bergmann JF. D-dimer can predict survival in patients with chronic atrial fibrillation. *Blood Coagul Fibrinolysis*. 2004;**15**:413-417

194. Mahe I, Bergmann JF, Chassany O, dit-Sollier CB, Simoneau G, Drouet L. A multicentric prospective study in usual care: D-dimer and cardiovascular events in patients with atrial fibrillation. *Thromb Res*. 2012;**129**:693-699

195. Nozawa T, Inoue H, Hirai T, Iwasa A, Okumura K, Lee JD, Shimizu A, Hayano M, Yano K. D-dimer level influences thromboembolic events in patients with atrial fibrillation. *Int J Cardiol*. 2006;**109**:59-65

196. Vene N, Mavri A, Kosmelj K, Stegnar M. High D-dimer levels predict cardiovascular events in patients with chronic atrial fibrillation during oral anticoagulant therapy. *Thromb Haemost*. 2003;**90**:1163-1172

197. Habara S, Dote K, Kato M, Sasaki S, Goto K, Takemoto H, Hasegawa D, Matsuda O. Prediction of left atrial appendage thrombi in non-valvular atrial fibrillation. *Eur Heart J*. 2007;**28**:2217-2222

198. Miceli A, Romeo F, Glauber M, de Siena PM, Caputo M, Angelini GD. Preoperative anemia increases mortality and postoperative morbidity after cardiac surgery. *J Cardiothorac Surg*. 2014;**9**:137

199. Sharma S, Gage BF, Deych E, Rich MW. Anemia: an independent predictor of death and hospitalizations among elderly patients with atrial fibrillation. *Am Heart J*. 2009;**157**:1057-1063

200. Abdelhafiz AH, Myint MP, Tayek JA, Wheeldon NM. Anemia, hypoalbuminemia, and renal impairment as predictors of bleeding complications in patients receiving anticoagulation therapy for nonvalvular atrial fibrillation: a secondary analysis. *Clin Ther*. 2009;**31**:1534-1539

201. Fang MC, Go AS, Chang Y, Borowsky LH, Pomernacki NK, Udaltsova N, Singer DE. A new risk scheme to predict warfarin-associated hemorrhage: The ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study. *J Am Coll Cardiol*. 2011;**58**:395-401

202. Katoh H, Nozue T, Asada T, Nakashima K, Kimura Y, Ito S, Nakata S, Iwaki T, Michishita I. Frequency and predictors of bleeding complications associated with anti-coagulant therapy using dabigatran in Japanese patients with atrial fibrillation. *Am J Cardiovasc Dis*. 2014;**4**:70-78

203. Lip GY, Banerjee A, Lagrenade I, Lane DA, Taillandier S, Fauchier L. Assessing the risk of bleeding in patients with atrial fibrillation: the Loire Valley Atrial Fibrillation project. *Circ Arrhythm Electrophysiol*. 2012;**5**:941-948

204. Benjamin EJ, Rice KM, Arking DE, Pfeufer A, van Noord C, Smith AV, Schnabel RB, Bis JC, Boerwinkle E, Sinner MF, Dehghan A, Lubitz SA, D'Agostino RB, Sr., Lumley T, Ehret GB, Heeringa J, Aspelund T, Newton-Cheh C, Larson MG, Marciante KD, Soliman EZ, Rivadeneira F, Wang TJ, Eiriksdottir G, Levy D, Psaty BM, Li M, Chamberlain AM, Hofman A, Vasan RS, Harris TB, Rotter JI, Kao WH, Agarwal SK, Stricker BH, Wang K, Launer LJ, Smith NL, Chakravarti A, Uitterlinden AG, Wolf PA, Sotoodehnia N, Kottgen A, van Duijn CM, Meitinger T, Mueller M, Perz S, Steinbeck G, Wichmann HE, Lunetta KL, Heckbert SR, Gudnason V, Alonso A, Kaab S, Ellinor PT, Witteman JC. Variants in ZFHX3 are associated with atrial fibrillation in individuals of European ancestry. *Nat Genet*. 2009;**41**:879-881

205. Gudbjartsson DF, Arnar DO, Helgadottir A, Gretarsdottir S, Holm H, Sigurdsson A, Jonasdottir A, Baker A, Thorleifsson G, Kristjansson K, Palsson A, Blondal T, Sulem P, Backman VM, Hardarson GA, Palsdottir E, Helgason A, Sigurjonsdottir R, Sverrisson JT, Kostulas K, Ng MC, Baum L, So WY, Wong KS, Chan JC, Furie KL, Greenberg SM, Sale M, Kelly P, MacRae CA, Smith EE, Rosand J, Hillert J, Ma RC, Ellinor PT, Thorgeirsson G, Gulcher JR, Kong A, Thorsteinsdottir U, Stefansson K. Variants conferring risk of atrial fibrillation on chromosome 4q25. *Nature*. 2007;**448**:353-357

