2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

Kirchhof, Paulus; Benussi, Stefano; Kotecha, Dipak; Ahlsson, Anders; Atar, Dan; Casadei, Barbara; Castella, Manuel; Diener, Hans-Christoph; Heidbuchel, Hein; Hendriks, Jeroen; Hindricks, Gerhard; Manolis, Antonis S.; Oldgren, Jonas; Popescu, Bogdan Alexandru; Schotten, Ulrich; Van Putte, Bart; Vardas, Panagiotis; Agewall, Stefan; Camm, John; Baron Esquivias, Gonzalo

DOI:
10.1093/europace/euw295

Document Version
Peer reviewed version

Citation for published version (Harvard):
Kirchhof, P, Benussi, S, Kotecha, D, Ahlsson, A, Atar, D, Casadei, B, Castella, M, Diener, H-C, Heidbuchel, H, Hendriks, J, Hindricks, G, Manolis, AS, Oldgren, J, Popescu, BA, Schotten, U, Van Putte, B, Vardas, P, Agewall, S, Camm, J, Baron Esquivias, G, Budts, W, Carerj, S, Casselman, F, Coca, A, De Caterina, R, Deftereos, S, Dobrev, D, Ferro, JM, Filippatos, G, Fitzsimons, D, Gorenek, B, Guenoun, M, Hohnloser, SH, Kolh, P, Lip, GYH, Manolis, A, McMurray, J, Ponikowski, P, Rosenhek, R, Ruschitzka, F, Savelieva, I, Sharma, S, Suwalski, P, Tamargo, JL, Taylor, CJ, Van Gelder, IC, Voors, AA, Windecker, S, Zamorano, JL & Zeppenfeld, K 2016, '2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS', *Europace*, vol. 18, no. 11, pp. 1609-1678. https://doi.org/10.1093/europace/euw295

2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

Kirchhof, Paulus; Benussi, Stefano; Kotecha, Dipak; Ahlsson, Anders; Atar, Dan; Casadei, Barbara; Castella, Manuel; Diener, Hans-Christoph; Heidbuchel, Hein; Hendriks, Jeroen; Hindricks, Gerhard; Manolis, Antonis S; Oldgren, Jonas; Popescu, Bogdan Alexandru; Schotten, Ulrich; Van Putte, Bart; Vardas, Panagiotis; Authors/Task Force Members

DOI:
10.1093/europace/euw295

Document Version
Peer reviewed version

doi: ...

ESC GUIDELINES

2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC)

Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC

Endorsed by the European Stroke Organisation (ESO)

Authors/Task Force Members: Paulus Kirchhof* (Chairperson) (UK/Germany), Stefano Benussi*[1] (Co-Chairperson) (Switzerland), Dipak Kotecha (UK), Anders Ahlsson[1] (Sweden), Dan Atar (Norway), Barbara Casadei (UK), Manuel Castella Pericas[1] (Spain), Hans-Christoph Diener[2] (Germany), Hein Heidbuchel (Belgium), Jeroen Hendriks (The Netherlands), Gerhard Hindricks (Germany), Antonis S. Manolis (Greece), Jonas Oldgren (Sweden), Bogdan Alexandru Popescu (Romania), Ulrich Schotten (The Netherlands), Bart Van Putte[1] (The Netherlands), Panagiotis Vardas (Greece)

Document Reviewers: Stefan Agewall (CPG Review Coordinator) (Norway), John Camm (CPG Review Coordinator) (UK), Gonzalo Baron Esquivias (Spain), Werner Budts (Belgium), Scipione Carerj (Italy), Filip Casselman (Belgium), Antonio Coca (Spain), Raffaele De Caterina (Italy), Spiridon Deftereos (Greece), Dobromir Dobrev (Germany), José M. Ferro (Portugal), Gerasimos Filippatos (Greece), Donna Fitzsimons (UK), Bulent Gorenek (Turkey), Maxine Guenoun (France), Stefan H. Hohnloser (Germany), Philippe Kolh (Belgium), Gregory Y. H. Lip (UK), Athanasios Manolis (Greece), John Mc Murray (UK), Piotr Ponikowski (Poland), Raphael Rosenhek (Austria), Frank Ruschitzka (Switzerland), Irina Savelieva (UK), Sanjay Sharma (UK), Piotr Suwalski (Poland), Juan Luis Tamargo (Spain), Clare J. Taylor (UK), Isabelle C. Van Gelder (The Netherlands), Adriaan A. Voors (The Netherlands), Stephan Windecker (Switzerland), Jose Luis Zamorano (Spain), Katja Zeppenfeld (The Netherlands)

ESC Committee for Practice Guidelines (CPG) and National Cardiac Society Reviewers can be found in the Appendix

The disclosure forms of all experts involved in the development of these guidelines are available on the ESC website www.escardio.org/guidelines

Keywords:
Guidelines - Atrial fibrillation - Anticoagulation - Vitamin K antagonists - Non vitamin-K-antagonist oral anticoagulants - Left atrial appendage occlusion - Rate control - Cardioversion - Rhythm control - Antiarrhythmic drugs - Upstream therapy - Catheter ablation - AF surgery - Valve repair - Pulmonary vein isolation - Left atrial ablation

* Corresponding authors: Paulus Kirchhof, Institute of Cardiovascular Sciences, University of Birmingham, SWBH and UHB NHS trusts, IBR, Room 136, Wolfson Drive, Birmingham B152TT, United Kingdom. Tel: +44 121 4147042, E-mail: p.kirchhof@bham.ac.uk
Stefano Benussi, Department of Cardiovascular Surgery, University Hospital Zurich, Rämistrasse 100, 8091 Zürich, Switzerland Tel: +41(0)788933835, E-mail: stefano.benussi@usz.ch

[1]**Representing the European Association for Cardio-Thoracic Surgery (EACTS);** [2]**Representing the**

European Stroke Association (ESO)

ESC entities having participated in the development of this document:
Associations: European Association of Cardiovascular Imaging (EACVI), European Heart Rhythm Association (EHRA), Heart Failure Association (HFA).
Councils: Council on Cardiovascular Nursing and Allied Professions
Working Groups: Cardiac Cellular Electrophysiology, Cardiovascular Pharmacotherapy

Disclaimer. The ESC Guidelines represent the views of the ESC and were produced after careful consideration of the scientific and medical knowledge and the evidence available at the time of their publication. The ESC is not responsible in the event of any contradiction, discrepancy and/or ambiguity between the ESC Guidelines and any other official recommendations or guidelines issued by the relevant public health authorities, in particular in relation to good use of healthcare or therapeutic strategies. Health professionals are encouraged to take the ESC Guidelines fully into account when exercising their clinical judgment, as well as in the determination and the implementation of preventive, diagnostic or therapeutic medical strategies; however, the ESC Guidelines do not override, in any way whatsoever, the individual responsibility of health professionals to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient and, where appropriate and/or necessary, the patient's caregiver. Nor do the ESC Guidelines exempt health professionals from taking into full and careful consideration the relevant official updated recommendations or guidelines issued by the competent public health authorities, in order to manage each patient's case in light of the scientifically accepted data pursuant to their respective ethical and professional obligations. It is also the health professional's responsibility to verify the applicable rules and regulations relating to drugs and medical devices at the time of prescription.

Table of Contents

Abbreviations and acronyms

ABC	age, biomarkers, clinical history
ACE	angiotensin-converting enzyme
ACS	acute coronary syndromes
AF	atrial fibrillation
AFFIRM	Atrial Fibrillation Follow-up Investigation of Rhythm Management
AFNET	German Competence NETwork on Atrial Fibrillation
AHRE	atrial high rate episodes
ARB	angiotensin receptor blocker
ARISTOTLE	Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation
ARNI	angiotensin receptor neprilysin inhibition
ATRIA	AnTicoagulation and Risk factors In Atrial fibrillation
AXAFA	Anticoagulation using the direct factor Xa inhibitor apixaban during Atrial Fibrillation catheter Ablation: Comparison to vitamin K antagonist therapy
BAFTA	Birmingham Atrial Fibrillation Treatment of the Aged Study
BMI	body mass index
bpm	beats per minute
CABANA	Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation Trial
CAD	coronary artery disease
CHA_2DS_2-VASc	Congestive Heart failure, hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female)
$CHADS_2$	Cardiac failure, Hypertension, Age, Diabetes, Stroke (Doubled)
CI	confidence interval
CKD	chronic kidney disease
CrCl	creatinine clearance
CT	computed tomography
DIG	Digitalis Investigation Group
EACTS	European Association for Cardio-Thoracic Surgery
EAST	Early treatment of Atrial fibrillation for Stroke prevention Trial
ECG	electrocardiogram/electrocardiography
EHRA	European Heart Rhythm Association
ENGAGE AF-TIMI 48	Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48
EORP	EURObservational Research Programme
FAST	Atrial Fibrillation Catheter Ablation vs Surgical Ablation Treatment
FEV1	forced expiratory volume in 1 second
GDF-15	growth differentiation factor 15
GFR	glomerular filtration rate
GFR	glomerular filtration rate
GUCH	grown up congenital heart disease
HARMONY	A Study to Evaluate the Effect of Ranolazine and Dronedarone When Given Alone and in Combination in Patients With Paroxysmal Atrial Fibrillation
HAS-BLED	hypertension, abnormal renal/liver function (1 point each), stroke, bleeding history or predisposition, labile INR, elderly (>65 years), drugs/alcohol concomitantly (1 point each)
HFmrEF	heart failure with mid-range ejection fraction
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HR	hazard ratio
INR	international normalized ratio
LA	left atrium/atrial
LAA	left atrial appendage
LAAOS	Left Atrial Appendage Occlusion Study
LV	left ventricular
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
MANTRA-PAF	Medical ANtiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation
MERLIN	Metabolic Efficiency With Ranolazine for Less Ischemia in Non ST-Elevation Acute Coronary Syndrome
MRI	magnetic resonance imaging

NOAC	non-vitamin K antagonist oral anticoagulant
NYHA	New York Heart Association
OAC	oral anticoagulation/oral anticoagulant
OR	odds ratio
ORBIT	Outcomes Registry for Better Informed Treatment of Atrial Fibrillation
PCI	percutaneous coronary intervention
PREVAIL	Prospective Randomized Evaluation of the Watchman LAA Closure Device In Patients with AF Versus Long Term Warfarin Therapy trial
PROTECT AF	Watchman Left Atrial Appendage System for Embolic Protection in Patients With AF trial
PVI	pulmonary vein isolation
RACE	Rate Control Efficacy in Permanent Atrial Fibrillation
RATE-AF	Rate Control Therapy Evaluation in Permanent Atrial Fibrillation
RCT	randomized controlled trial
RE-CIRCUIT	Randomized Evaluation of dabigatran etexilate Compared to warfarin in pulmonaRy vein ablation: assessment of different peri-proCedUral anticoagulation sTrategies
RE-LY	Randomized Evaluation of Long-Term Anticoagulation Therapy
ROCKET-AF	Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation
RR	risk ratio
SD	standard deviation
SPAF	Stroke Prevention in Atrial Fibrillation
TIA	transient ischaemic attack
TIMI	Thrombolysis In Myocardial Infarction
TOE	transoesophageal echocardiography
TTR	time in therapeutic range
UFH	unfractionated heparin
US	United States
VKA	vitamin K antagonist
WOEST	What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing
WPW	Wolff-Parkinson-White syndrome

1 Preamble

Guidelines summarize and evaluate all available evidence on a particular issue at the time of the writing process, with the aim of assisting health professionals in selecting the best management strategies for an individual patient with a given condition, taking into account the impact on outcome, as well as the risk–benefit ratio of particular diagnostic or therapeutic means. Guidelines and recommendations should help health professionals to make decisions in their daily practice. However, the final decisions concerning an individual patient must be made by the responsible health professional(s) in consultation with the patient and caregiver as appropriate.

A great number of Guidelines have been issued in recent years by the European Society of Cardiology (ESC) and by the European Association for Cardio-Thoracic Surgery (EACTS), as well as by other societies and organisations. Because of the impact on clinical practice, quality criteria for the development of guidelines have been established in order to make all decisions transparent to the user. The recommendations for formulating and issuing ESC Guidelines can be found on the ESC website (http://www.escardio.org/Guidelines-&-Education/Clinical-Practice-Guidelines/Guidelines-development/Writing-ESC-Guidelines). ESC Guidelines represent the official position of the ESC on a given topic and are regularly updated.

Members of this Task Force were selected by the ESC, including representation from the European Heart Rhythm Association (EHRA), and EACTS as well as by the European Stroke Organisation (ESO) to represent professionals involved with the medical care of patients with this pathology. Selected experts in the field undertook a comprehensive review of the published evidence for management (including diagnosis, treatment, prevention and rehabilitation) of a given condition according to ESC Committee for Practice Guidelines (CPG) policy and approved by the EACTS and ESO. A critical evaluation of diagnostic and therapeutic procedures was performed, including assessment of the risk–benefit ratio. Estimates of expected health outcomes for larger populations were included, where data exist. The level of evidence and the strength of the recommendation of particular management options were weighed and graded according to predefined scales, as outlined in *Tables 1* and *2*.

The experts of the writing and reviewing panels provided declaration of interest forms for all relationships that might be perceived as real or potential sources of conflicts of interest. These forms were compiled into one file and can be found on the ESC website (http://www.escardio.org/guidelines). Any changes in declarations of interest that arise during the writing period must be notified to the ESC and EACTS and updated. The Task Force received its entire financial support from the ESC and EACTS without any involvement from the healthcare industry.

The ESC CPG supervises and coordinates the preparation of new Guidelines produced by task forces, expert groups or consensus panels. The Committee is also responsible for the endorsement process of these Guidelines. The ESC Guidelines undergo extensive review by the CPG and external experts, and in this case by EACTS and ESO-appointed experts. After appropriate revisions the Guidelines are approved by all the experts involved in the Task Force. The finalized document is approved by the CPG, EACTS and ESO for publication in the European Heart Journal, Europace, and in the European Journal of Cardio-Thoracic Surgery as well as in the International Journal of Stroke (TBC). The Guidelines were developed after careful consideration of the scientific and medical knowledge and the evidence available at the time of their dating.

The task of developing ESC and EACTS Guidelines covers not only integration of the most recent research, but also the creation of educational tools and implementation programmes for the recommendations. To implement the guidelines, condensed pocket guideline versions, summary slides, booklets with essential messages, summary cards for non-specialists and an electronic version for digital applications (smartphones, etc.) are produced. These versions are abridged and thus, if needed, one should always refer to the full text version, which is freely available on the ESC website. The National Societies of the ESC are encouraged to endorse, translate and implement all ESC Guidelines. Implementation programmes are needed because it has been shown that the outcome of disease may be favourably influenced by the thorough application of clinical recommendations.

Surveys and registries are needed to verify that real-life daily practice is in keeping with what is recommended in the guidelines, thus completing the loop between clinical research, writing of guidelines, disseminating them and implementing them into clinical practice.

Health professionals are encouraged to take the ESC and EACTS Guidelines fully into account when exercising their clinical judgment, as well as in the determination and the implementation of preventive, diagnostic or therapeutic medical strategies. However, the ESC and EACTS Guidelines do not override in any way whatsoever the individual responsibility of health professionals to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient and the patient's caregiver where appropriate and/or necessary. It is also the health professional's responsibility to verify the rules and regulations applicable to drugs and devices at the time of prescription.

Table 1 Classes of recommendations

Table 1: Classes of Recommendations		
Classes of Recommendations	**Definition**	**Suggested wording to use**
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

Table 2 Levels of evidence

Level of Evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of Evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of Evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

2 Introduction

Despite good progress in the management of patients with atrial fibrillation (AF), this arrhythmia remains one of the major causes of stroke, heart failure, sudden death, and cardiovascular morbidity in the world. Furthermore, the number of patients with AF is predicted to rise steeply in the coming years. To meet the growing demand for effective care of patients with AF, new information is continually generated and published, and the last few years have seen substantial progress. It therefore seems timely to publish this 2nd edition of the ESC guidelines on AF.

Reflecting the multidisciplinary input into the management of patients with AF, the Task Force includes cardiologists with varying subspecialty expertise, cardiac surgeons, stroke neurologists, and specialist nurses amongst its members. Supplementing the evidence review as outlined in the preamble, this task force identified three PICOT questions on relevant topics for the guideline. The ESC commissioned external systematic reviews to answer these three questions. These reviews informed specific recommendations.

Further to adhering to the standards for generating recommendations that is common to all ESC guidelines (see preamble), this task force discussed each draft recommendation during web-based conference calls dedicated to specific chapters, followed by consensus modifications and an online vote on each recommendation. Only recommendations that were supported by at least 75% of the task force members were included in the guideline.

We hope that this guideline will help to deliver good care to all patients with AF based on the current state-of-the-art evidence in 2016.

3 Epidemiology and impact for patients

3.1. Incidence and prevalence of atrial fibrillation

In 2010, the estimated numbers of men and women with atrial fibrillation (AF) worldwide were 20.9 million and 12.6 million, respectively, with higher incidence and prevalence rates in developed countries.[1, 2] One in four middle-aged adults in Europe and the United States (US) will develop AF.[3-5] By 2030, 14–17 million AF patients are anticipated in the European Union, with 120,000–215,000 newly diagnosed patients per year.[2, 6, 7] Estimates suggest an AF prevalence of approximately 3% in adults age 20 years or older,[8, 9] with more AF in elderly persons[1] and in patients with conditions such as hypertension, heart failure, coronary artery disease (CAD), valvular heart disease, diabetes mellitus, and chronic kidney disease (CKD).[7, 10-15] The increase in AF prevalence can be attributed to better detection of silent AF[16-18] and increasing age and conditions predisposing to AF.[19]

3.2. Morbidity, mortality, and healthcare burden of atrial fibrillation

AF is independently associated with a twofold increased risk of all-cause mortality in women and a 1.5-fold increase in men[20-22] (*Table 3*). Death due to stroke can largely be mitigated by anticoagulation, while other cardiovascular deaths, for example due to heart failure and sudden death, remain common even in AF patients treated according to the current evidence-base.[23] AF is also associated with increased morbidity, such as heart failure and stroke.[21, 24, 25] Contemporary studies show that 20–30% of patients with an ischaemic stroke have AF diagnosed before, during, or after the initial event.[17, 26, 27] White matter lesions in the brain, cognitive impairment,[28-30] decreased quality of life,[31, 32] and depressed mood[33] are common in AF patients, and between 10% and 40% of AF patients are hospitalized each year.[23, 34, 35]

The direct costs of AF already amount to approximately 1% of total healthcare spending in the UK, and between $6.0 and $26.0 billion in the US for 2008,[36, 37] driven by AF-related complications (e.g. stroke) and AF-related treatment costs (e.g. hospitalizations). These costs will increase dramatically unless AF is prevented and treated in a timely and effective manner.

Table 3 Cardiovascular morbidity and mortality associated with AF

Event	Association with AF
Death	Increased mortality, especially cardiovascular mortality due to sudden death, heart failure, or stroke
Stroke	20–30% of all strokes are due to AF. A growing number of patients with stroke are diagnosed with 'silent', paroxysmal AF
Hospitalizations	10–40% of AF patients are hospitalized every year
Quality of life	Quality of life is impaired in AF patients independent of other cardiovascular conditions
LV dysfunction and heart failure	LV dysfunction is found in 20–30% of all AF patients. AF causes or aggravates LV dysfunction in many AF patients, while others have completely preserved LV function despite long-standing AF
Cognitive decline and vascular dementia	Cognitive decline and vascular dementia increase even in anticoagulated patients. Brain white matter lesions are more common in AF patients than in patients without AF

AF = atrial fibrillation; LV = left ventricular.

3.3. Impact of evidence-based management on outcomes in atrial fibrillation patients

Figure 1 depicts the major milestones in the management of AF. Despite these advances, substantial morbidity remains. Oral anticoagulation (OAC) with vitamin K antagonists (VKAs) or non-VKA oral anticoagulants (NOACs) markedly reduces stroke and mortality in AF patients.[38, 39] Other interventions such as rhythm control and rate control improve AF-related symptoms and may preserve cardiac function, but have not demonstrated a reduction in long-term morbidity or mortality.[40, 41]

Figure 1 Timeline of major landmarks in AF management, including treatment of concomitant conditions and prevention (green), anticoagulation (blue), rate and rhythm control (orange and red), and surgical therapy (purple).
ACEi = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; LVH = left ventricular hypertrophy; NOAC = non-vitamin K antagonist oral anticoagulant; PUFA = polyunsaturated fatty acid; PVI = pulmonary vein isolation; QoL = quality of life; RACE = Rate Control Efficacy in Permanent Atrial Fibrillation; RF = radiofrequency; SR = sinus rhythm; VKA = vitamin K antagonist.

In contemporary, well-controlled, randomized clinical trials in AF, the average annual stroke rate is about 1.5% and the annualized death rate is around 3%.[40] In real life, the annual mortality can be different (both higher and lower).[42] A minority of these deaths are related to stroke, while sudden cardiac death and death from progressive heart failure are more frequent, emphasizing the need for interventions beyond anticoagulation.[43, 44] Furthermore, AF is also associated with high rates of hospitalization, commonly for AF management, but often also for heart failure, myocardial infarction, and treatment-associated bleeding.[34, 45]

3.4. Gender

In both developed and developing countries, the age-adjusted incidence and prevalence of AF are lower in women, while the risk of death in women with AF is similar to or higher than that in men with AF.[1, 46, 47] Female AF patients who have additional stroke risk factors (particularly older age) are also at greater risk than men of having a stroke,[48, 49] even those anticoagulated with warfarin[50] (see Chapter 8 for details). Women with diagnosed AF can be more symptomatic than men and are typically older with more comorbidities.[51, 52] Bleeding risk on anticoagulation is similar in both sexes,[49, 50, 53] but women appear less likely to receive specialist care and rhythm control therapy,[54] while the outcomes of catheter ablation or AF surgery are comparable to those in men.[55, 56] These observations highlight the need to offer effective diagnostic tools and therapeutic management equally in women and men.

Recommendations relating to gender

Recommendations	Class [a]	Level [b]	Refs [c]
AF clinicians must offer effective diagnostic tools and therapeutic management to women and men equally to prevent stroke and death	I	A	39, 46, 57
Catheter or surgical ablation techniques should be regarded as equally effective in women and men	IIa	B	55, 56

AF = atrial fibrillation
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

4 Pathophysiological and genetic aspects that guide management

4.1. Genetic predisposition

AF, especially early-onset AF, has a strong heritable component, independent of concomitant cardiovascular conditions.[58, 59] A few young AF patients suffer from inherited cardiomyopathies or channelopathies mediated by disease-causing mutations. These monogenic diseases also convey a risk for sudden death (see Chapter 5). Up to one-third of AF patients carry common genetic variants that predispose to AF, albeit with a relatively low added risk. At least 14 of these common variants, often single nucleotide polymorphisms, are known to increase the risk of prevalent AF in populations.[60-62] The most important variants are located close to the paired-like homeodomain transcription factor 2 gene on chromosome 4q25.[63, 64] These variants modify the risk of AF up to sevenfold.[64] Several of the AF risk variants are also associated with cardioembolic or ischaemic stroke, possibly due to silent AF (see section 4.1).[62, 65, 66] Changes in atrial action potential characteristics,[67-70] atrial remodelling, and modified penetration of rare gene defects[61] have been suggested as potential mechanisms mediating increased AF risk in carriers of common gene variants. Genetic variants could in the future become useful for patient selection of rhythm control strategies,[71-73] but it is currently unknown whether common gene variants differentially affect the efficacy of antiarrhythmic drugs or rate control medication.[74] While genomic analysis may provide an opportunity to improve diagnosis and management of AF in the future,[75, 76] routine genetic testing for common gene variants associated with AF cannot be recommended at present.[77]

4.2. Mechanisms leading to atrial fibrillation

4.2.1. Remodelling of atrial structure and ion channel function

External stressors such as structural heart disease, hypertension, possibly diabetes, but also AF itself induce a slow but progressive process of structural remodelling in the atria (*Figure 2*). Activation of fibroblasts, enhanced connective tissue deposition, and fibrosis are the hallmarks of this process.[78-80] In addition, atrial fatty infiltration, inflammatory infiltrates, myocyte hypertrophy, necrosis, and amyloidosis are found in AF patients with concomitant conditions predisposing to AF.[81-84] Structural remodelling results in electrical dissociation between muscle bundles and local conduction heterogeneities,[85] favouring reentry and perpetuation of the arrhythmia.[86] In many patients, the structural remodelling process occurs before the onset of AF.[78] As some of the structural remodelling will be irreversible, early initiation of treatment seems desirable.[87] *Table 4* gives an overview of the most relevant pathophysiological alterations in atrial tissue associated with AF, and lists corresponding clinical conditions that can contribute to these changes.

The functional and structural changes in atrial myocardium and stasis of blood, especially in the left atrial appendage (LAA), generate a prothrombotic milieu. Furthermore, even short episodes of AF lead to myocardial damage and expression of prothrombotic factors on the atrial endothelial surface, and activation of platelets and inflammatory cells, and contribute to a generalized prothrombotic state.[88, 89] The atrial and systemic activation of the coagulation system can partially explain why short episodes of AF convey a long-term stroke risk.

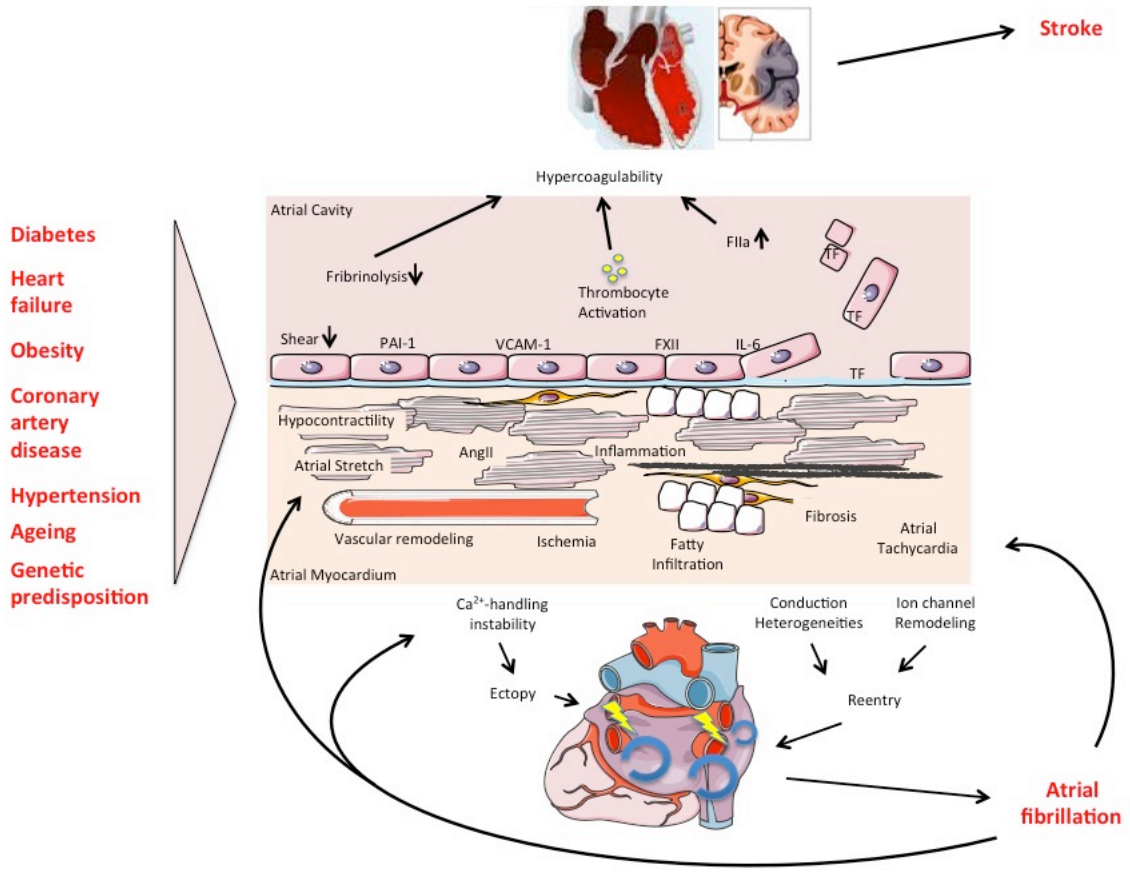


Figure 2 Major mechanisms causing AF that can be considered when guiding therapy. The various aetiological factors (left) cause a complex array of pathophysiological changes in the atria, including stretch-induced atrial fibrosis, hypocontractility, fatty infiltration, inflammation, vascular remodelling, ischaemia, ion channel dysfunction, and Ca^{2+}-instability. These changes enhance both ectopy and conduction disturbances, increasing the propensity of the atria to develop or maintain AF. At the same time, some of these alterations are involved in the occurrence of the hypercoagulable state associated with AF. For example, hypocontractility reduces local endothelial shear stress, which increases PAI-1 expression, and ischaemia-induced inflammation enhances the expression of endothelial adhesion molecules or promotes shedding of endothelial cells, resulting in tissue factor exposure to the blood stream. These changes contribute to the thrombogenic milieu in the atria of AF patients. AF in itself can aggravate many of the mechanisms shown, which may explain the progressive nature of the arrhythmia.
AngII = angiotensin II; TF = tissue factor; FXII = factor XII; IL-6 = interleukin 6; PAI-1 = plasminogen activator inhibitor 1; VCAM-1 = vascular cell adhesion molecule 1.

Table 4 Pathophysiological alterations in atrial tissue associated with AF and clinical conditions that could contribute to such alterations

Pathophysiological alteration	Clinical conditions contributing to the alteration	Proarrhythmic mechanism/ functional consequence	References
Changes of the extracellular matrix, fibroblast function, and fat cells			
Interstitial and replacement fibrosis	AF (especially forms with a high AF burden), hypertension, heart failure, valvular heart disease (via pressure and volume overload)	Electrical dissociation, conduction block, enhanced AF complexity	78, 79, 90, 91
Inflammatory infiltration		Profibrotic responses, enhanced AF complexity	81
Fatty infiltration	Obesity (fatty infiltration)	Profibrotic/proinflammatory responses, localized conduction	82, 92

		block	
Amyloid deposition	Ageing, heart failure, CAD (via atrial scarring), genetic factors	Conduction disturbances	83, 93
Ion channel alterations			
Ion channel remodelling	AF (especially forms with a high AF burden), genetic predisposition to AF	AF cycle shortening (if due to atrial tachycardia), AF cycle length prolongation (if due to heart failure), enhanced heterogeneity of atrial repolarization	94-96
Ca^{2+} handling instability	AF (especially forms with a high AF burden), possibly heart failure and hypertension (possibly through increased sympathetic activation)	Enhanced propensity to ectopy	97, 98
Gap-junction redistribution	AF	Conduction disturbances	99
Myocyte alterations			
Apoptosis and necrosis	CAD, heart failure (through cardiomyocyte death and atrial scarring)	May induce replacement fibrosis	100
Myocyte hypertrophy	Atrial dilatation, AF	Aggravates conduction disturbances	84, 101
Endothelial and vascular alterations			
Microvascular changes	Atherosclerosis, CAD and peripheral artery disease, possibly AF	Aggravation of atrial ischaemia, heterogeneity of electrical function, structural remodelling	102
Endocardial remodelling		Enhanced risk for thrombus formation	103, 104
Changes of the autonomic nervous system			
Sympathetic hyperinnervation	Heart failure, hypertension	Enhanced propensity to ectopy	80, 105

AF = atrial fibrillation; CAD = coronary artery disease.

3.2.1. Electrophysiological mechanisms of atrial fibrillation

AF provokes a shortening of the atrial refractory period and AF cycle length during the first days of the arrhythmia, largely due to downregulation of the Ca^{2+}-inward current and upregulation of inward rectifier K^+ currents.[94, 95] Structural heart disease, in contrast, tends to prolong the atrial refractory period, illustrating the heterogeneous nature of mechanisms that cause AF in different patients.[96] Hyperphosphorylation of various Ca^{2+} handling proteins may contribute to enhanced spontaneous Ca^{2+} release events and triggered activity,[97, 98] thus causing ectopy and promoting AF. Although the concept of Ca^{2+} handling instability has been challenged recently,[106, 107] it may mediate AF in structurally remodelled atria and explain how altered autonomic tone can generate AF.[80, 105]

Focal initiation and maintenance of AF: The seminal observation by Haissaguerre et al[108] was that a focal source in the pulmonary veins can trigger AF, and ablation of this source can extinguish the arrhythmia. The mechanism of focal activity might involve both triggered activity and localized reentry.[109, 110] Hierarchic organization of AF with rapidly activated areas driving the arrhythmia has been documented in patients with paroxysmal AF,[111, 112] but is more challenging in patients with persistent AF.[113]

The multiple wavelet hypothesis and rotors as sources of AF: Moe and Abildskov[114] proposed that AF can be perpetuated by continuous conduction of several independent wavelets propagating through the atrial musculature in a seemingly chaotic manner. As long as the number of wavefronts does not decline below a critical level, they will be capable of sustaining the arrhythmia. Numerous experimental and clinical observations can be reconciled with the multiple wavelet hypothesis.[115] All localized sources of AF (ectopic

foci, rotors, or other stable reentry circuits) cause fibrillatory conduction remote from the source, which is difficult to distinguish from propagation sustaining AF by multiple wavelets, and either of these phenomena may generate 'rotors' picked up by intracardiac[116, 117] or body surface[117] recordings.

5 Diagnosis and timely detection of atrial fibrillation

5.1. Overt and silent atrial fibrillation

The diagnosis of AF requires rhythm documentation using an electrocardiogram (ECG), with the typical pattern of AF. ECG-documented AF was the entry criterion in trials forming the evidence for these guidelines. By accepted convention, an episode lasting at least 30 seconds is diagnostic. Individuals with AF may be symptomatic or asymptomatic ('silent AF'). Many AF patients have both symptomatic and asymptomatic episodes of AF.[118-121]

Silent, undetected AF is common,[120, 122] with severe consequences such as stroke and death.[123-125] Prompt recording of an ECG is an effective and cost-effective method to document chronic forms of AF.[126] The technology to detect paroxysmal, self-terminating AF episodes is rapidly evolving (see Chapter 5 for a definition of AF patterns). There is good evidence that prolonged ECG monitoring enhances the detection of undiagnosed AF, for 72 hours after a stroke,[27, 127] for even longer periods,[18, 128] or by daily short-term ECG recording in patients over 75 years of age[129] (*Web Addenda Figure 1*). Ongoing studies will determine whether such early detection alters management (e.g. initiation of anticoagulation) and improves outcomes.

Once the ECG diagnosis of AF has been established, further ECG monitoring can inform management in the context of: (1) a change in symptoms or new symptoms; (2) suspected progression of AF; (3) monitoring of drug effects on ventricular rate; and (4) ECG monitoring of antiarrhythmic drug effects or catheter ablation for rhythm control.

5.2. Screening for silent atrial fibrillation

5.2.1. Screening for atrial fibrillation by electrocardiogram in the community

Undiagnosed AF is common, especially in older populations and in patients with heart failure.[130] Opportunistic screening for silent AF seems cost-effective in elderly populations (e.g. > 65 years),[131] and similar effects have been reported using single-lead ECG screening in other at-risk populations.[132, 133] Screening of elderly populations (mean age 64 years) yielded a prevalence of 2.3% for chronic forms of AF in 122,571 participants using either short-term ECG or pulse palpation (followed by ECG in those with an irregular pulse).[134] Previously undiagnosed AF was found in 1.4% of those aged > 65 years, suggesting a number needed to screen of 70. These findings encourage the further evaluation of systematic AF screening programmes in at-risk populations.

5.2.2. Prolonged monitoring for paroxysmal atrial fibrillation

Paroxysmal AF is often missed.[120] Repeated daily ECG recordings increased the detection of silent, asymptomatic paroxysmal AF in an unselected Swedish population aged > 75 years.[120, 135] Several patient-operated devices[136, 137] and extended continuous ECG monitoring using skin patch recorders[138] have been validated for detection of paroxysmal AF.[139] The detection rate of asymptomatic AF by new technologies such as smartphone cases with ECG electrodes, smart watches, and blood pressure machines with AF detection algorithms, has not yet been formally evaluated against an established arrhythmia detection method.[140]

5.2.3. Patients with pacemakers and implanted devices

Implanted pacemakers or defibrillators with an atrial lead allow continuous monitoring of atrial rhythm. Using this technology, patients with atrial high rate episodes (AHRE) can be identified. Depending on the risk profile of the population studied, such AHRE are detected in 10–15% of pacemaker patients.[141] AHRE are associated with an increased risk of overt AF (hazard ratio [HR] 5.56; 95% confidence interval [CI] 3.78–8.17; $P < 0.001$) and ischaemic stroke or systemic embolism (HR 2.49; 95% CI 1.28–4.85; $P = 0.007$). The stroke risk in AHRE patients seems lower than the stroke risk in patients with diagnosed AF, and not all AHRE represent AF.[142] Strokes often occur without AHRE detected within 30 days before the event.[143-147] Consequently, it is unclear whether AHRE imply the same therapeutic requirements as overt AF,[148] and the benefit of OAC in patients with AHRE is being evaluation in ongoing clinical trials (e.g. ARTESiA [NCT01938248] and NOAH [NCT02618577]). At present, pacemakers and implanted devices should be interrogated on a regular basis for AHRE, and patients with AHRE should undergo further assessment of stroke risk factors and for overt AF,

including ECG monitoring (*Figure 3*).[149]

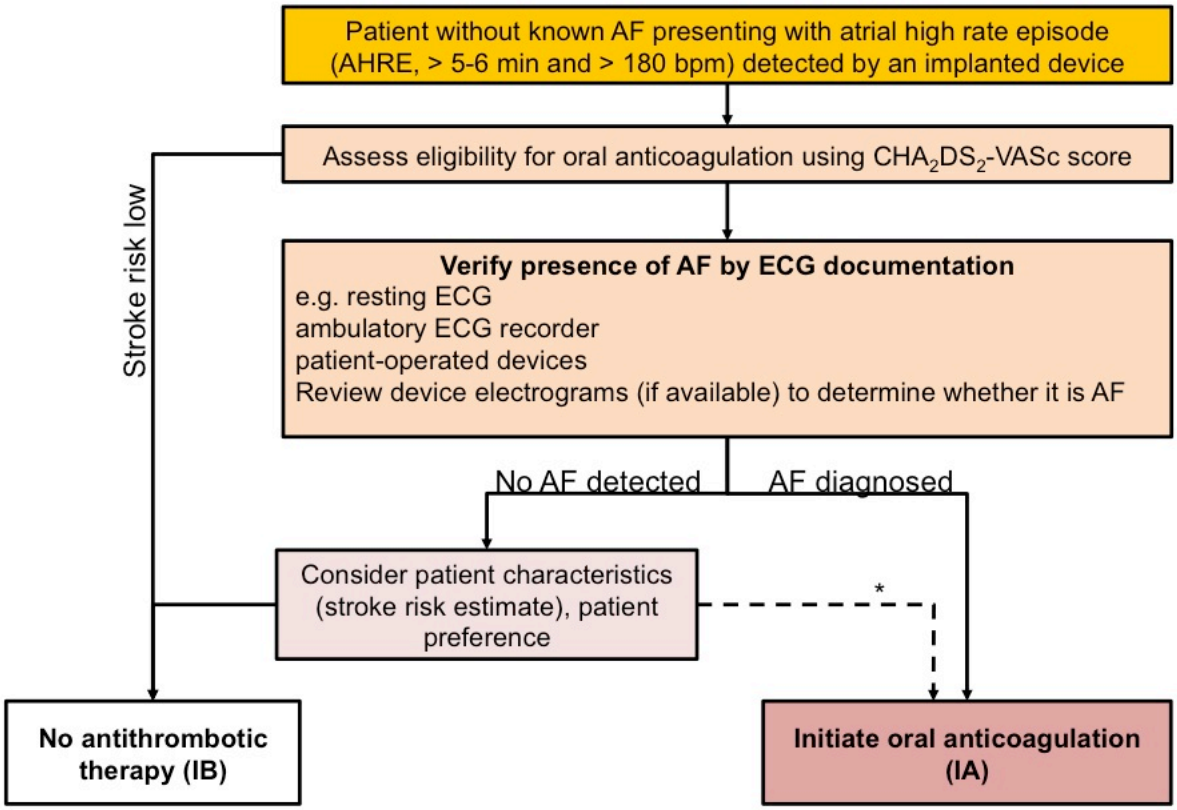


Figure 3 Management of AHRE detected on an implanted device. Adapted from the report of the 3rd AFNET/EHRA consensus conference.[150]
AF = atrial fibrillation; AFNET = German Competence NETwork on Atrial Fibrillation; AHRE = atrial high rate episodes; bpm = beats per minute; CHA_2DS_2-VASc = Congestive Heart failure, hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female); ECG = electrocardiogram; EHRA = European Heart Rhythm Association.

5.2.4. Detection of atrial fibrillation in stroke survivors

Sequential stratified ECG monitoring detected AF in 24% (95% CI 17–31) of stroke survivors,[151] and in 11.5% (95% CI 8.9%–14.3%) in another meta-analysis,[17] with large variations depending on the timing, duration, and method of monitoring. AF detection is not uncommon in unselected stroke patients (6.2%, 95% CI 4.4–8.3),[128] but is more likely in patients with cryptogenic stroke implanted with loop recorders or who have had ECG monitors for several weeks.[18, 128, 152] Cryptogenic stroke is defined as a stroke in which the cause could not be identified after extensive investigations.[153] A broader definition is embolic stroke of undetermined source.[154] Several studies have also found AF in patients in whom another competing cause for stroke has been identified clinically (e.g. hypertension or carotid artery stenosis).[27, 127] Hence, prolonged ECG monitoring seems reasonable in all survivors of an ischaemic stroke without an established diagnosis of AF.