206. Han HG, Wang HS, Yin Z, Jiang H, Fang M, Han J. KCNE1 112G>a polymorphism and atrial fibrillation risk: a meta-analysis. *Genet Mol Res*. 2014;**13**:8367-8377

207. Jabbari J, Olesen MS, Yuan L, Nielsen JB, Liang B, Macri V, Christophersen IE, Nielsen N, Sajadieh A, Ellinor PT, Grunnet M, Haunso S, Holst AG, Svendsen JH, Jespersen T. Common and Rare Variants in

SCN10A Modulate the Risk of Atrial Fibrillation. *Circ Cardiovasc Genet*. 2014;10.1161/CIRCGENETICS.113.000442

208. Ritchie MD, Denny JC, Zuvich RL, Crawford DC, Schildcrout JS, Bastarache L, Ramirez AH, Mosley JD, Pulley JM, Basford MA, Bradford Y, Rasmussen LV, Pathak J, Chute CG, Kullo IJ, McCarty CA, Chisholm RL, Kho AN, Carlson CS, Larson EB, Jarvik GP, Sotoodehnia N, Manolio TA, Li R, Masys DR, Haines JL, Roden DM. Genome- and phenome-wide analyses of cardiac conduction identifies markers of arrhythmia risk. *Circulation*. 2013;**127**:1377-1385

209. Smith JG, Almgren P, Engstrom G, Hedblad B, Platonov PG, Newton-Cheh C, Melander O. Genetic polymorphisms for estimating risk of atrial fibrillation: a literature-based meta-analysis. *J Intern Med*. 2012;**272**:573-582

210. Virani SS, Brautbar A, Lee VV, Elayda M, Sami S, Nambi V, Frazier L, Wilson JM, Willerson JT, Boerwinkle E, Ballantyne CM. Usefulness of single nucleotide polymorphism in chromosome 4q25 to predict in-hospital and long-term development of atrial fibrillation and survival in patients undergoing coronary artery bypass grafting. *Am J Cardiol*. 2011;**107**:1504-1509

211. Cao YY, Ma F, Wang Y, Wang DW, Ding H. Rs2200733 and rs10033464 on chromosome 4q25 confer risk of cardioembolic stroke: an updated meta-analysis. *Mol Biol Rep*. 2013;**40**:5977-5985

212. Gretarsdottir S, Thorleifsson G, Manolescu A, Styrkarsdottir U, Helgadottir A, Gschwendtner A, Kostulas K, Kuhlenbaumer G, Bevan S, Jonsdottir T, Bjarnason H, Saemundsdottir J, Palsson S, Arnar DO, Holm H, Thorgeirsson G, Valdimarsson EM, Sveinbjornsdottir S, Gieger C, Berger K, Wichmann HE, Hillert J, Markus H, Gulcher JR, Ringelstein EB, Kong A, Dichgans M, Gudbjartsson DF, Thorsteinsdottir U, Stefansson K. Risk variants for atrial fibrillation on chromosome 4q25 associate with ischemic stroke. *Ann Neurol*. 2008;**64**:402-409

213. Wnuk M, Pera J, Jagiella J, Szczygiel E, Ferens A, Spisak K, Wolkow P, Kmiec M, Burkot J, Chrzanowska-Wasko J, Turaj W, Slowik A. The rs2200733 variant on chromosome 4q25 is a risk factor for cardioembolic stroke related to atrial fibrillation in Polish patients. *Neurol Neurochir Pol*. 2011;**45**:148-152

214. Malik R, Bevan S, Nalls MA, Holliday EG, Devan WJ, Cheng YC, Ibrahim-Verbaas CA, Verhaaren BF, Bis JC, Joon AY, de Stefano AL, Fornage M, Psaty BM, Ikram MA, Launer LJ, van Duijn CM, Sharma P, Mitchell BD, Rosand J, Meschia JF, Levi C, Rothwell PM, Sudlow C, Markus HS, Seshadri S, Dichgans M, Wellcome Trust Case Control C. Multilocus genetic risk score associates with ischemic stroke in case-control and prospective cohort studies. *Stroke*. 2014;**45**:394-402

215. Shi L, Li C, Wang C, Xia Y, Wu G, Wang F, Xu C, Wang P, Li X, Wang D, Xiong X, Bai Y, Liu M, Liu J, Ren X, Gao L, Wang B, Zeng Q, Yang B, Ma X, Yang Y, Tu X, Wang QK. Assessment of association

of rs2200733 on chromosome 4q25 with atrial fibrillation and ischemic stroke in a Chinese Han population. *Hum Genet*. 2009;**126**:843-849