Recommendations for screening for AF

Recommendations	Class [a]	Level [b]	Refs [c]
Opportunistic screening for AF is recommended by pulse taking or ECG rhythm strip in patients > 65 years of age	I	B	130, 134, 155
In patients with TIA or ischaemic stroke, screening for AF is recommended by short-term ECG recording followed by continuous ECG monitoring for at least 72 hours	I	B	27, 127

It is recommended to interrogate pacemakers and ICDs on a regular basis for atrial high rate episodes (AHRE). Patients with AHRE should undergo further ECG monitoring to document AF before initiating AF therapy	I	B	141, 156
In stroke patients, additional ECG monitoring by long-term non-invasive ECG monitors or implanted loop recorders should be considered to document silent AF	IIa	B	18, 128
Systematic ECG screening may be considered to detect AF in patients aged > 75 years, or those at high stroke risk	IIb	B	130, 135, 157

AF = atrial fibrillation; AHRE = atrial high rate episodes; ECG = electrocardiogram; ICD = implantable cardioverter defibrillator; TIA = transient ischaemic attack.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

5.3. Electrocardiogram detection of atrial flutter

Right atrial isthmus-dependent flutter has a typical ECG pattern and ventricular rate.[158] The prevalence of atrial flutter is less than one-tenth of the prevalence of AF.[159] Atrial flutter often coexists with or precedes AF.[160] In typical, isthmus-dependent flutter, P waves will often show a 'saw tooth' morphology, especially in the inferior leads (II, III, aVF). The ventricular rate can be variable (usual ratio of atrial to ventricular contraction 4:1 to 2:1, in rare cases 1:1) and macro-reentrant tachycardias may be missed in stable 2:1 conduction. Vagal stimulation or intravenous adenosine may be helpful to unmask atrial flutter. The management of atrial flutter is discussed in Section 12.7. Left or right atrial macro-reentrant tachycardia is usually confined to patients after catheter ablation for AF, AF surgery, or after open heart surgery.[158]

6 Classification of atrial fibrillation

6.1. Atrial fibrillation pattern

In many patients, AF progresses from short, infrequent episodes to longer and more frequent attacks. Over time, many patients will develop sustained forms of AF. In a small proportion of patients, AF will remain paroxysmal over several decades (2–3% of AF patients).[161] The distribution of paroxysmal AF recurrences is not random, but clustered.[162] AF may also regress from persistent to paroxysmal AF. Furthermore, asymptomatic recurrences of AF are common in patients with symptomatic AF.[120]

Based on presentation, duration, and spontaneous termination of AF episodes, five types of AF are traditionally distinguished: first diagnosed, paroxysmal, persistent, long-standing persistent, and permanent AF (*Table 5*). If patients suffer from both paroxysmal and persistent AF episodes, the more common type should be used for classification. Clinically determined AF patterns do not correspond well to the AF burden measured by long-term ECG monitoring.[163] Even less is known about the response to therapy in patients with long-standing persistent AF or long-standing paroxysmal AF. Despite these inaccuracies, the distinction between paroxysmal and persistent AF has been used in many trials and therefore still forms the basis of some recommendations.

There is some evidence suggesting that AF burden may influence stroke risk[44, 124, 164] and could modify the response to rhythm control therapy.[76, 165] The evidence for this is weak. Therefore, AF burden should not be a major factor in deciding on the usefulness of an intervention that is deemed suitable for other reasons.

Table 5 Patterns of AF

AF pattern	Definition
First diagnosed AF	AF that has not been diagnosed before, irrespective of the duration of the arrhythmia or the presence and severity of AF-related symptoms.
Paroxysmal AF	Self-terminating, in most cases within 48 hours. Some AF paroxysms may continue for up to 7 days.[a] Most AF episodes that are cardioverted within 24-48 hours should be considered paroxysmal.[a]
Persistent AF	AF that lasts longer than 7 days, including episodes that are terminated by cardioversion, either with drugs or by direct current cardioversion, after 7 days or more.
Long-standing persistent AF	Continuous AF lasting for ≥ 1 year when it is decided to adopt a rhythm control strategy.
Permanent AF	AF is accepted by the patient (and physician). Hence, rhythm control

	interventions are, by definition, not pursued in patients with permanent AF. Should a rhythm control strategy be adopted, the arrhythmia would be re-classified as 'long-standing persistent AF'.

AF = atrial fibrillation.
[a]The distinction between paroxysmal and persistent AF is often not made correctly without access to long-term monitoring.[163] Hence, this classification alone is often insufficient to select specific therapies. If both persistent and paroxysmal episodes are present, the predominant pattern should guide the classification.

6.2. Atrial fibrillation types reflecting different causes of the arrhythmia

The risk of developing AF is increased in a variety of physiological and disease states, and the historic term 'lone AF' is probably misleading and should be avoided.[166] Although the pattern of AF may be the same, the mechanisms underpinning AF vary substantially between patients[167] (*Table 6*). This suggests that stratifying AF patients by underlying drivers of AF could inform management, for example, considering cardiac and systemic comorbidity (e.g. diabetes and obesity[168]), lifestyle factors (e.g. activity level, smoking, alcohol intake[169, 170]), markers of cardiac structural remodelling (e.g. fibrosis[171-173] or electrocardiographic parameters of AF complexity[174]), or genetic background. *Table 6* provides such a taxonomy, informed by expert consensus,[76, 120, 175] but without much evidence to underpin its clinical use.[176] Systematic research defining the major drivers of AF is clearly needed to better define different types of AF.[176]

Table 6 Clinical types of AF (modified from the report on the 4th AFNET/EHRA consensus conference[76])[a]

AF type	Clinical presentation	Possible pathophysiology
AF secondary to structural heart disease	AF in patients with LV systolic or diastolic dysfunction, long-standing hypertension with LVH, and/or other structural heart diseases. The onset of AF in these patients is a common cause of hospitalization and a predictor of poor outcome	Increased atrial pressure and atrial structural remodelling, together with activation of the sympathetic and renin–angiotensin system
Focal AF	Patients with repetitive atrial runs and frequent, short episodes of paroxysmal AF. Often highly symptomatic, younger patients with distinguishable atrial waves (coarse AF), atrial ectopy, and/or atrial tachycardia deteriorating in AF	Localized triggers, in most cases originating from the pulmonary veins, initiate AF. AF due to one or a few reentrant drivers is also considered to be part of this type of AF
Polygenic AF	AF in carriers of common gene variants that have been associated with early onset AF	Currently under study. The presence of some gene variants may also influence treatment outcomes
Postoperative AF	New onset of AF (usually self-terminating) after major (typically cardiac) surgery in patients who were in sinus rhythm before surgery and had no history of AF	Acute factors: inflammation, atrial oxidative stress, high sympathetic tone, electrolyte changes, and volume overload, possibly interacting with a pre-existing substrate
AF in patients with mitral stenosis or prosthetic heart valves	AF in patients with mitral stenosis, after mitral valve surgery and in some cases other valvular disease	Left atrial pressure (stenosis) and volume (regurgitation) load are the main drivers of atrial enlargement and structural atrial remodelling in these patients
AF in athletes	Usually paroxysmal, related to duration and intensity of training	Increased vagal tone and atrial volume
Monogenic AF	AF in patients with inherited cardiomyopathies, including channelopathies	The arrhythmogenic mechanisms responsible for sudden death are likely to contribute to the occurrence of AF in these patients

AF = atrial fibrillation; LV = left ventricular; LVH = left ventricular hypertrophy.
[a]It is recognized that these types of AF will overlap in clinical practice, and that their impact for management needs to be evaluated systematically.

6.3. Symptom burden in atrial fibrillation

Patients with AF have significantly poorer quality of life than healthy controls, experiencing a variety of symptoms including lethargy, palpitations, dyspnoea, chest tightness, sleeping difficulties, and psychosocial distress.[32, 177-180] Improved quality of life has been noted with both pharmacological and interventional therapies,[181-185] but there are limited data to compare the benefit of different treatments.[32, 186] Assessment of quality of life is further constrained by a lack of cross-validation of the several AF-specific quality-of-life tools.[187-191] With regard to symptom assessment, the European Heart Rhythm Association (EHRA) suggested the EHRA symptom scale (*Table 7*) to describe symptom severity in AF patients.[192] A similar scale (the Canadian Cardiovascular Society Severity of Atrial Fibrillation Scale) is used in Canada.[193] The EHRA scale has been used and validated.[194-199] A modification was proposed in 2014, subdividing EHRA class 2 into mild (2a) or moderate (2b) impact.[199] As symptoms in class 2b ('troubling' symptoms) identified patients with a health utility benefit of rhythm control in that study, this modification may provide a threshold for potential treatment decisions, but this remains to be tested. While some AF patients had no or minimal symptoms (25–40%), many (15–30%) reported severe or disabling symptoms.[194, 196] The EHRA scale should be used to guide symptom-orientated treatment decisions and for longitudinal patient profiling.

Table 7 Modified EHRA symptom scale (modified from Wynn et al[199])

Modified EHRA score	Symptoms	Description
1	None	AF does not cause any symptoms
2a	Mild	Normal daily activity not affected by symptoms related to AF[a]
2b	Moderate	Normal daily activity not affected[a]
3	Severe	Normal daily activity affected
4	Disabling	Normal daily activity discontinued

AF = atrial fibrillation; EHRA = European Heart Rhythm Association.
[a]EHRA class 2a and 2b can be differentiated by evaluating whether patients are functionally affected by their AF symptoms. AF-related symptoms are most commonly fatigue/tiredness and exertional shortness of breath, or less frequently palpitations and chest pain.[42, 194, 200-202]

Recommendation on use of the modified EHRA symptom scale

Recommendation	Class [a]	Level [b]	Refs [c]
Use of the modified EHRA symptom scale is recommended in clinical practice and research studies to quantify AF-related symptoms	I	C	192, 199

AF = atrial fibrillation; EHRA = European Heart Rhythm Association.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

7 Detection and management of risk factors and concomitant cardiovascular diseases

Many cardiovascular diseases and concomitant conditions increase the risk of developing AF (*Table 8*), recurrent AF, and AF-associated complications. Identification of such conditions, their prevention and treatment is an important leverage to prevent AF and its disease burden. Knowledge of these factors and their management is hence important for optimal management of AF patients.[203, 204]

Table 8 Cardiovascular and other conditions independently associated with AF

Characteristic/comorbidity	Association with AF
Genetic predisposition (based on multiple common gene variants associated with AF)[64]	HR range 0.4–3.2

Older age[19]	HR:
50–59 years	1.00 (reference)
60–69 years	4.98 (95% CI 3.49–7.10)
70–79 years	7.35 (95% CI 5.28–10.2)
80–89 years	9.33 (95% CI 6.68–13.0)
Hypertension (treated) vs. none[19]	HR 1.32 (95% CI 1.08–1.60)
Heart failure vs. none[19]	HR 1.43 (95% CI 0.85–2.40)
Valvular heart disease vs. none[205]	RR 2.42 (95% CI 1.62–3.60)
Myocardial infarction vs. none[19]	HR 1.46 (95% CI 1.07–1.98)
Thyroid dysfunction[206, 207]	(reference: euthyroid)
hypothyroidism	HR 1.23 (95% CI 0.77-1.97)
subclinical hyperthyroidism	RR 1.31 (95% CI 1.19–1.44)
overt hyperthyroidism	RR 1.42 (95% CI 1.22–1.63)
Obesity[19, 208]	HR:
none (BMI < 25 kg/m²)	1.00 (reference)
overweight (BMI 25–30 kg/m²)	1.13 (95% CI 0.87–1.46)
obese (BMI ≥ 31 kg/m²)	1.37 (95% CI 1.05–1.78)
Diabetes mellitus vs. none[19]	HR 1.25 (95% CI 0.98–1.60)
Chronic obstructive pulmonary disease[209]	RR:
FEV1	
≥ 80%	1.00 (reference)
60–80%	1.28 (95% CI 0.79–2.06)
< 60%	2.53 (95% CI 1.45–4.42)
Obstructive sleep apnoea vs. none[210]	HR 2.18 (95% CI 1.34–3.54)
Chronic kidney disease[211]	OR:
none	1.00 (reference)
stage 1 or 2	2.67 (95% CI 2.04–3.48)
stage 3	1.68 (95% CI 1.26–2.24)
stage 4 or 5	3.52 (95% CI 1.73–7.15)
Smoking[212]	HR:
never	1.00 (reference)
former	1.32 (95% CI 1.10–1.57)
current	2.05 (95% CI 1.71–2.47)
Alcohol consumption[213]	RR:
None	1.00 (reference)
1–6 drinks/week	1.01 (95% CI 0.94–1.09)
7–14 drinks/week	1.07 (95% CI 0.98–1.17)
15–21 drinks/week	1.14 (95% CI 1.01–1.28)
> 21 drinks/week	1.39 (95% CI 1.22–1.58)
Habitual vigorous exercise[214]	RR:
Non-exercisers	1.00 (reference)
< 1 day/week	0.90 (95% CI 0.68−1.20)
1−2 days/week	1.09 (95% CI 0.95−1.26)
3−4 days/week	1.04 (95% CI 0.91−1.19)
5−7 days/week	1.20 (95% CI 1.02−1.41)

AF = atrial fibrillation; BMI = body mass index; CI = confidence interval; FEV1 = forced expiratory volume in 1 second; HR = hazard ratio; OR = odds ratio; RR = risk ratio

7.1. Heart failure

Heart failure and AF coincide in many patients.[215-217] They are linked by similar risk factors and share a common pathophysiology.[218] Heart failure and AF can cause and exacerbate each other through mechanisms such as structural cardiac remodelling, activation of neurohormonal mechanisms, and rate-related impairment of left ventricular (LV) function. Patients with AF and concomitant heart failure, both with preserved ejection fraction (LV ejection fraction [LVEF] ≥ 50%) and reduced ejection fraction (LVEF < 40%),[219, 220] suffer from a worse prognosis, including increased mortality.[16, 221] The recent ESC Guidelines on heart failure[222] have also introduced a new category of heart failure with mid-range ejection fraction (HFmrEF; LVEF 40–49%), although data on AF patients in this group are currently limited. Prevention of adverse outcomes and maintenance of a good quality of life are the aims of management in all patients with AF and concomitant heart failure, regardless

of LVEF.[223] The general approach to AF management does not differ between heart failure patients and others, but a few considerations are worthwhile to consider. Of note, the only therapy with proven prognostic value in these patients is anticoagulation, and appropriate OAC should be prescribed in all patients at risk of stroke (see Chapter 8).

7.1.1. Patients with atrial fibrillation and heart failure with reduced ejection fraction

In addition to OAC, standard heart-failure therapy should be used in patients with heart failure with reduced ejection fraction (HFrEF), as detailed in the ESC Guidelines.[222] This includes angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), mineralocorticoid antagonists, defibrillators and cardiac resynchronization therapy,[218] in addition to combined angiotensin receptor neprilysin inhibition (ARNI) in patients able to tolerate an ACE inhibitor or ARB with ongoing symptoms.[224]

Rate control of AF is discussed in detail in Chapter 9. In brief, only beta-blockers and digoxin are suitable in HFrEF because of the negative inotropic potential of verapamil and diltiazem. Beta-blockers are usually the first-line option in patients with clinically stable HFrEF, although a meta-analysis using individual patient data from randomized controlled trials (RCTs) found no reduction in mortality from beta-blockers versus placebo in those with AF at baseline (HR 0.97, 95% CI 0.83–1.14).[23] Digoxin is commonly prescribed in clinical practice but no head-to-head RCTs in AF patients have been performed. In a meta-analysis of observational studies, digoxin had a neutral effect on mortality in patients with AF and concomitant heart failure (adjusted observational studies HR 0.90, 95% CI 0.70–1.16; propensity-matched observational studies RR 1.08, 95% CI 0.93–1.26).[225] Initial and combination rate-control therapy for AF in HFrEF should therefore take account of individual patient characteristics and symptoms; beta-blocker initiation should be delayed in patients with acute decompensated heart failure, and digoxin has more adverse effects in patients with renal impairment (see Chapter 9).

Patients with AF and HFrEF who present with severe symptoms may require rhythm control therapy in addition to rate control therapy. For patients who develop HFrEF as a result of rapid AF (tachycardiomyopathy), a rhythm control strategy is preferred, based on several relatively small patient cohorts and trials reporting improved LV function after restoration of sinus rhythm.[185, 226-228] The diagnosis of tachycardiomyopathy can be challenging, and at times requires restoration of sinus rhythm.[229] Catheter ablation may be a useful method to restore LV function and quality of life in AF patients with HFrEF,[185, 226-228] but further data are needed. *Figure 4* summarizes the approach to patients with AF and heart failure.

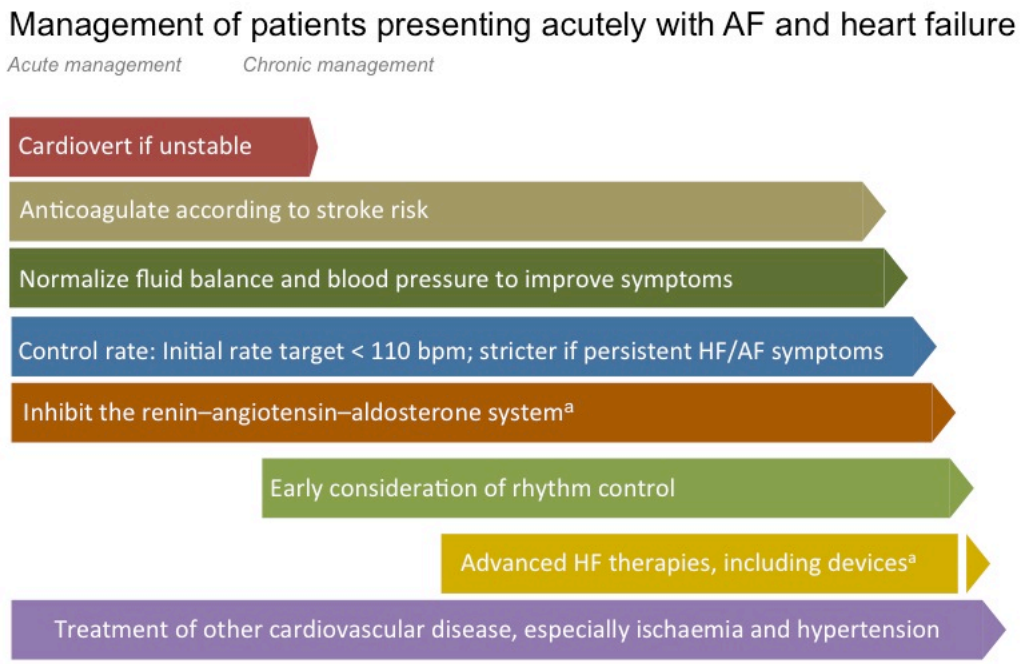


Figure 4 Initial management of newly diagnosed with AF and heart failure. Adapted from Kotecha and Piccini.[218]
ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibition; bpm = beats per minute; HF = heart failure.
[a]In patients with heart failure and reduced ejection fraction; also consider combined ARNI in patients able to tolerate an ACE inhibitor or ARB with ongoing symptoms.

7.1.2. Atrial fibrillation patients with heart failure with preserved ejection fraction

The diagnosis of heart failure with preserved ejection fraction (HFpEF) in patients with AF is problematic because of the difficulty in separating symptoms that are due to HF from those due to AF. Although diagnostic differentiation can be achieved by cardioversion and clinical reassessment, this option is often not appropriate in this group, particularly as a specific therapy that improves prognosis in HFpEF is currently lacking. Echocardiography can support detection of HFpEF in patients with symptomatic AF by providing evidence of relevant structural heart disease (e.g. LV hypertrophy [LVH]) and/or measurement of diastolic dysfunction. Reduced early diastolic myocardial velocity e' by tissue Doppler reflects impaired LV relaxation, while the ratio of E/e' has demonstrated a significant correlation with invasive measurement of LV filling pressures.[230-234] Natriuretic peptide levels are part of the diagnostic assessment of HFpEF,[222] although natriuretic peptide levels are elevated in AF patients and the optimum diagnostic cut-off is still unknown.[235] The management of patients with AF and concomitant HFpEF should focus on control of fluid balance and concomitant conditions such as hypertension and ischaemia.

7.1.3. Atrial fibrillation patients with heart failure with mid-range ejection fraction

HFmrEF is a recently defined entity, describing patients with symptoms and signs of heart failure, LVEF 40–49%, elevated levels of natriuretic peptides, and either LV hypertrophy, left atrial (LA) enlargement, or evidence of diastolic dysfunction.[222] However, diagnosis is more difficult in patients with AF, as natriuretic peptides are elevated in AF and LA dilatation is common, regardless of concomitant heart failure. LVEF is also variable and difficult to assess in AF patients because of AF-induced reduction in systolic LV function and

variable cardiac cycle length. Further study of this group is required before particular treatment strategies in AF patients with HFmrEF can be recommended.

7.1.4. Prevention of atrial fibrillation in heart failure

Retrospective analyses from large randomized trials have reported a lower incidence of new-onset AF in patients treated with ACE inhibitors/ARBs compared with placebo.[236-238] The reduced incidence of AF with ACE inhibitors/ARBs is less evident in patients with HFpEF[239] and is lost in patients without heart failure.[240-242] Neprilysin inhibition does not seem to add to this effect.[224] Beta-blocker therapy was associated with a 33% reduction in the adjusted odds of incident AF in HFrEF patients pretreated with ACE inhibitors/ARBs, reinforcing the importance of beta-blocker therapy in HFrEF patients in sinus rhythm.[23] Eplerenone, a mineralocorticoid receptor antagonist, also reduced the risk of new-onset AF in patients with LVEF ≤ 35%, New York Heart Association (NYHA) Class II, and pretreatment with ACE inhibitors/ARBs and beta-blockers.[243]

7.2. Hypertension

7.2.1. Treatment of hypertension to prevent incident atrial fibrillation

Inhibition of the renin–angiotensin–aldosterone system can prevent structural remodelling and recurrent AF.[236, 244] A recent analysis of the Danish healthcare database with long-term monitoring of the effect of different antihypertensive agents on the occurrence of overt AF suggests a beneficial effect of ACE inhibitors or ARBs.[245] Secondary analyses of ACE inhibitors or ARBs in patients with heart failure or LVH show a lower incidence of new-onset AF.[238, 246]

7.2.2. Blood pressure control in patients with atrial fibrillation

Hypertension is a stroke risk factor in AF, and uncontrolled high blood pressure enhances the risk of stroke and bleeding events and may lead to recurrent AF. Good blood-pressure control should therefore form an integral part of the management of AF patients.[247] In patients with established AF, but without LV dysfunction or heart failure, ARBs do not prevent recurrent AF better than placebo.[240, 241] ACE inhibitors or ARBs may reduce recurrent AF after cardioversion when coadministered with antiarrhythmic drug therapy compared with an antiarrhythmic drug alone.[248, 249] Meta-analyses driven by these studies suggested a lower risk of recurrent AF,[236-238, 250] but at least one controlled trial failed to demonstrate benefit.[240, 251]

7.3. Valvular heart disease

Valvular heart disease is independently associated with incident AF.[252] Approximately 30% of patients with AF have some form of valvular heart disease, often detected only by echocardiography.[201, 253-255] AF worsens prognosis in patients with severe valvular heart disease,[256] including those undergoing surgery or transcatheter interventions for aortic or mitral valve disease.[257-262] Valvular heart disease can be associated with an increased thromboembolic risk, which probably also adds to the stroke risk in AF patients.[263] Similar to heart failure, valvular disease and AF interact and sustain each other through volume and pressure overload, tachycardiomyopathy, and neurohumoral factors.[264-270] When valve dysfunction is severe, AF can be regarded as a marker for progressive disease, thus favouring valve repair or replacement.[271]

Traditionally, patients with AF have been dichotomized into ‘valvular’ and ‘non-valvular’ AF.[272] Although slightly different definitions have been used, valvular AF mainly refers to AF patients that have either rheumatic valvular disease (predominantly mitral stenosis) or mechanical heart valves. In fact, while AF implies an incremental risk for thromboembolism in patients with mitral valve stenosis,[263, 273, 274] there is no clear evidence that other valvular diseases, including mitral regurgitation or aortic valve disease, need to be considered when choosing an anticoagulant or indeed to estimate stroke risk.[275] We have therefore decided to replace the historic term ‘non-valvular’ AF with reference to the specific underlying conditions.

Recommendations for patients with valvular heart disease and AF

Recommendations	Class [a]	Level [b]	Refs [c]
Early mitral valve surgery should be considered in severe mitral regurgitation, preserved LV function, and new-onset AF, even in the absence of symptoms, particularly when valve repair is feasible	IIa	C	276

Mitral valvotomy should be considered for asymptomatic patients with severe mitral stenosis and suitable valve anatomy who have new-onset AF	IIa	C	

AF = atrial fibrillation; LV = left ventricular.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

7.4. Diabetes mellitus

Diabetes and AF frequently coexist because of associations with other risk factors.[277-283] Diabetes is a risk factor for stroke and other complications in AF.[284] In patients with AF, a longer duration of diabetes appears to confer a higher risk of thromboembolism, albeit without greater risk of OAC-related bleeding.[285] Unfortunately, intensive glycaemic control does not affect the rate of new-onset AF,[284] while treatment with metformin seems to be associated with a decreased long-term risk of AF in diabetic patients[286] and may even lower long-term stroke risk.[13] Diabetic retinopathy, a measure of disease severity, does not increase the risk of ocular bleeding in anticoagulated patients.[287]

7.5. Obesity and weight loss

7.5.1. Obesity as a risk factor

Obesity increases the risk for AF (risk ratio 1.5–1.8),[288-291] with a progressive increase according to body mass index.[288, 290-292] Obese patients may have more LV diastolic dysfunction, increased sympathetic activity and inflammation, and increased fatty infiltration of the atria.[293-295] Obesity may also be a risk factor for ischaemic stroke, thromboembolism, and death in AF patients.[292]

7.5.2. Weight reduction in obese patients with atrial fibrillation

Intensive weight-reduction management in addition to management of other cardiovascular risk factors (in the range of 10–15 kg weight loss achieved) led to fewer AF recurrences and symptoms compared with an approach based on general advice in obese patients with AF.[203, 204, 296] Improved cardiorespiratory fitness can further decrease AF burden in obese patients with AF.[297] Although the findings in these studies have to be confirmed, they underpin the positive effect of weight reduction in obese patients.

7.5.3. Catheter ablation in obese patients

Obesity may increase the rate of AF recurrence after catheter ablation,[298-301] with obstructive sleep apnoea as an important potential confounder. Obesity has also been linked to a higher radiation dose and complication rate during AF ablation.[302, 303] Notably, the symptomatic improvement after catheter ablation of AF in obese patients seems comparable to the improvement in normal-weight patients.[298] In view of the potential to reduce AF episodes by weight reduction (see Section 6.5.2.), AF ablation should be offered to obese patients in conjunction with lifestyle modifications that lead to weight reduction.

Recommendation for obese patients with AF

AF = atrial fibrillation.

Recommendation	Class [a]	Level [b]	Refs[c]
In obese patients with AF, weight loss together with management of other risk factors should be considered to reduce AF burden and symptoms	IIa	B	204, 288, 296

[a] Class of recommendation
[b] Level of evidence
[c] Reference(s) supporting recommendation(s)

7.6. Chronic obstructive pulmonary disease, sleep apnoea, and other respiratory diseases

AF has been associated with obstructive sleep apnoea.[304, 305] Multiple pathophysiological mechanisms can contribute to AF in obstructive sleep apnoea, including autonomic dysfunction, hypoxia, hypercapnia, and inflammation.[96, 304-307] Obstructive sleep apnoea exaggerates intrathoracic pressure changes, which in itself and via vagal activation can provoke shortening of the atrial action potential and induce AF. Risk factor reduction and continuous positive airway pressure ventilation can reduce AF recurrence.[308-312] It seems reasonable to consider obstructive sleep apnoea screening in AF patients with risk factors. Obstructive sleep apnoea treatment should be optimized to improve AF treatment results in appropriate patients. Servo-controlled pressure support therapy should not be used in HFrEF patients with predominantly central sleep apnoea (of which 25% had concomitant AF).[313]

Patients with chronic obstructive pulmonary disease often suffer from atrial tachycardias, which need to be differentiated from AF by ECG. Agents used to relieve bronchospasm, notably theophyllines and beta-adrenergic agonists, may precipitate AF and make control of the ventricular response rate difficult. Non-selective beta-blockers, sotalol, propafenone, and adenosine should be used with caution in patients with significant bronchospasm, while they can safely be used in patients with chronic obstructive pulmonary disease. Beta-1 selective blockers (e.g. bisoprolol, metoprolol, and nebivolol), diltiazem, and verapamil are often tolerated and effective (see Chapter 9).

Recommendations for patients with AF and respiratory diseases

Recommendations	Class [a]	Level [b]	Refs [c]
Correction of hypoxaemia and acidosis should be considered as initial management for patients who develop AF during an acute pulmonary illness or exacerbation of chronic pulmonary disease	IIa	C	
Interrogation for clinical signs of obstructive sleep apnoea in all AF patients should be considered	IIa	B	304, 305, 314, 315
Obstructive sleep apnoea treatment should be optimized to reduce AF recurrences and improve AF treatment results	IIa	B	307-311

AF = atrial fibrillation.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

7.7. Chronic kidney disease

AF is present in 15–20% of patients with CKD.[316] The definition of CKD in most AF trials is relatively strict. Although an estimated creatinine clearance (CrCl) rate of < 60 mL/min is indicative of CKD, a number of trials in AF patients have used CrCl < 50 mL/min to adapt NOAC dosage, usually estimated using the Cockroft–Gault formula. CrCl in AF patients can deteriorate over time.[317] The management of OAC in patients with CKD is discussed in Section 8.2.4.

Recommendations for patients with kidney disease and AF

Recommendations	Class [a]	Level [b]	Refs [c]
The assessment of kidney function by serum creatinine or creatinine clearance is recommended in all AF patients to detect kidney disease and to support correct dosing of AF therapy	I	A	316, 318-321
All AF patients treated with oral anticoagulation should be considered for at least yearly renal function evaluation to detect kidney disease	IIa	B	

AF = atrial fibrillation.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

8 Integrated management of patients with atrial fibrillation

Most patients access the healthcare system initially through pharmacists, community health workers, or primary care physicians. As AF is often asymptomatic, these healthcare professionals are important stakeholders to enable adequate detection of AF and to ensure consistent management. The initial assessment should be performed at the point of first contact with the healthcare system, and is feasible in most healthcare settings (when an ECG is available). We propose to consider five domains in the initial assessment of patients presenting with newly diagnosed AF (*Figure 5*). These domains are:

1. Haemodynamic instability or limiting, severe symptoms
2. Presence of precipitating factors (e.g. thyrotoxicosis, sepsis, or postoperative AF) and underlying cardiovascular conditions
3. Stroke risk and need for anticoagulation
4. Heart rate and need for rate control
5. Symptom assessment and decision for rhythm control

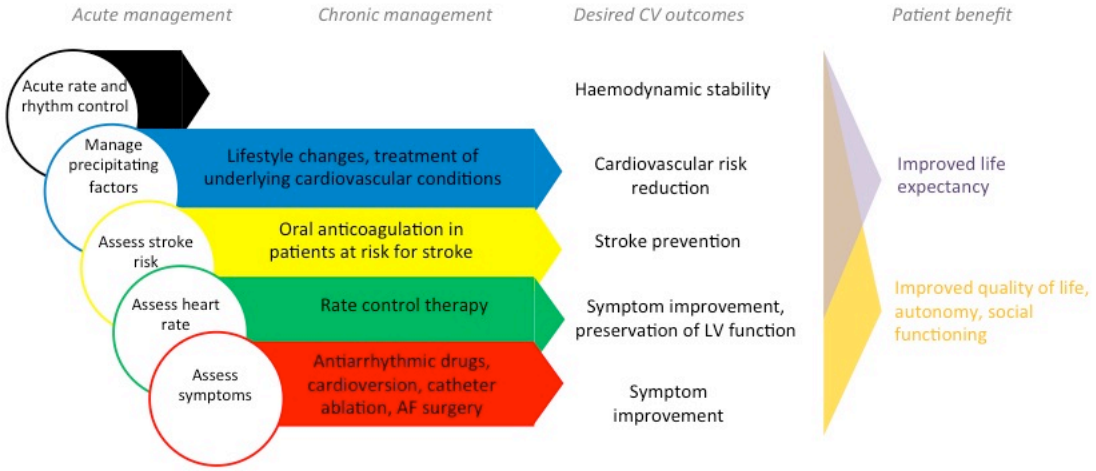


Figure 5 Acute and chronic management of AF patients, desired cardiovascular outcomes, and patient benefits. Adapted from the report on the 4th AFNET/EHRA consensus conference.[76]
AF = atrial fibrillation; AFNET = German Competence NETwork on Atrial Fibrillation; EHRA = European Heart Rhythm Association.

An integrated, structured approach to AF care, as applied successfully to other domains of medicine,[322-324] will facilitate consistent, guideline-adherent AF management for all patients[325] (*Figure 6*), with the potential to improve outcomes.[42, 326, 327] Such approaches are consistent with the Innovative Care for Chronic Conditions Framework proposal put forward by the World Health Organization.[328] Review by an AF service, or at least referral to a cardiologist, will usually be required after the initial assessment to fully evaluate the effect of AF on cardiovascular health.[329] There may also be reasons for early or urgent referral (*Table 9*). Integrated care of all patients with newly diagnosed AF should help to overcome the current shortcomings of AF management, such as underuse of anticoagulation, access to rate and rhythm control therapy, and inconsistent approaches to cardiovascular risk reduction. Integrated AF care requires the cooperation of primary care physicians, cardiologists, cardiac surgeons, AF specialists, stroke specialists, allied health practitioners and patients,

encompassing lifestyle interventions, treatment of underlying cardiovascular diseases and AF-specific therapy (*Figure 7*).

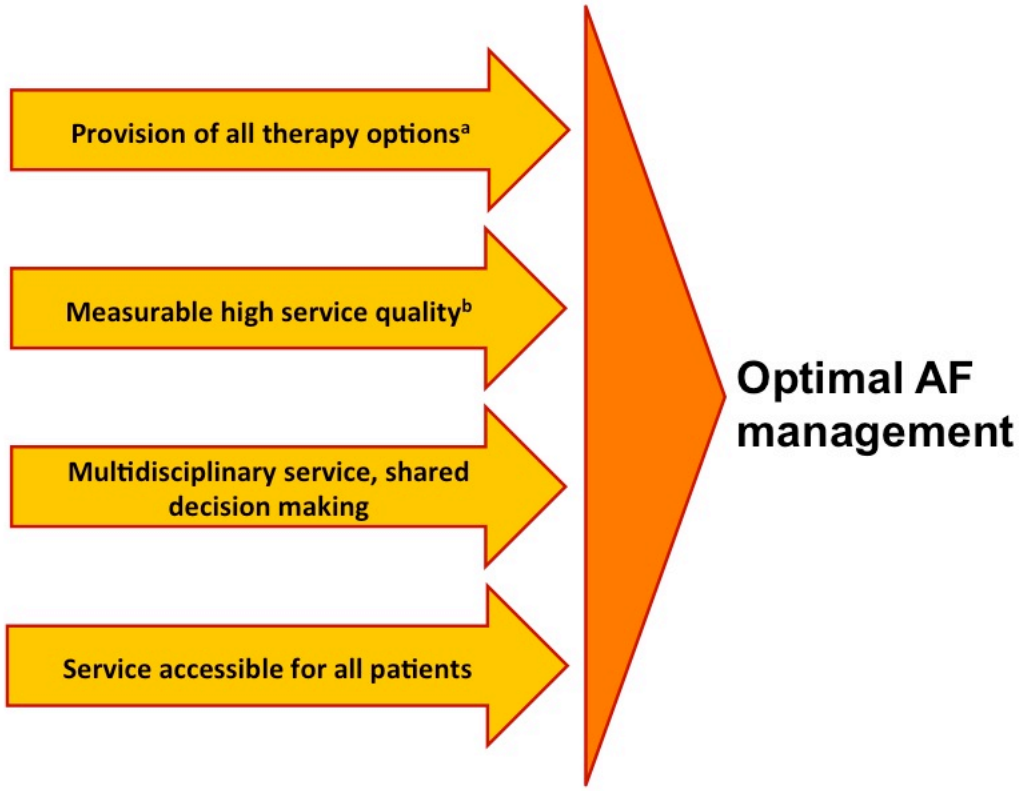


Figure 6 Achieving optimal management of AF patients.
AF = atrial fibrillation.
[a]On-site or through institutionalized cooperation.
[b]Safety outcomes should be collected in published and monitored central databases.

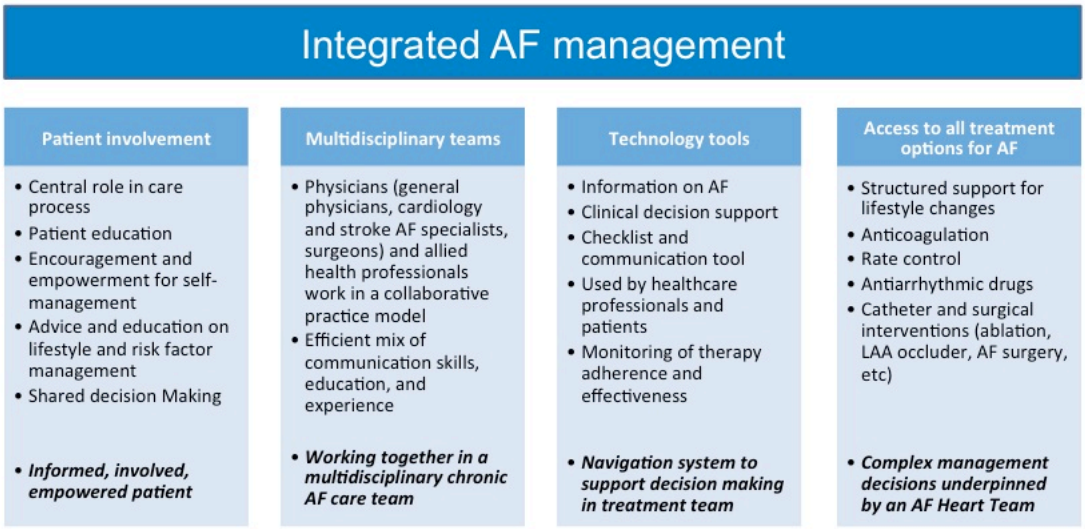


Figure 7 Fundamentals of integrated care in AF patients.
AF = atrial fibrillation; LAA = left atrial appendage.

Table 9 Clinical signs calling for urgent involvement of a specialized AF service.[a]

Haemodynamic instability
Uncontrollable rate
Symptomatic bradycardia not amenable to reduced dosing of rate control agents
Severe angina or worsening left ventricular function
Transient ischemic attack or stroke

AF = atrial fibrillation
[a]Anticoagulation should be initiated early in all suitable patients and will not routinely require specialist input.

8.1. Evidence supporting integrated atrial fibrillation care

Several structured approaches to AF care have been developed. Some evidence underpins their use, while more research is needed into the best way of delivering integrated AF care. Integrated AF management in an RCT increased the use of evidence-base care and reduced by approximately one-third the composite outcome of cardiovascular hospitalization and cardiovascular death over a mean follow-up of 22 months (14.3% vs. 20.8%, HR 0.65; 95% CI 0.45–0.93; *P* = 0.017) compared with usual care in a large tertiary care centre.[330] Integrated AF management appeared cost-effective in that study.[331] However, an Australian RCT showed only a marginal effect on unplanned admissions and death using integrated AF care limited to the initial care period, possibly emphasizing the need for sustained integration of AF care.[332] Two observational studies of integrated AF care found fewer hospitalizations,[333, 334] one study showed fewer cases of stroke,[333] and a further non-randomized study identified a trend for a lower rate of the composite outcome of death, cardiovascular hospitalization, and AF-related emergency visits.[335] More research is needed, and integrated AF care is likely to require different designs in different healthcare settings.

8.2. Components of integrated atrial fibrillation care

8.2.1. Patient involvement

Patients should have a central role in the care process. As treatment of AF requires patients to change their lifestyles and adhere to chronic therapy, at times without an immediately tangible benefit, they need to understand their responsibilities in the care process. Physicians and healthcare professionals are responsible for providing access to evidence-based therapy, but adherence to therapy is ultimately the responsibility of informed and autonomous patients, best described as 'shared accountability'.[336] Hence, information and education of patients and often of their partners and relatives is indispensable to encourage a self-management role and to empower patients to participate in shared decision-making,[326, 328] and to support their understanding of the disease and the suggested treatments.[337]

8.2.2. Multidisciplinary atrial fibrillation teams

Delegation of tasks from specialists to general physicians and from physicians to allied health professionals is a fundamental concept of integrated care models. A multidisciplinary AF team approach includes an efficient mix of interpersonal and communication skills, education and expertise in AF management, as well as the use of dedicated technology. This approach underlines the importance of redesigning daily practice in a way that encourages non-specialists and allied professionals to have an important role in educating patients and coordinating care, while the specialist remains medically responsible. Cultural and regional differences will determine the composition of AF teams.

8.2.3. Role of non-specialists

AF patients often initially present to general practitioners or pharmacists. Some physicians in primary care have extensive expertise in stroke prevention and initial management of AF patients. Others may seek training to acquire such knowledge. Other components of AF management (e.g. assessment of concomitant cardiovascular conditions, antiarrhythmic drug therapy, or interventional treatment) often require specialist input. Integrated AF care structures should support treatment initiation by non-specialists where appropriate, and provide ready access to specialist knowledge to optimize AF care.

8.2.4. Technology use to support atrial fibrillation care

Technology, such as decision support software, has the potential to enhance the implementation of evidence-based care and improve outcomes, when used to enhance expert advice.[338] Electronic tools can also ensure coherent communication within the AF team. With a view to support the wider use of such technology, this Task Force is providing tools free of charge, in the form of smartphone apps, to AF healthcare professionals and to AF patients.

Recommendations for an integrated approach to care

Recommendations	Class [a]	Level [b]	Refs [c]
An integrated approach with structured organization of care and follow-up should be considered in all patients with AF, aiming to improve guideline adherence and reduce hospitalization and mortality	IIa	B	330-332
Placing patients in a central role in the decision-making should be considered in order to tailor management to patient preferences and improve adherence to chronic therapy	IIa	C	330, 332, 334

AF = atrial fibrillation
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

8.3. Diagnostic workup of atrial fibrillation patients

AF is often found in patients with other, at times undiagnosed, cardiovascular conditions. Thus, all AF patients will benefit from a comprehensive cardiovascular assessment.[339]

8.3.1. Recommended evaluation in all atrial fibrillation patients

A complete medical history should be taken and all patients should undergo clinical evaluation that includes thorough assessment for concomitant conditions, establishing the AF pattern, estimation of stroke risk and AF-related symptoms, and assessment of arrhythmia-related complications such as thromboembolism or LV dysfunction. A 12-lead ECG is recommended to establish a suspected diagnosis of AF, to determine rate in AF,

and to screen for conduction defects, ischaemia, and signs of structural heart disease. Initial blood tests should evaluate thyroid and kidney function as well as serum electrolytes and full blood count. Transthoracic echocardiography is recommended in all AF patients to guide treatment decisions. Transthoracic echocardiography should be used to identify structural disease (e.g. valvular disease) and assess LV size and function (systolic and diastolic), atrial size, and right heart function.[339, 340] Although biomarkers such as natriuretic peptides are elevated in AF patients, there is insufficient data to suggest that blood-based parameters are independent markers for AF.[341-343]

8.3.2. Additional investigations in selected patients with atrial fibrillation

Ambulatory ECG monitoring in AF patients can assess the adequacy of rate control, relate symptoms with AF recurrences, and detect focal induction of bouts of paroxysmal AF. Transoesophageal echocardiography (TOE) is useful to further assess valvular heart disease and to exclude intracardiac thrombi, especially in the LAA, to facilitate early cardioversion or catheter ablation.[344] Patients with symptoms or signs of myocardial ischaemia should undergo coronary angiography or stress testing as appropriate. In patients with AF and signs of cerebral ischaemia or stroke, computed tomography (CT) or magnetic resonance imaging (MRI) of the brain is recommended to detect stroke and support decisions regarding acute management and long-term anticoagulation. Delayed-enhancement MRI of the left atrium using gadolinium contrast,[345-347] T1 mapping using cardiac MRI,[347] and intracardiac echo[348] may help to guide treatment decisions in AF, but require external validation in multicentre studies.

8.4. Structured follow-up

Most AF patients need regular follow-up to ensure continued optimal management. Follow-up may be undertaken in primary care, by specially trained nurses, by cardiologists, or by AF specialists.[325, 330] A specialist should coordinate care and follow-up. Follow-up should ensure implementation of the management plan, continued engagement of the patient, and therapy adaptation where needed.

Recommendations for diagnostic workup of AF patients

Recommendations	Class [a]	Level [b]	Refs [c]
ECG documentation is required to establish the diagnosis of AF	I	B	349
A full cardiovascular evaluation, including an accurate history, careful clinical examination, and assessment of concomitant conditions, is recommended in all AF patients	I	C	
Transthoracic echocardiography is recommended in all AF patients to guide management	I	C	339
Long-term ECG monitoring should be considered in selected patients to assess the adequacy of rate control in symptomatic patients and to relate symptoms with AF episodes	IIa	C	

AF = atrial fibrillation; ECG = electrocardiogram.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

8.5. Defining goals of atrial fibrillation management

AF management comprises therapies with prognostic impact (anticoagulation and treatment of cardiovascular conditions) and therapies predominantly providing symptomatic benefit (rate control, rhythm control, *Table 10*). Therapies with prognostic benefit need careful explanation to patients when their benefits are not directly felt. Rhythm control therapy can be successful if symptoms are controlled, even when AF recurs. Explaining the expected benefits to each patient at the start of AF management will prevent unfounded expectations and has the potential to optimize quality of life.

Table 10 Goal-based follow-up

Category	Intervention	Follow-up aspects	Performance indicator (examples)

Prognostic	Comorbidity control (relevant examples given)	Obesity	Weight loss
		Arterial hypertension	Blood pressure control
		Heart failure	Heart failure therapy
		Coronary artery disease	Statin and antiplatelet therapy Revascularization
		Diabetes	Glycaemic control
		Valvular Heart Disease	Valve repair or replacement
Prognostic	Anticoagulation	Indication (risk profile; timing, e.g. post-cardioversion); Adherence (NOAC or VKA) and INR (if VKA); NOAC dosing (co-medications, age, weight, renal function)	Stroke Bleeding Mortality
Mainly symptomatic Partly prognostic	Rate control	Symptoms Average resting heart rate < 110 bpm	EHRA score Heart failure status LV function Exercise capacity Hospitalization Therapy complications
Symptomatic at present	Rhythm control	Symptoms vs. side-effects Exclusion of proarrhythmia (PR; QRS; QTc interval)	
Relevant for implementation of and adherence to therapy	Patient education and self-care capabilities	Knowledge (about disease; about treatment; about management goals) Capabilities (what to do if…)	Adherence to therapy Directed evaluation, preferably based on systematic checklists
Relevant for chronic care management	Caregiver involvement	Who? (spouse; GP; home nurse; pharmacist) Clearly spelling out participation roles Knowledge and capabilities	Directed evaluation of task performance (e.g. via patient card) Dispensed medication GP log of follow-up visits

bpm = beats per minute; EHRA = European Heart Rhythm Association; GP = general practitioner; INR = international normalized ratio; LV = left ventricular; NOAC = non-vitamin K antagonist oral anticoagulant; VKA = vitamin K antagonist.

9 Stroke prevention therapy in atrial fibrillation patients

OAC therapy can prevent the majority of ischaemic strokes in AF patients and can prolong life.[38, 39, 42, 194, 201, 329, 350-352] It is superior to no treatment or aspirin in patients with different profiles for stroke risk.[353, 354] The net clinical benefit is almost universal, with the exception of patients at very low stroke risk, and OAC should therefore be used in most patients with AF (*Figure 8*). Despite this evidence, underuse or premature termination of OAC therapy is still common. Bleeding events, both severe and nuisance bleeds, a perceived 'high risk of bleeding' on anticoagulation, and the efforts required to monitor and dose-adjust VKA therapy are among the most common reasons for withholding or ending OAC.[352, 355-359] However, the considerable stroke risk without OAC often exceeds the bleeding risk on OAC, even in the elderly, in patients with cognitive dysfunction, or in patients with frequent falls or frailty.[360, 361] The bleeding risk on aspirin is not different to the bleeding risk on VKA[362] or NOAC therapy,[354, 363] while VKA and NOACs, but not aspirin, effectively prevent strokes in AF patients.[38, 354, 362, 363]

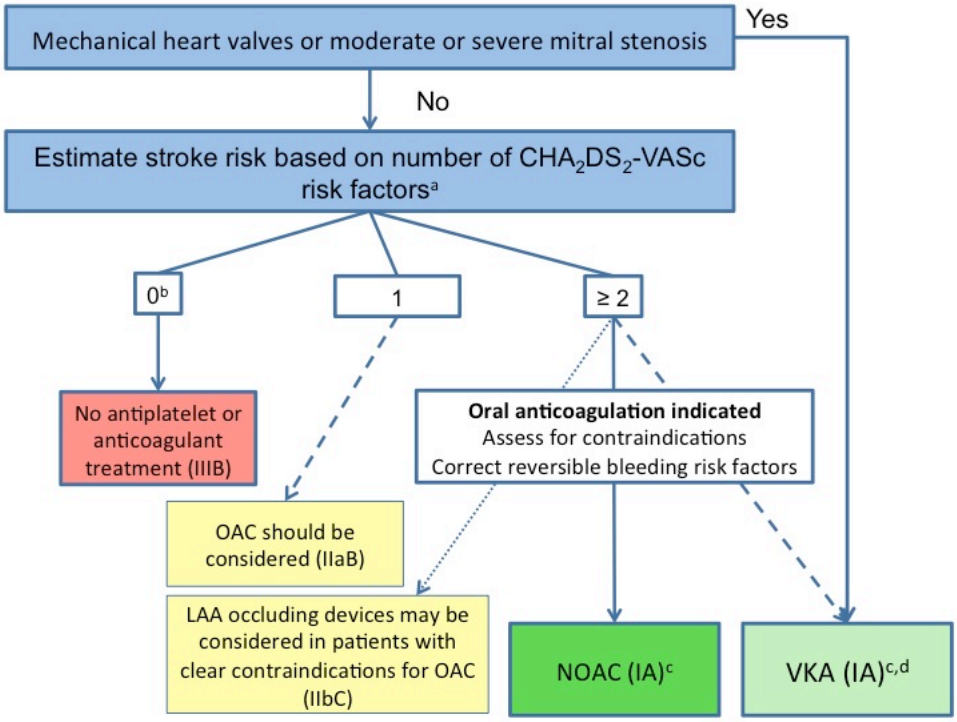


Figure 8 Stroke prevention in AF.
AF = atrial fibrillation; CHA_2DS_2-VASc = Congestive Heart failure, hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female); LAA = left atrial appendage; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulation; VKA = vitamin K antagonist.
[a]Congestive heart failure, hypertension, age ≥75 years (2 points), diabetes, prior stroke/TIA/embolus (2 points), vascular disease, age 65–74, female sex.
[b]Includes women without other stroke risk factors.
[c]IIaB for women with only one additional stroke risk factor,
[d]IB for patients with mechanical heart valves or mitral stenosis

9.1. Prediction of stroke and bleeding risk

9.1.1. Clinical risk scores for stroke and systemic embolism

Simple, clinically applicable stroke risk-stratification schemes in AF patients were developed in the late 1990s in small cohort studies and have later been refined and validated in larger populations.[364-368] The introduction of the CHA_2DS_2-VASc score (*Table 11*) has clearly simplified the initial decision for OAC in AF patients. Since its first incorporation in the ESC guidelines in 2010,[369] it has been widely used.[370] We recommend estimating stroke risk in AF patients based on the CHA_2DS_2-VASc score.[368] In general, patients without clinical stroke risk factors do not need antithrombotic therapy, while patients with stroke risk factors (i.e. CHA_2DS_2-VASc score of 1 or more for men, and 2 or more for women) are likely to benefit from OAC.

Table 11 Clinical risk factors for stroke, transient ischemic attack, and systemic embolism in the CHA_2DS_2-VASc score.

CHA_2DS_2-VASc risk factor	Points
Congestive heart failure Signs/symptoms of heart failure or objective evidence of reduced left-ventricular ejection fraction	+1

Hypertension Resting blood pressure > 140/90 mmHg on at least two occasions or current antihypertensive treatment	+1
Age 75 years or older	+2
Diabetes mellitus Fasting glucose > 125 mg/dL or treatment with oral hypoglycaemic agent and/or insulin	+1
Previous stroke, transient ischemic attack, or thromboembolism	+2
Vascular disease Previous myocardial infarction, peripheral artery disease, or aortic plaque	+1
Age 65 to 74 years	+1
Sex category (female)	+1

CHA_2DS_2-VASc = Congestive Heart failure, hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female).

Other, less established risk factors for stroke include unstable international normalized ratio (INR) and low time in therapeutic range (TTR) in patients treated with VKAs; previous bleed or anaemia; alcohol excess and other markers for decreased therapy adherence; CKD; elevated high-sensitivity troponin T; and elevated N-terminal pro-B-type natriuretic peptide.

9.1.2. Anticoagulation in patients with a CHA_2DS_2-VASc score of 1 in men and 2 in women

Controlled trials studying OAC in AF patients have been enriched for patients at high risk of stroke,[38, 39, 42, 194, 201, 329, 351, 352] and hence there is strong evidence that patients with a CHA_2DS_2-VASc risk score of 2 or more in men, and 3 or more in women benefit from OAC. Fortunately, we now have a growing evidence-base regarding stroke risk in patients with one clinical risk factor (i.e. CHA_2DS_2-VASc score of 1 for men, and 2 for women), although this relies largely on observed stroke rates in patients not receiving OAC. In many of these patients, anticoagulation seems to provide a clinical benefit.[371-375] The rates of stroke and thromboembolism vary considerably in patients with CHA_2DS_2-VASc scores of 1 or 2 due to differences in outcomes, populations, and anticoagulation status (*Web Addenda Table 1).*[371, 376, 377, 1041] OAC should be considered for men with a CHA_2DS_2-VASc score of 1 and women with a score of 2, balancing the expected stroke reduction, bleeding risk, and patient preference. Importantly, age (65 years and older) conveys a relatively high and continuously increasing stroke risk that also potentiates other risk factors (such as heart failure and sex). Hence, an individualized weighing of risk, as well as patient preferences, should inform the decision to anticoagulate patients with only one CHA_2DS_2-VASc risk factor, apart from female sex. Female sex does not appear to increase stroke risk in the absence of other stroke risk factors (*Web Addenda Table 1*).[378, 379]

Measurement of cardiac troponin (high-sensitivity troponin T or I) and N-terminal pro-B-type natriuretic peptide may provide additional prognostic information in selected AF patients.[380-382] Biomarker-based risk scores may in the future prove helpful to better stratify patients (e.g. those at a truly low risk of stroke).[75, 382]

9.1.3. Clinical risk scores for bleeding

Several bleeding risk scores have been developed, mainly in patients on VKAs. These include HAS-BLED (hypertension, abnormal renal/liver function [1 point each], stroke, bleeding history or predisposition, labile INR, elderly [>65 years], drugs/alcohol concomitantly [1 point each]), ORBIT (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation), and more recently, the ABC (age, biomarkers, clinical history) bleeding score, which also makes use of selected biomarkers.[383-385] Stroke and bleeding risk factors overlap (compare *Table 11* and *Table 12*). For example, older age is one of the most important predictors of both ischaemic stroke and bleeding in AF patients.[386, 387] A high bleeding risk score should generally not result in withholding OAC. Rather, bleeding risk factors should be identified and treatable factors corrected (see Section 8.5). *Table 12* provides details of modifiable bleeding risk factors.

Table 12 Modifiable and non-modifiable risk factors for bleeding in anticoagulated patients based on bleeding risk scores.

Modifiable bleeding risk factors
Hypertension (especially when systolic blood pressure is > 160 mmHg)[a,b,c]

Labile INR (in patients on vitamin K antagonists) or time in therapeutic range < 60%[a]
Medication predisposing to bleeding, such as antiplatelet drugs and non-steroidal anti-inflammatory drugs[a,d]
Excess alcohol (≥ 8 drinks/week)[a,b]
Potentially modifiable bleeding risk factors
Anaemia[b,c,d]
Impaired renal function[a,b,c,d]
Impaired liver function[a,b]
Reduced platelet count or function[b]
Non-modifiable bleeding risk factors
Age[e] (> 65 years)[a] (≥ 75 years)[b,c,d]
History of major bleeding[a,b,c,d]
Previous stroke[a,b]
Dialysis-dependent CKD or renal transplant[a,c]
Cirrhotic liver disease[a]
Malignancy[b]
Genetic factors[b]
Biomarker-based bleeding risk factors
High-sensitivity troponin T[e]
Growth differentiation factor-15[e]
Serum creatinine/estimated CrCL[e]

ABC = age, biomarkers, clinical history; ATRIA = AnTicoagulation and Risk factors In Atrial fibrillation; CKD = chronic kidney disease; CrCl = creatinine clearance; HAS-BLED = hypertension, abnormal renal/liver function (1 point each), stroke, bleeding history or predisposition, labile INR, elderly (>65 years), drugs/alcohol concomitantly (1 point each); INR = international normalized ratio; ORBIT = Outcomes Registry for Better Informed Treatment of Atrial Fibrillation; TTR = time in therapeutic range; VKA = vitamin K antagonist.
[a]Derived from the HAS-BLED score.[384]
[b]Derived from the HEMORR$_2$HAGES score.[383]
[c]Derived from the ATRIA score.[385]
[d]Derived from the ORBIT score.[388]
[e]Derived from the ABC bleeding score.[387]

Recommendations for prediction of stroke and bleeding risk

Recommendations	Class [a]	Level [b]	Refs [c]
The CHA_2DS_2-VASc score is recommended for stroke risk prediction in patients with AF	I	A	368, 371, 386
Bleeding risk scores should be considered in AF patients on oral anticoagulation to identify modifiable factors for major bleeding	IIa	B	384, 386, 387, 389-392
Biomarkers such as high-sensitivity troponin and N-terminal pro-B-type natriuretic peptide may be considered to further refine stroke and bleeding risk in AF patients	IIb	B	380-382, 387, 393

AF = atrial fibrillation; CHA_2DS_2-VASc = Congestive Heart failure, hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female); OAC = oral anticoagulation.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

9.2. Stroke prevention

9.2.1. Vitamin K antagonists

Warfarin and other VKAs were the first anticoagulants used in AF patients. VKA therapy reduces risk of stroke by two-thirds and mortality by one-quarter compared with control (aspirin or no therapy).[38] VKAs have been used in many patients throughout the world with good outcomes,[394-396] and this is reflected in the warfarin arms of the NOAC trials (see Section 8.2.2.). The use of VKAs is limited by the narrow therapeutic interval, necessitating frequent monitoring and dose adjustments, but VKAs, when delivered with adequate TTR, are

effective for stroke prevention in AF patients. Clinical parameters can help to identify patients who are likely to achieve a decent TTR on VKA therapy.[397] These have been summarized in the SAMe-TT_2R_2 score. Patients who fare well on this score, when treated with a VKA, have on average a higher TTR than patients who do not fare well on the score.[398, 399] VKAs are currently the only treatment with established safety in AF patients with rheumatic mitral valve disease and/or a mechanical heart valve prosthesis.[400]

9.2.2. Non-vitamin K antagonist oral anticoagulants

NOACs, including the direct thrombin inhibitor dabigatran and the factor Xa inhibitors apixaban, edoxaban, and rivaroxaban, are suitable alternatives to VKAs for stroke prevention in AF (*Table 13*). Their use in clinical practice is increasing rapidly.[401] All NOACs have a predictable effect (onset and offset) without need for regular anticoagulation monitoring. The phase III trials have been conducted with carefully selected doses of the NOACs, including clear rules for dose reduction that should be followed in clinical practice (*Table 13*).

Apixaban

In the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial,[319] apixaban reduced stroke or systemic embolism by 21% compared with warfarin, combined with a 31% reduction in major bleeding and an 11% reduction in all-cause mortality (all statistically significant). Rates of haemorrhagic stroke and intracranial haemorrhage, but not of ischaemic stroke, were lower on apixaban. Rates of gastrointestinal bleeding were similar between the two treatment arms.[402]

Apixaban is the only NOAC that has been compared with aspirin in AF patients: apixaban significantly reduced stroke or systemic embolism by 55% compared with aspirin, with no significant difference in rates of major bleeding or intracranial haemorrhage.[354, 403]

Dabigatran

In the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) study,[318, 404] dabigatran 150 mg twice daily reduced stroke and systemic embolism by 35% compared with warfarin without a significant difference in major bleeding events. Dabigatran 110 mg twice daily was non-inferior to warfarin for prevention of stroke and systemic embolism, with 20% fewer major bleeding events. Both dabigatran doses significantly reduced haemorrhagic stroke and intracranial haemorrhage. Dabigatran 150 mg twice daily significantly reduced ischaemic stroke by 24% and vascular mortality by 12%, while gastrointestinal bleeding was significantly increased by 50%. There was a non-significant numerical increase in the rate of myocardial infarction with both dabigatran doses,[318, 404] which has not been replicated in large post-authorization analyses.[396] These data have also replicated the benefit of dabigatran over VKAs found in the RE-LY trial in patients enriched for the higher dabigatran dose (150 mg twice daily).[396]

Edoxaban

In the ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48) trial,[321] edoxaban 60 mg once daily and edoxaban 30 mg once daily (with dose reductions in certain patients according to *Table 13*), were compared with adjusted-dose warfarin.[405] Edoxaban 60 mg once daily was non-inferior to warfarin (primary outcome, HR 0.87; 97.5% CI 0.73–1.04; P = 0.08). In an on-treatment analysis, edoxaban 60 mg once daily significantly reduced stroke or systemic embolism by 21% and significantly reduced major bleeding events by 20% compared with warfarin, while edoxaban 30 mg once daily was non-inferior to warfarin for prevention of stroke and systemic embolism but significantly reduced major bleeding events by 53%. Cardiovascular death was reduced in patients randomized to edoxaban 60 mg once daily or edoxaban 30 mg once daily compared with warfarin. Only the higher dose regimen has been approved for stroke prevention in AF.

Rivaroxaban

In the ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial,[320] patients were randomized to rivaroxaban 20 mg once daily or VKA, with a dose adjustment to 15 mg daily for those with estimated CrCl 30–49 mL/min by the Cockroft–Gault formula. Rivaroxaban was non-inferior to warfarin for the prevention of stroke and systemic embolism in the intent-to-treat analysis, while the per-protocol on-treatment analysis achieved statistical superiority with a 21% reduction in stroke or systemic embolism compared with warfarin. Rivaroxaban did not reduce the rates of mortality, ischaemic stroke, or major bleeding events compared to VKA. There was an increase in gastrointestinal bleeding events, but a significant reduction in haemorrhagic stroke and intracranial haemorrhage with rivaroxaban compared with warfarin. Comparable event rates have been reported in post-authorization analyses, which are part of the post-approval risk-management process.[406, 407]

Table 13 NOACs compared with warfarin in controlled trials

	Dabigatran (RE-LY)	Rivaroxaban (ROCKET-AF)	Apixaban (ARISTOTLE)	Edoxaban (ENGAGE AF-TIMI 48)
Mechanism	Oral direct thrombin inhibitor	Oral direct factor Xa inhibitor	Oral direct factor Xa inhibitor	Oral direct factor Xa inhibitor
Bioavailability, %	6	66 fasting, 80–100 with food	50	62
Time to peak levels, h	3	2–4	3	1–2
Half-life, h	12–17	5–13	9–14	10–14
Excretion	80% renal	66% liver, 33% renal	27% renal	50% renal
Dose	150 mg or 110 mg twice daily	20 mg once daily	5 mg twice daily	60 mg or 30 mg once daily
Dose reduction in selected patients		Rivaroxaban 15 mg once daily if CrCl 30–49 mL/min	Apixaban 2.5 mg twice daily if at least 2 of age ≥ 80 years, body weight ≤ 60 kg or serum creatinine level ≥ 1.5 mg/dL (133 µmol/L)	Edoxaban 60 mg reduced to 30 mg once daily, and edoxaban 30 mg reduced to 15 mg once daily, if any of the following: CrCl 30–50 mL/min, body weight ≤ 60 kg, concomitant use of verapamil or quinidine or dronedarone
Study design	Randomized, open-label	Randomized, double-blind	Randomized, double-blind	Randomized, double-blind
Number of patients	18,113	14,264	18,201	21,105
Follow-up period, years	2	1.9	1.8	2.8
Randomized groups	Dose-adjusted warfarin vs. blinded doses of dabigatran (150 mg twice daily or 110 mg twice daily)	Dose-adjusted warfarin vs. rivaroxaban 20 mg once daily	Dose-adjusted warfarin vs. apixaban 5 mg twice daily	Dose-adjusted warfarin vs. edoxaban (60 mg once daily or 30 mg once daily)
Age, years	Mean ± SD 71.5 ± 8.7	Median 73; IQR 65–78	Median 70; IQR 63–76	Median 72; IQR 64–78
Men, %	63.6	60.3	64.5	61.9
$CHADS_2$ score (mean)	2.1	3.5	2.1	2.8

	Warfarin	Dabigatran 150	Dabigatran 110	Warfarin	Rivaroxaban	Warfarin	Apixaban	Warfarin	Edoxaban 60	Edoxaban 30
	n = 6022	*n* = 6076	*n* = 6015	*n* = 7133	*n* = 7131	*n* = 9081	*n* = 9120	*n* = 7036	*n* = 7035	*n* = 7034
	Event rate, %/year	Event rate, %/year (RR vs. warfarin)	Event rate, %/year (RR vs. warfarin)	Event rate, %/year	Event rate, %/year (HR vs. warfarin)	Event rate, %/year	Event rate, %/year (HR vs. warfarin)	Event rate, %/year	Event rate, %/year (HR vs. warfarin)	Event rate, %/year (HR vs. warfarin)
Stroke/systemic embolism	1.72	1.12 (0.65, 0.52–0.81; *P* for non-inferiority and superiority < 0.001)	1.54 (0.89, 0.73–1.09; *P* for non-inferiority < 0.001)	2.42	2.12 (0.88, 0.75–1.03; *P* for non-inferiority < 0.001, *P* for superiority = 0.12)	1.60	1.27 (0.79, 0.66–0.95; *P* < 0.001 for non-inferiority, *P* = 0.01 for superiority)	1.80	1.57 (0.87, 0.73–1.04; *P* < 0.001 for non-inferiority, *P* = 0.08 for superiority)	2.04 (1.13, 0.96–1.34; *P* = 0.005 for non-inferiority, *P* = 0.10 for superiority)
Ischaemic stroke	1.22	0.93 (0.76, 0.59–0.97; *P* = 0.03)	1.34 (1.10, 0.88–1.37; *P* = 0.42)	1.42	1.34 (0.94; 0.75–1.17; *P* = 0.581)	1.05	0.97 (0.92, 0.74–1.13; *P* = 0.42)	1.25	1.25 (1.00, 0.83–1.19; *P* = 0.97)	1.77 (1.41, 1.19–1.67; *P* < 0.001)
Haemorrhagic stroke	0.38	0.10 (0.26, 0.14–0.49; *P* < 0.001)	0.12 (0.31, 0.17–0.56; *P* < 0.001)	0.44	0.26 (0.59; 0.37–0.93; *P* = 0.024)	0.47	0.24 (0.51, 0.35–0.75; *P* < 0.001)	0.47	0.26 (0.54, 0.38–0.77; *P* < 0.001)	0.16 (0.33, 0.22–0.50; *P* < 0.001)
Major bleeding	3.61	3.40 (0.94, 0.82–1.08; *P* = 0.41)	2.92 (0.80, 0.70–0.93; *P* = 0.003)	3.45	3.60 (1.04; 0.90-2.30; *P* = 0.58)	3.09	2.13 (0.69, 0.60–0.80; *P* < 0.001)	3.43	2.75 (0.80, 0.71–0.91; *P* < 0.001)	1.61 (0.47, 0.41–0.55; *P* < 0.001)
Intracranial bleeding	0.77	0.32 (0.42, 0.29–0.61; *P* < 0.001)	0.23 (0.29 0.19–0.45; *P* < 0.001)	0.74	0.49 (0.67; 0.47–0.93; *P* = 0.02)	0.80	0.33 (0.42, 0.30–0.58; *P* < 0.001)	0.85	0.39 (0.47, 0.34–0.63; *P* < 0.001)	0.26 (0.30, 0.21–0.43; *P* < 0.001)
Gastrointestinal major bleeding	1.09	1.60 (1.48, 1.19–1.86; *P* < 0.001)	1.13 (1.04, 0.82–1.33; *P* = 0.74)	1.24	2.00 (1.61; 1.30-1.99; *P* < 0.001)	0.86	0.76 (0.89, 0.70–1.15; *P* = 0.37)	1.23	1.51 (1.23, 1.02–1.50; *P* = 0.03)	0.82 (0.67, 0.53–0.83; *P* < 0.001)
Myocardial infarction	0.64	0.81 (1.27, 0.94-1.71; *P* = 0.12)	0.82 (1.29, 0.96-1.75; P = 0.09)	1.12	0.91 (0.81; 0.63–1.06; P = 0.12)	0.61	0.53 (0.88, 0.66–1.17; P = 0.37)	0.75	0.70 (0.94, 0.74–1.19; P = 0.60)	0.89 (1.19, 0.95–1.49; P = 0.13)
Death from any cause	4.13	3.64 (0.88, 0.77–1.00; *P* = 0.051)	3.75 (0.91, 0.80–1.03; *P* = 0.13)	2.21	1.87 (0.85; 0.70–1.02; *P* = 0.07)	3.94	3.52 (0.89, 0.80–0.99; *P* = 0.047)	4.35	3.99 (0.92, 0.83–1.01; *P* = 0.08)	3.80 (0.87, 0.79–0.96; *P* = 0.006)

AF = atrial fibrillation; $CHADS_2$ = Cardiac failure, Hypertension, Age, Diabetes, Stroke (Doubled); CrCl = creatinine clearance; HR = hazard ratio; IQR = interquartile range (25^{th} to 75^{th} quartiles); RR = risk ratio; SD = standard deviation.

RRs and HRs compared to warfarin therapy are presented with 95% confidence intervals and *P*-values.

9.2.3. Non-vitamin K antagonist oral anticoagulants or vitamin K antagonists

Both VKAs and NOACs are effective for the prevention of stroke in AF. A meta-analysis[39] based on the high-dose treatment groups of the pivotal studies of warfarin versus NOACs included 42,411 patients receiving a NOAC and 29,272 receiving warfarin. NOACs in these dosages significantly reduced stroke or systemic embolic events by 19% compared with warfarin (RR 0.81; 95% CI 0.73–0.91; $P < 0.0001$), mainly driven by a reduction in haemorrhagic stroke (RR 0.49; 95% CI 0.38–0.64; $P < 0.0001$). Mortality was 10% lower in patients randomized to NOAC therapy (RR 0.90; 95% CI 0.85–0.95; $P = 0.0003$) and intracranial haemorrhage was halved (RR 0.48; 95% CI 0.39–0.59; $P < 0.0001$), while gastrointestinal bleeding events were more frequent (RR 1.25; 95% CI 1.01–1.55; $P = 0.04$).[39] The stroke reduction with NOACs was consistent in all evaluated subgroups, while there was a suggestion of greater relative reduction in bleeding with NOACs at centres with poor INR control (interaction $P = 0.022$). Notably, the substantial reduction in intracranial haemorrhage by NOACs compared with warfarin seems unrelated to poor or good INR control.[408, 409]

9.2.4. Oral anticoagulation in atrial fibrillation patients with chronic kidney disease

CKD is associated with stroke and bleeding in large data sets.[410, 411] Anticoagulation can be safely used in AF patients with moderate or moderate-to-severe CKD (glomerular filtration rate [GFR] ≥ 15 mL/min): the SPAF (Stroke Prevention in Atrial Fibrillation) III trial randomized 805/1936 participants with stage 3 CKD (estimated GFR < 59 mL/min/1.73 m^2), and reported good outcomes on warfarin (INR 2–3).[412] This finding is supported by a large Swedish database, in which stroke risk was lower in CKD patients with AF treated with warfarin (adjusted HR 0.76; 95% CI 0.72–0.80),[413] while bleeding was also slightly increased, especially during therapy initiation.[414] In a meta-analysis of the major NOAC trials, patients with mild or moderate CKD suffered fewer strokes, systemic emboli, or major bleeding events on NOACs than on warfarin.[415] Kidney function should be regularly monitored in AF patients on OAC to allow dose adaptation for those on NOACs (*Table 14*) and to refine risk estimation.[416]

Table 14 Inclusion criteria, dose adjustments, and outcomes in patients with chronic kidney disease in the four major randomized trials comparing NOACs with warfarin in patients with AF. Adapted from Hart *et al.*[316]

	Dabigatran (RE-LY)[318, 425]	Rivaroxaban (ROCKET-AF)[320, 426]	Apixaban (ARISTOTLE)[319, 427]	Edoxaban (ENGAGE AF-TIMI 48)[321]
Renal clearance	80%	35%	25%	50%
Number of patients	18,113	14,264	18,201	21,105
Dose	150 mg or 110 mg twice daily	20 mg once daily	5 mg twice daily	60 mg or 30 mg once daily
Exclusion criteria for CKD	CrCl < 30 mL/min	CrCl < 30 mL/min	Serum creatinine > 2.5 mg/dL or CrCl < 25 mL/min	CrCl < 30 mL/min
Dose adjustment with CKD	None	15 mg once daily if CrCl < 30–49 mL/min	2.5 mg twice daily if serum creatinine ≥ 1.5 mg/dL plus age ≥ 80 years or weight ≤ 60 kg	30 mg or 15 mg once daily if CrCl < 50 mL/min
Per cent of patients with CKD	20% with CrCl 30–49 mL/min	21% with CrCl 30–49 mL/min	15% with CrCl 30–50 mL/dL	19% with CrCl < 50 mL/min
Reduction of stroke and systemic embolism	No interaction with CKD status	No interaction with CKD status	No interaction with CKD status	NA
Reduction of major haemorrhages compared with warfarin	Reduction in major haemorrhage with dabigatran was greater in patients with	Major haemorrhage similar	Reduction in major haemorrhage with apixaban	NA

	estimated GFR > 80 mL/min with either dose			

AF = atrial fibrillation; CKD = chronic kidney disease; CrCl = creatinine clearance; GFR = glomerular filtration rate; NA = not available; NOAC = non-vitamin K antagonist oral anticoagulant.

9.2.5. Oral anticoagulation in atrial fibrillation patients on dialysis

Approximately one in eight dialysis patient suffers from AF, with an incidence rate of 2.7/100 patient-years.[417] AF is associated with increased mortality in patients on dialysis.[417] There are no randomized trials assessing OAC in haemodialysis patients,[418] and no controlled trials of NOACs in patients with severe CKD (CrCl < 25–30 mL/min).[318-321] Warfarin use was associated either with a neutral or increased risk of stroke in database analyses of patients on dialysis,[419-421] including a population-based analysis in Canada (adjusted HR for stroke 1.14; 95% CI 0.78–1.67, adjusted HR for bleeding 1.44; 95% CI 1.13–1.85).[422] In contrast, data from Denmark suggest a benefit of OAC in patients on renal replacement therapy.[423] Hence, controlled studies of anticoagulants (both VKAs and NOACs) in AF patients on dialysis are needed.[424]

9.2.6. Patients with atrial fibrillation requiring kidney transplantation

There are no randomized trials assessing OAC in patients after kidney transplantation. The prescription of NOAC therapy should be guided by the estimated GFR of the transplanted kidney. Potential pharmacokinetic interactions of OAC with immunosuppressive agents should be considered.

9.2.7. Antiplatelet therapy as an alternative to oral anticoagulants

The evidence supporting antiplatelet monotherapy for stroke prevention in AF is very limited.[38, 428-430] VKA therapy prevents stroke, non-central nervous system embolus, myocardial infarction, and vascular death better than single or dual antiplatelet therapy with aspirin and clopidogrel (annual risk of 5.6% for aspirin and clopidogrel vs. 3.9% with VKA therapy).[431] Even greater benefits were seen in VKA-treated patients with a high TTR.[432] Antiplatelet therapy increases bleeding risk, especially dual antiplatelet therapy (2.0% vs. 1.3% with antiplatelet monotherapy; $P < 0.001$),[433] with bleeding rates that are similar to those on OAC.[354, 362, 431, 434] Thus, antiplatelet therapy cannot be recommended for stroke prevention in AF patients.

Recommendations for stroke prevention in patients with AF

Recommendations	Class [a]	Level [b]	Refs [c]
Oral anticoagulation therapy to prevent thromboembolism is recommended for all male AF patients with a CHA_2DS_2-VASc score of 2 or more	I	A	38, 318-321, 354, 404
Oral anticoagulation therapy to prevent thromboembolism is recommended in all female AF patients with a CHA_2DS_2-VASc score of 3 or more	I	A	38, 318-321, 354, 404
Oral anticoagulation therapy to prevent thromboembolism should be considered in male AF patients with a CHA_2DS_2-VASc score of 1, considering individual characteristics and patient preferences	IIa	B	371, 375-377
Oral anticoagulation therapy to prevent thromboembolism should be considered in female AF patients with a CHA_2DS_2-VASc score of 2, considering individual characteristics and patient preferences	IIa	B	371, 376, 377
Vitamin K antagonist therapy (INR 2.0–3.0 or higher) is recommended for stroke prevention in AF patients with moderate-to-severe mitral stenosis or mechanical heart valves	I	B	274, 435-440
When oral anticoagulation is initiated in a patient with AF who is eligible for a NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), a NOAC is recommended in preference to a Vitamin K antagonist	I	A	39, 318-321, 404
When patients are treated with a vitamin K antagonist, time	I	A	395, 432, 441-444

in therapeutic range (TTR) should be kept as high as possible and closely monitored			
AF patients already on treatment with a vitamin K antagonist may be considered for NOAC treatment if TTR is not well controlled despite good adherence, or if patient preference without contraindication (e.g. prosthetic valve)	IIb	A	39, 318, 319, 404, 408
Combinations of oral anticoagulants and platelet inhibitors increase bleeding risk and should be avoided in AF patients without another indication for platelet inhibition	III (harm)	B	429, 445
In male or female AF patients without additional stroke risk factors, anticoagulant or antiplatelet therapy is not recommended for stroke prevention	III (harm)	B	368, 371, 376, 377
Antiplatelet monotherapy is not recommended for stroke prevention in AF patients, regardless of stroke risk	III (harm)	A	38, 429, 430
NOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) are not recommended in patients with mechanical heart valves (Level of evidence B) or moderate-to-severe mitral stenosis (Level of evidence C)	III (harm)	B/C	318-321, 400, 404

AF = atrial fibrillation; CHA_2DS_2-VASc = Congestive Heart failure, hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female); INR = international normalized ratio; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulation; TTR = time in therapeutic range; VKA = vitamin K antagonist.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

9.3. Left atrial appendage occlusion and exclusion

9.3.1. Left atrial appendage occlusion devices

Interventional LAA occlusion,[446-449] and limited experience with percutaneous LAA ligation, has mainly been reported in observational studies and registries. Only one device (Watchman®) has been compared with VKA therapy in randomized trials (PROTECT AF [Watchman Left Atrial Appendage System for Embolic Protection in Patients With AF trial], see *Web Addenda Table 2*; and PREVAIL [Prospective Randomized Evaluation of the Watchman LAA Closure Device In Patients with AF Versus Long Term Warfarin Therapy trial]).[449-451] In these data sets, LAA occlusion was non-inferior to VKA treatment for the prevention of stroke in AF patients with moderate stroke risk, with a possibility of lower bleeding rates in the patients who continued follow-up.[452, 453] These data were confirmed in a patient-level meta-analysis of the two trials and their associated registries.[453] LAA occlusion may also reduce stroke risk in patients with contraindications to OAC.[454, 455] The implantation procedure can cause serious complications,[446, 456-458] with high event rates reported in analyses from insurance databases and systematic reviews, possibly identifying a certain degree of reporting bias.[446, 456] A large recent European registry reported a high rate of implantation success (98%), with an acceptable procedure-related complication rate of 4% at 30 days.[459] Most patients who historically would be considered unsuitable for OAC therapy seem to do relatively well on contemporarily managed OAC.[396, 407, 460] Adequately powered controlled trials are urgently needed to inform the best use of these devices, including LAA occluders in patients who are truly unsuitable for OAC or in patients who suffer a stroke on OAC, randomized comparisons of LAA occluders with NOACs, and assessment of the minimal antiplatelet therapy acceptable after LAA occlusion.

9.3.2. Surgical left atrial appendage occlusion or exclusion

Surgical LAA occlusion or exclusion concomitant to cardiac surgery has been performed for many decades and with various techniques. Multiple observational studies indicate the feasibility and safety of surgical LAA occlusion/exclusion, but only limited controlled trial data are available.[461-464] Residual LAA flow or incomplete LAA exclusion can increase stroke risk.[465] In most studies, LAA occlusion/exclusion was performed during other open heart surgery, and more recently in combination with surgical ablation of AF[463] or as a stand-alone thoracoscopic procedure. One randomized trial evaluating the role of concomitant AF surgery and LAA occlusion reported in 2015, without a clear benefit of LAA exclusion for stroke prevention in the subgroup undergoing AF surgery.[466] A large randomized trial is currently underway.[467]

Recommendations for occlusion or exclusion of the LAA

Recommendations	Class [a]	Level [b]	Refs [c]
After surgical occlusion or exclusion of the LAA, it is recommended to continue anticoagulation in at-risk patients with AF for stroke prevention	I	B	461, 462
LAA occlusion may be considered for stroke prevention in patients with AF and contraindications for long-term anticoagulant treatment (e.g. those with a previous life-threatening bleed without a reversible cause)	IIb	B	449, 453, 454
Surgical occlusion or exclusion of the LAA may be considered for stroke prevention in patients with AF undergoing cardiac surgery	IIb	B	463
Surgical occlusion or exclusion of the LAA may be considered for stroke prevention in patients undergoing thoracoscopic ablation surgery	IIb	B	468

AF = atrial fibrillation; LAA = left atrial appendage.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

9.4. Secondary stroke prevention

The most important risk factors for stroke in patients with AF are advanced age and previous cardioembolic stroke or TIA,[382] emphasizing the need for OAC in these patients. The highest risk of recurrent stroke is in the early phase after a first stroke or TIA.[469, 470]

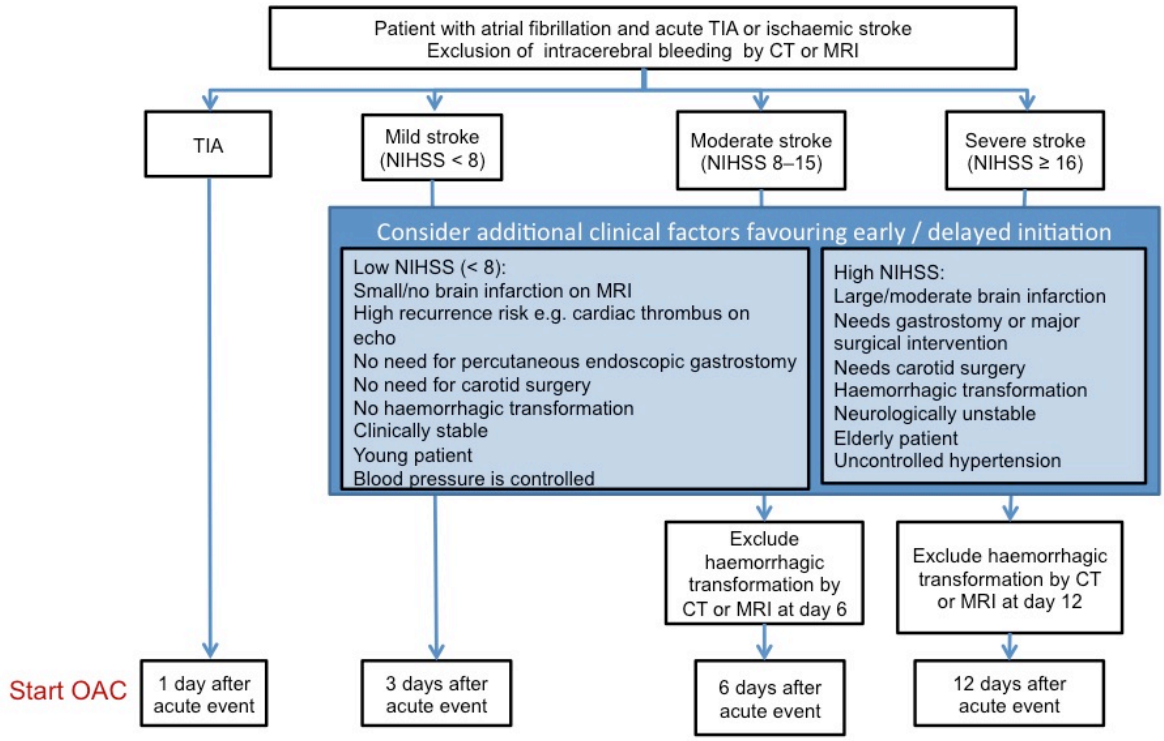
9.4.1. Treatment of acute ischaemic stroke

Systemic thrombolysis with recombinant tissue plasminogen activator (rtPA) is an effective and approved medical treatment for acute ischaemic stroke in patients presenting within 4.5 hours of symptom onset.[471] Systemic thrombolysis is contraindicated in patients on therapeutic OAC.[472, 473] Recombinant tissue plasminogen activator can be given in patients treated with a VKA if the INR is below 1.7,[474] or in dabigatran-treated patients with a normal activated partial thromboplastin time and last intake of drug > 48 hours previously (based on expert consensus).[472] Whether specific NOAC antidotes[475] could be used followed by systemic thrombolysis needs to be investigated. Thrombectomy can be performed in anticoagulated patients with distal occlusion of the internal carotid artery or middle cerebral artery in a 6-hour window.[476]

9.4.2. Initiation of anticoagulation after transient ischaemic attack or ischaemic stroke

Data on the optimal use of anticoagulants (heparin, low-molecular-weight heparin, heparinoid, VKA, NOAC) in the first days after a stroke are scarce. Parenteral anticoagulants seem to be associated with a non-significant reduction in recurrent ischaemic stroke when administered 7 to 14 days after the acute stroke (odds ratio [OR] 0.68; 95% CI 0.44–1.06), with a significant increase in symptomatic intracranial bleeding (OR 2.89; 95% CI 1.19–7.01), and a similar rate of death or disability at final follow-up.[477] It seems likely that the bleeding risk on parenteral anticoagulation exceeds the stroke prevention benefit in the first days after a large stroke, whereas patients with a TIA or a small stroke may benefit from early (immediate) initiation or continuation of anticoagulation. Therefore, we propose to initiate anticoagulation in AF patients between 1 and 12 days after an ischaemic stroke, depending on its severity (*Figure 9*).[478] We suggest repeat brain imaging to determine the optimal initiation of anticoagulation in patients with a large stroke at risk for haemorrhagic transformation. Long-term OAC with a VKA[363, 479-481] or NOAC[482] conveys benefits in AF patients who survived a stroke. NOACs seem to convey slightly better outcomes, mainly driven by fewer intracranial haemorrhages and haemorrhagic strokes (OR 0.44, 95% CI 0.32–0.62).[482] Detailed data for edoxaban have not yet been published.[321] If a patient suffers a stroke or TIA whilst taking an anticoagulant, switching to another anticoagulant should be considered.

Figure 9 Initiation or continuation of anticoagulation in AF patients after a stroke or TIA. This approach is based on consensus rather than prospective data.



AF = atrial fibrillation; CT = computed tomography; MRI = magnetic resonance imaging; NIHSS = National Institutes of Health stroke severity scale (available at http://www.strokecenter.org/wp-content/uploads/2011/08/NIH_Stroke_Scale.pdf); OAC = oral anticoagulation; TIA = transient ischaemic attack.

9.4.3. Initiation of anticoagulation after intracranial haemorrhage

No prospective studies have investigated the benefit or risk of the initiation of OAC after intracranial haemorrhage,[483] and patients with a history of intracranial bleeding were excluded from the randomized trials comparing NOACs with VKAs. The available evidence indicates that anticoagulation in patients with AF can be reinitiated after 4–8 weeks, especially when the cause of bleeding or the relevant risk factor (e.g. uncontrolled hypertension) has been treated, and that such treatment leads to fewer recurrent (ischaemic) strokes and lower mortality.[460, 484] If anticoagulation is resumed, it seems reasonable to consider anticoagulants with a low bleeding risk.[39] *Figure 10* depicts a consensus opinion on the initiation or resumption of OAC after an intracranial haemorrhage. We recommend a multidisciplinary decision with input from stroke physicians/neurologists, cardiologists, neuroradiologists, and neurosurgeons.

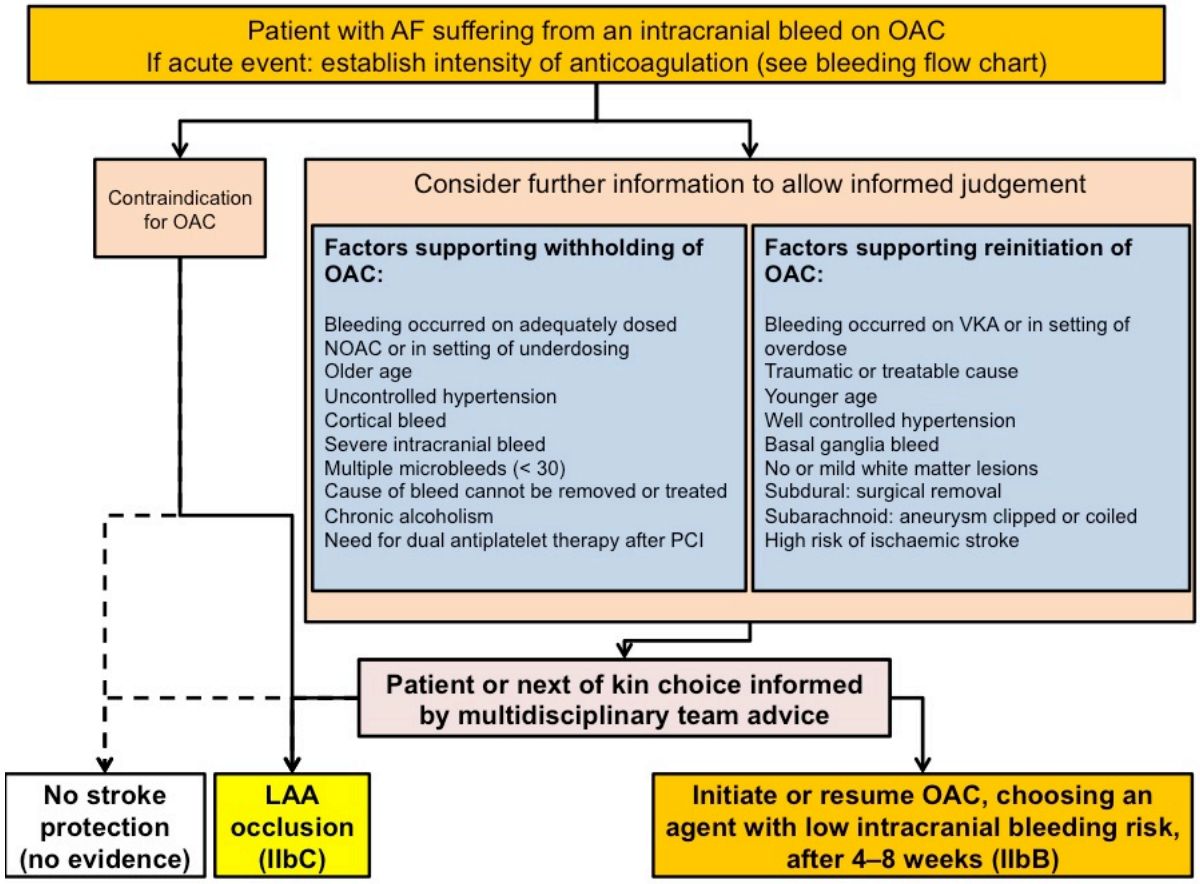


Figure 10 Initiation or resumption of anticoagulation in AF patients after an intracranial bleed. This approach is based on consensus and retrospective data. In all patients, evaluation by a multidisciplinary panel is required before treatment (stroke physician/neurologist, cardiologist, neuroradiologist, and neurosurgeon).
AF = atrial fibrillation; LAA = left atrial appendage; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulation; PCI = percutaneous coronary intervention; VKA = vitamin K antagonist.

Recommendations for secondary stroke prevention

Recommendations	Class [a]	Level [b]	Refs [c]
Anticoagulation with heparin or low-molecular-weight heparin immediately after ischaemic stroke is not recommended in AF patients	III (harm)	A	477
In patients who suffer a transient ischemic attack or stroke while on anticoagulation, adherence to therapy should be assessed and optimized	IIa	C	
In patients who suffer a moderate-to-severe ischaemic stroke while on anticoagulation, anticoagulation should be interrupted for 3–12 days based on a multidisciplinary assessment of acute stroke and bleeding risk	IIa	C	
In AF patients who suffer a stroke, aspirin should be considered for prevention of secondary stroke until the initiation or resumption of oral anticoagulation.	IIa	B	485
Systemic thrombolysis with a recombinant tissue plasminogen activator is not recommended if the INR is above 1.7 (or, for patients on dabigatran, if activated partial thromboplastin time is outside the normal range)	III (harm)	C	472, 474
NOACs are recommended in preference to VKAs or aspirin in AF patients with a previous stroke	I	B	363, 482
After TIA or stroke, combination therapy of OAC and an	III (harm)	B	486

antiplatelet is not recommended			
After intracranial haemorrhage, oral anticoagulation in patients with AF may be reinitiated after 4–8 weeks provided the cause of bleeding or the relevant risk factor has been treated or controlled	IIb	B	483, 484, 487

AF = atrial fibrillation; INR = international normalized ratio; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulation; TIA = transient ischaemic attack; VKA = vitamin K antagonist.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

9.5. Strategies to minimize bleeding on anticoagulant therapy

In a meta-analysis of 47 studies, the overall incidence of major bleeding with VKAs was 2.1 (range 0.9–3.4) per 100 patient-years in controlled trials and 2.0 (range 0.2–7.6) per 100 patient-years for observational data sets.[488] Minimizing treatable bleeding risk factors (see *Table 12*) seems paramount to reduce the bleeding rate on anticoagulants.

9.5.1. Uncontrolled hypertension

Uncontrolled blood pressure increases the risk of bleeding on OAC.[53] Hence, keeping systolic blood pressure well controlled is of particular relevance in anticoagulated patients with AF. Treatment according to current guidelines is recommended in patients with known hypertension.[489]

9.5.2. Previous bleeding event

History of bleeding events and the presence of anaemia are important parts of the assessment of all patients receiving OAC. The majority of bleeding events are gastrointestinal. Compared with warfarin, the risk of gastrointestinal bleeds was increased for dabigatran 150 mg twice daily,[396, 490] rivaroxaban 20 mg once daily,[491] and edoxaban 60 mg once daily.[321] The risk of gastrointestinal bleeds was comparable to warfarin on dabigatran 110 mg twice daily[490] and on apixaban 5 mg twice daily[319] Recent observational analyses do not replicate these findings, suggesting a smaller effect.[396, 492, 493] In patients in whom the source of bleeding has been identified and corrected, OAC can be reinitiated. This also appears true for patients who have had an intracranial haemorrhage, once modifiable bleeding risk factors (e.g. uncontrolled hypertension) have been corrected.[460, 484]

9.5.3. Labile international normalized ratio and adequate non-vitamin K antagonist oral anticoagulant dosing

TTR on VKA therapy is an important predictor of major haemorrhage.[432, 441, 494] Therefore we recommend targeting the INR between 2.0 and 3.0 in patients on VKAs, maintaining a high TTR (e.g. $\geq$ 70%[494]), and to consider switching to a NOAC when a high TTR cannot be sustained.[444] NOAC dosing should follow the dose-reduction criteria evaluated in the clinical trials, considering renal function, age, and weight. Patient information and empowerment, best delivered through integrated AF management, seem paramount to achieve this goal.

9.5.4. Alcohol abuse

Alcohol excess is a risk factor for bleeding in anticoagulated patients,[384] mediated by poor adherence, liver disease, variceal bleeding, and risk of major trauma. Severe alcohol abuse and binge drinking habits should be corrected in patients eligible for OAC.

9.5.5. Falls and dementia

Falls and dementia are associated with increased mortality in AF patients,[495] without evidence that these conditions markedly increase the risk of intracranial haemorrhage.[495, 496] Hence, anticoagulation should only be withheld from patients with severe uncontrolled falls (e.g. epilepsy or advanced multisystem atrophy with backwards falls), or in selected patients with dementia where compliance and adherence cannot be ensured by a caregiver.

9.5.6. Genetic testing

In addition to food and drug interactions, multiple genetic variations affect the metabolism of VKAs.[497] The systematic use of genetic information for adjustment of VKA dosage has been evaluated in several controlled clinical studies.[498-500] Genetic testing has little effect on TTR or bleeding risk on warfarin, and is not recommended for clinical use at present.[501]

9.5.7. Bridging periods off oral anticoagulation

Most cardiovascular interventions (e.g. percutaneous coronary intervention or pacemaker implantation) can be performed safely on continued OAC. When interruption of OAC is required, bridging does not seem to be beneficial, except in patients with mechanical heart valves. In a randomized trial of 1884 patients with AF, interruption of anticoagulation was non-inferior to heparin administration for the outcome of arterial thromboembolism (incidence of 0.4% and 0.3%, respectively) and resulted in a lower risk of major bleeding (1.3% and 3.2%, respectively).[502] A short interruption or continued OAC should be considered in patients at highest risk of stroke.

9.6. Management of bleeding events in anticoagulated patients with atrial fibrillation

9.6.1. Management of minor, moderate, and severe bleeding

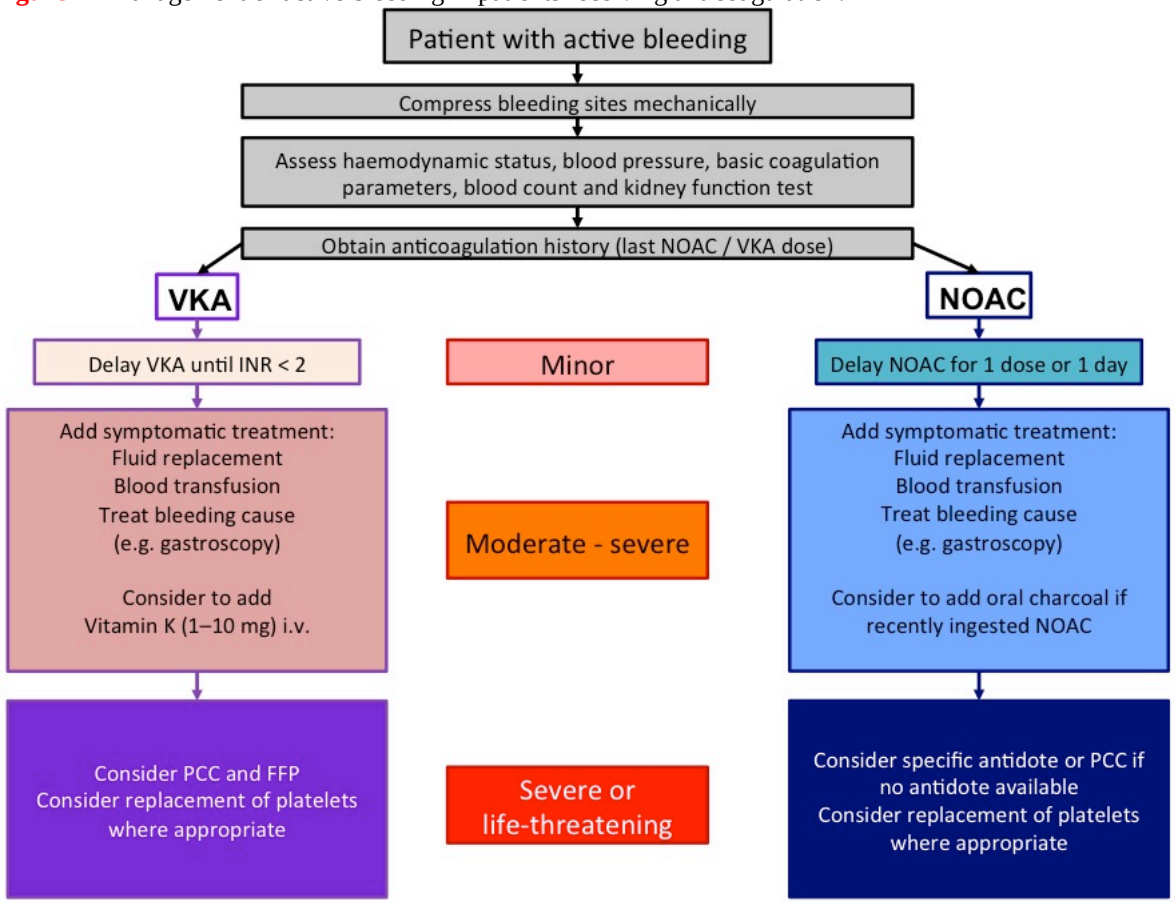
General assessment of an anticoagulated patient with AF experiencing a bleeding event should include assessment of bleeding site, onset, and severity of the bleeding, the time-point of last intake of OAC and other antithrombotic drugs, and other factors influencing bleeding risk such as CKD, alcohol abuse, and concurrent medications. Laboratory tests should include haemoglobin, haematocrit, platelet count, renal function, and for VKA patients, prothrombin time, activated partial thromboplastin time, and INR. Coagulation tests do not provide much information in patients on NOACs, except for activated partial thromboplastin time in the case of dabigatran. More specific coagulation tests do exist, including diluted thrombin time (HEMOCLOT) for dabigatran and calibrated quantitative anti-factor Xa assays for factor Xa inhibitors.[503] However, these tests are not always readily available and are often unnecessary for bleeding management.[504]

We propose a simple scheme to manage bleeding events in patients on OAC (*Figure 11*). Minor bleeding events should be treated with supportive measures such as mechanical compression or minor surgery to achieve haemostasis. In patients receiving VKAs, the next dose of VKA can be postponed. NOACs have a short plasma half-life of approximately 12 hours and improved haemostasis is expected within 12–24 hours after a delayed or omitted dose. Treatment of moderate bleeding events may require blood transfusions and fluid replacement. Specific diagnostic and treatment interventions directed against the cause of the bleeding (e.g. gastroscopy) should be performed promptly. If the intake of NOAC was recent (< 2–4 h), charcoal administration and/or gastric lavage will reduce further exposure. Dialysis clears dabigatran but is not effective for the other NOACs.

Immediate reversal of the antithrombotic effect is indicated in severe or life-threatening bleeding events. An agreed, the institutional procedure for the management of life-threatening bleeds should be documented and accessible at all times to ensure adequate initial management. For VKAs, administration of fresh frozen plasma restores coagulation more rapidly than vitamin K, and prothrombin complex concentrates achieve even faster blood coagulation.[505] Registry data suggest that the combination of plasma and prothrombin complex concentrates is associated with the lowest case fatality following intracranial haemorrhage on VKA treatment with an INR $\geq$ 1.3.[506] In a multicentre randomized trial of 188 patients, four-factor prothrombin complex concentrates achieved more rapid INR reversal and effective haemostasis than plasma in patients undergoing urgent surgical or invasive procedures.[507] Administration of prothrombin complex concentrates may also be considered for severe bleeding on NOAC treatment if specific antidotes are not available.

Several antidotes to NOACs are under development. Idarucizumab (approved in 2015 by the US Food and Drug Administration and the European Medicines Agency) is a clinically available humanized antibody fragment that binds dabigatran and rapidly and dose-dependently reverses the effects without over-correction or thrombin generation.[475] Andexanet alpha, a modified recombinant human factor Xa that lacks enzymatic activity, reverses the anticoagulant activity of apixaban and rivaroxaban in healthy probands within minutes after administration and for the duration of infusion, with a transient increase in markers of coagulation activity of uncertain clinical relevance.[508] Another agent under development is ciraparantag (PER977), an antidote targeted to reverse both direct thrombin and factor Xa inhibitors as well as the indirect inhibitor enoxaparin.[509] The clinical usefulness of these specific antidotes needs further evaluation.

Figure 11 Management of active bleeding in patients receiving anticoagulation.



INR = international normalized ratio; i.v. = intravenous; NOAC = non-vitamin K antagonist oral anticoagulant; PCC = prothrombin complex concentrates; FFP = four-factor prothrombin complex concentrates; VKA = vitamin K antagonist.

9.6.2. Oral anticoagulation in atrial fibrillation patients at risk of or having a bleeding event

While anticoagulation therapy should be paused to control active bleeding, absolute contraindications to long-term OAC after a bleeding episode are rare. When nuisance bleeds are the reason to stop OAC, a change from one anticoagulant to another seems reasonable. Many causes or triggers of major bleeding events can be treated and/or eliminated, including uncontrolled hypertension, gastrointestinal ulcers, and intracranial aneurysms. Reinitiation of anticoagulation after a bleeding event is often clinically justified.[460, 510] Difficult decisions, including the discontinuation and recommencement of OAC, should be taken by a multidisciplinary team, balancing estimated risk of recurrent stroke and bleeding, and considering the bleeding risk of different stroke prevention therapies. LAA exclusion or occlusion might be an alternative in selected patients.

Recommendations for management of bleeding

Recommendations	Class [a]	Level [b]	Refs [c]
Blood pressure control in anticoagulated patients with hypertension should be considered to reduce the risk of bleeding	IIa	B	511
When dabigatran is used, a reduced dose of dabigatran (110 mg twice daily) may be considered in patients > 75 years to reduce the risk of bleeding	IIb	B	490
In patients at high risk of gastrointestinal bleeding, a VKA or another NOAC should be preferred over dabigatran 150 mg twice daily, rivaroxaban 20 mg once daily, or edoxaban 60 mg once daily	IIa	B	321, 396, 402, 405, 490, 492, 493, 512

Advice and treatment to avoid alcohol excess should be considered in all AF patients considered for OAC	IIa	C	
Genetic testing before the initiation of VKA therapy is not recommended.	III (no benefit)	B	[497]
Reinitiation of OAC after a bleeding event should be considered in all eligible patients by a multidisciplinary AF team, considering different anticoagulants and stroke-prevention interventions, improved management of factors that contributed to bleeding, and stroke risk	IIa	B	[460]
In AF patients with severe active bleeding events, it is recommended to interrupt OAC therapy until the underlying cause is resolved	I	C	

AF = atrial fibrillation; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulation; VKA = vitamin K antagonist

[a]Class of recommendation.

[b]Level of evidence.

[c]Reference(s) supporting recommendations.

9.7. Combination therapy with oral anticoagulants and antiplatelets

Approximately 15% of AF patients in contemporary trials[513] and registries[514-516] have a history of myocardial infarction. Between 5% and 15% of AF patients will require stenting at some point in their lives. This scenario requires careful consideration of antithrombotic therapy, balancing bleeding risk, stroke risk, and risk of acute coronary syndromes (ACS).[516] Co-prescription of OAC with antiplatelet therapy, in particular triple therapy, increases the absolute risk of major haemorrhage.[445, 517, 518] A recent meta-analysis involving 30,866 patients with a recent ACS evaluated the effects of adding NOAC therapy to single (4135 patients) or dual (26,731 patients) antiplatelet therapy.[519] The addition of a NOAC increased the bleeding risk by 79–134%, while reducing recurrent ischaemic events only marginally in patients without AF. OAC monotherapy, and not combination therapy with antiplatelets, is recommended in AF patients with stable CAD but without an ACS and/or coronary intervention in the previous 12 months. In patients treated for ACS and in those receiving a coronary stent, short-term triple combination therapy of OAC, clopidogrel, and aspirin seems warranted (*Figure 12).*

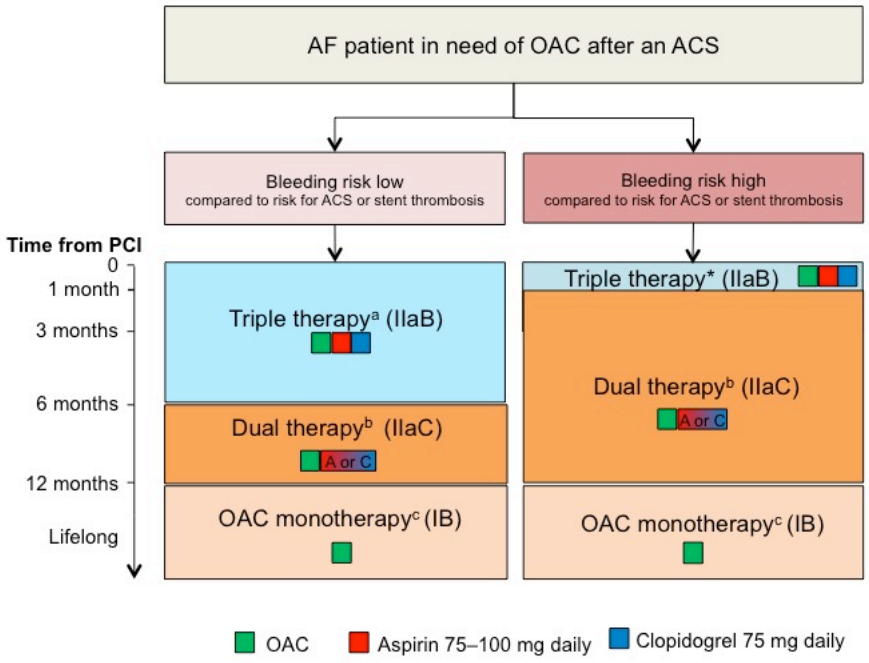


Figure 12 Antithrombotic therapy after an ACS in AF patients requiring anticoagulation.
ACS = acute coronary syndrome; AF = atrial fibrillation; OAC = oral anticoagulation (using vitamin K antagonists or non-vitamin K antagonist oral anticoagulants); PCI = percutaneous coronary intervention.
[a]Dual therapy with OAC and aspirin or clopidogrel may be considered in selected patients, especially those not receiving a stent or patients at a longer time from the index event.
[b]OAC plus single antiplatelet.
[c]Dual therapy with OAC and an antiplatelet agent (aspirin or clopidogrel) may be considered in patients at high risk of coronary events.

9.7.1. Antithrombotic therapy after acute coronary syndromes and percutaneous coronary intervention in patients requiring oral anticoagulation

The optimal combination antithrombotic therapy or duration of combination therapy for AF patients undergoing percutaneous coronary intervention is not known, but the continued bleeding risk suggests a short duration. Expert consensus,[520] reviewed and reconsidered by this Task Force, suggests the following principles: AF patients at risk for stroke, patients with mechanical valves, and patients with recent or recurrent deep vein thrombosis or pulmonary embolism should continue OAC during and after stenting. In general, a short period of triple therapy (OAC, aspirin, clopidogrel) is recommended, followed by a period of dual therapy (OAC plus a single antiplatelet) (*Figure 13*). When a NOAC is used, the consensus recommendation is that the lowest dose effective for stroke prevention in AF should be considered. Dose reduction beyond the dosing regimens tested in the phase III trials is not currently recommended, and awaits assessment in ongoing controlled trials. The combination of aspirin, clopidogrel, and low-dose rivaroxaban (2.5 mg twice daily) is not recommended for stroke prevention in AF.[521]

The use of prasugrel or ticagrelor as part of triple therapy should be avoided unless there is a clear need for these agents (e.g. stent thrombosis on aspirin plus clopidogrel), given the lack of evidence and the greater risk of major bleeding compared with clopidogrel.[522, 523] Ongoing trials will inform about such combination therapies in the future.

The omission of aspirin while maintaining clopidogrel and OAC has been evaluated in the WOEST (What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary

StenTing) trial, in which 573 anticoagulated patients undergoing percutaneous coronary intervention (70% with AF) were randomized to either dual therapy with OAC and clopidogrel (75 mg once daily) or to triple therapy with OAC, clopidogrel, and aspirin.[524] Bleeding was lower in the dual versus triple therapy arm, driven by fewer minor bleeding events. The rates of myocardial infarction, stroke, target vessel revascularization, and stent thrombosis did not differ (albeit with low event numbers), but all-cause mortality was lower in the dual therapy group at 1 year (2.5% vs. triple 6.4%). Although the trial was too small to assess ischaemic outcomes, dual therapy with OAC and clopidogrel may emerge in the future as an alternative to triple therapy in patients with AF and ACS and/or coronary intervention.[525]

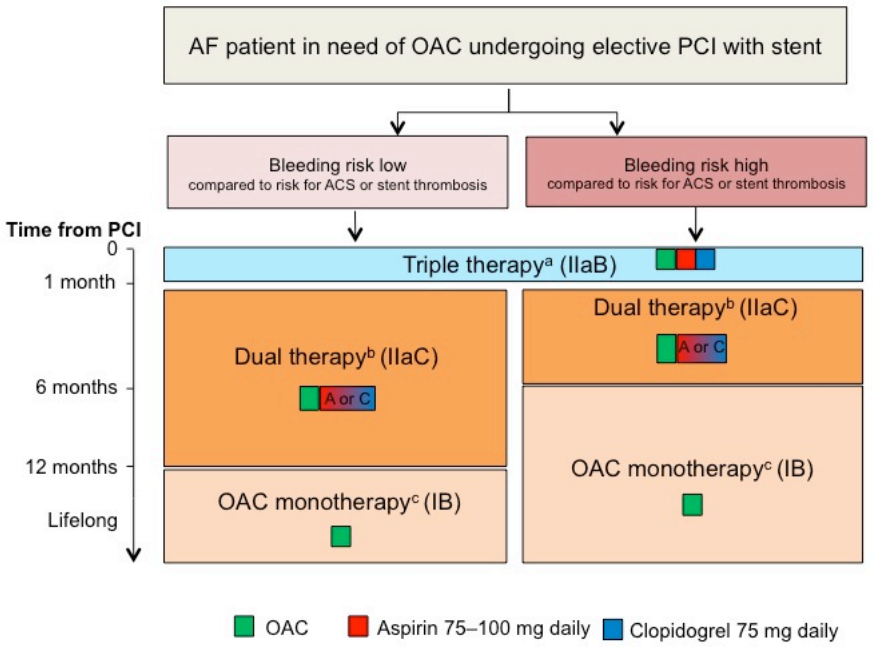


Figure 13 Antithrombotic therapy after percutaneous intervention in AF patients requiring anticoagulation. ACS = acute coronary syndrome; AF = atrial fibrillation; OAC = oral anticoagulation (using vitamin K antagonists or non-vitamin K antagonist oral anticoagulants); PCI = percutaneous coronary intervention.
[a]Dual therapy with OAC and aspirin or clopidogrel may be considered in selected patients.
[b]OAC plus single antiplatelet.
[c]Dual therapy with OAC and an antiplatelet agent (aspirin or clopidogrel) may be considered in patients at high risk of coronary events.

Recommendations for combination therapy with oral anticoagulants and antiplatelets

Recommendations	Class [a]	Level [b]	Refs [c]
After elective coronary stenting for stable coronary artery disease in AF patients at risk of stroke, combination triple therapy with aspirin, clopidogrel and an oral anticoagulant should be considered for 1 month to prevent recurrent coronary and cerebral ischaemic events	IIa	B	522, 524
After an ACS with stent implantation in AF patients at risk of stroke, combination triple therapy with aspirin, clopidogrel, and an oral anticoagulant should be considered for 1–6 months to prevent recurrent coronary and cerebral ischaemic events	IIa	C	520

After an ACS without stent implantation in AF patients at risk of stroke, dual therapy with an oral anticoagulant and aspirin or clopidogrel should be considered for up to 12 months to prevent recurrent coronary and cerebral ischaemic events	IIa	C	
The duration of combination antithrombotic therapy, especially triple therapy, should be kept to a limited period, balancing the estimated risk of recurrent coronary events and bleeding	IIa	B	520
Dual therapy with any oral anticoagulant plus clopidogrel 75 mg/day may be considered as an alternative to initial triple therapy with aspirin in selected patients.	IIb	C	524, 525

ACS = acute coronary syndromes; AF = atrial fibrillation
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

10 Rate control therapy in AF

Rate control is an integral part of the management of AF patients, and is often sufficient to improve AF-related symptoms. Compared with stroke prevention and rhythm control, very little robust evidence exists to inform the best type and intensity of rate control treatment, with the majority of data derived from short-term crossover trials and observational studies.[41, 526-528] Pharmacological rate control can be achieved for acute or long-term rate control with beta-blockers, digoxin, the calcium channel blockers diltiazem and verapamil, or combination therapy (*Table 15*). A number of antiarrhythmic drugs also have rate-limiting properties (amiodarone, dronedarone, sotalol, and to some extent propafenone), but they should only be used in patients needing rhythm control therapy (see Chapter 10).

10.1. Acute rate control

In the setting of acute new-onset AF, patients are often in need of heart rate control. Physicians should evaluate underlying causes of elevated heart rate, such as infection, endocrine imbalance, anaemia, and pulmonary embolism. For acute rate control, beta-blockers and diltiazem/verapamil are preferred over digoxin because of their rapid onset of action and effectiveness at high sympathetic tone.[528-532] The choice of drug (*Table 15*) and target heart rate will depend on patient characteristics, symptoms, LVEF and haemodynamics, but a lenient initial approach to heart rate seems acceptable. Combination therapy may be required (*Figure 14*). In patients with evidence of HFrEF, beta-blockers, digitalis (digoxin or digitoxin), or their combination should be used,[218, 533] as diltiazem and verapamil can have negative inotropic effects in patients with LVEF < 40%.[222, 534, 535] In critically ill patients and those with severely impaired LV systolic function, intravenous amiodarone can be used where excess heart rate is leading to haemodynamic instability.[536-538] Urgent cardioversion should be considered in unstable patients (see Chapter 10.2).

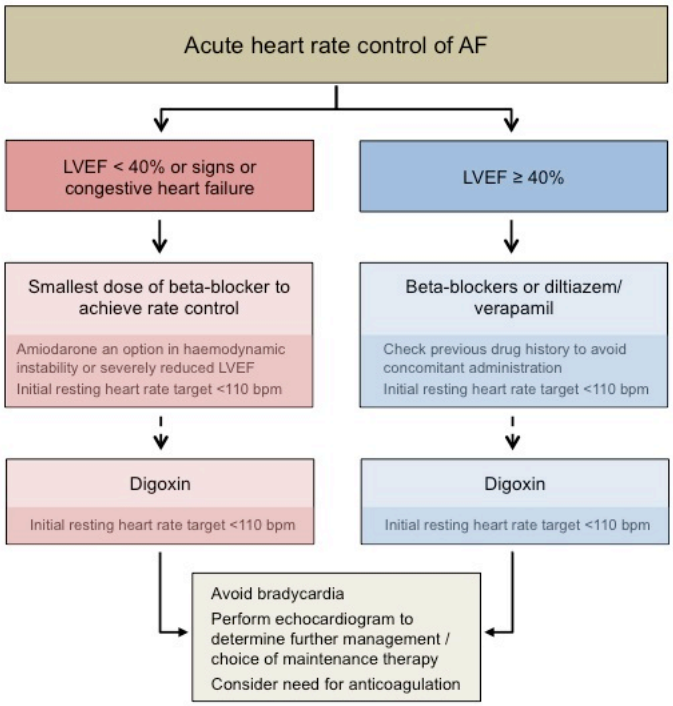


Figure 14 Acute heart rate control of AF.
See *Table 15* for medication dosage. Digitoxin is a suitable alternative to digoxin, where available.
AF = atrial fibrillation; bpm = beats per minute; LVEF = left ventricular ejection fraction.

10.2. Long-term pharmacological rate control

10.2.1. Beta-blockers

Beta-adrenoreceptor blocker monotherapy is often the first-line rate-controlling agent,[539] largely based on observations of better acute heart rate control than digoxin. Interestingly, the prognostic benefit of beta-blockers seen in HFrEF patients with sinus rhythm is lost in those with AF. In an individual patient-level meta-analysis of RCTs, beta-blockers did not reduce all-cause mortality compared to placebo in those with AF at baseline (HR 0.97; 95% CI 0.83–1.14; $P = 0.73$), whereas there was a clear benefit in patients with sinus rhythm (HR 0.73; 95% CI 0.67–0.80; $P < 0.001$).[23] The study, which included 3066 participants with HFrEF and AF, showed consistency across all subgroups and outcomes, with no heterogeneity between the 10 RCTs included ($I^2 = 0\%$). Despite this lack of prognostic benefit in HFrEF, this Task Force still considers beta-blockers as a useful first-line rate control agent across all AF patients, based on the potential for symptomatic and cardiac function improvement as a result of rate control, the lack of harm from published studies, and the good tolerability profile across all ages in sinus rhythm and in AF.[23, 540]

10.2.2. Non-dihydropyridine calcium channel blockers

Verapamil or diltiazem provides reasonable rate control in AF patients.[541] They should be avoided in patients with HFrEF because of their negative inotropic effects.[222, 534, 535] Verapamil or diltiazem can improve arrhythmia-related symptoms,[526] in comparison with beta-blockers, which reduced exercise capacity and increased B-type natriuretic peptide in one small trial of low-risk patients with preserved LVEF.[542]

10.2.3. Digitalis

Cardiac glycosides such as digoxin and digitoxin have been in use for over two centuries, although prescriptions have been declining steadily over the past 15 years.[543] In the randomized Digitalis Investigation Group (DIG) trial, digoxin had no effect on mortality compared to placebo in HFrEF patients in sinus rhythm (RR 0.99; 95%

CI 0.91–1.07), but reduced hospital admissions (RR 0.72; 95% CI 0.66–0.79).[544, 545] There have been no head-to-head RCTs of digoxin in AF patients.[546] Observational studies have associated digoxin use with excess mortality in AF patients,[547-549] but this association is likely due to selection and prescription biases rather than harm caused by digoxin,[550-553] particularly as digoxin is commonly prescribed to sicker patients.[225] In a crossover mechanistic trial of 47 patients with HFrEF and AF, there were no differences in heart rate, blood pressure, walking distance, or LVEF between carvedilol and digoxin, although beta-blockers did result in higher B-type natriuretic peptide levels, combination carvedilol/digoxin improved LVEF, and digoxin withdrawal reduced LVEF.[554] Comparisons with other rate control therapies are based on small, short-duration studies that identify no or marginal differences in exercise capacity, quality of life, or LVEF compared to digoxin.[526, 554-558] Lower doses of digoxin (≤ 250 μg once daily), corresponding to serum digoxin levels of 0.5–0.9 ng/mL, may be associated with better prognosis.[225]

10.2.4. Amiodarone

Amiodarone can be useful for rate control as a last resort. The wide array of extracardiac adverse effects associated with amiodarone renders it a reserve agent in patients whose heart rate cannot be controlled with combination therapy (e.g. beta-blocker or verapamil/diltiazem combined with digoxin).

In summary, there is equipoise for the use of different rate control agents in AF. The choice of beta-blocker, diltiazem/verapamil, digoxin, or combination therapy should be made on an individual basis, after consideration of patient characteristics and patient preference. All available therapies have the potential for adverse effects and patients should initially be treated with a low dose and uptitrated to achieve symptom improvement. In practice, achieving a heart rate < 110 bpm will often require combination therapy (*Figure 15*). The benefit of different rate control strategies on symptoms, quality of life, and other intermediate outcomes is under investigation.[559]

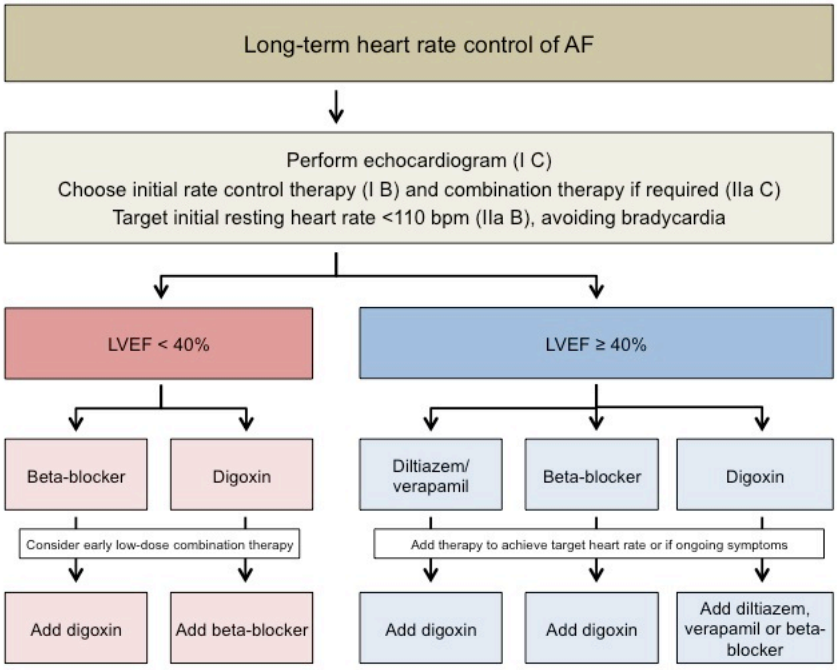


Figure 15 Long-term heart rate control of AF.
See *Table 15* for medication dosage. Digitoxin is a suitable alternative to digoxin, where available.
AF = atrial fibrillation; bpm = beats per minute; LVEF = left ventricular ejection fraction.

10.3. Heart rate targets in atrial fibrillation

The optimal heart rate target in AF patients is unclear. The RACE (Rate Control Efficacy in Permanent Atrial Fibrillation) II study randomized 614 patients with permanent AF to either a target heart rate < 80 bpm at rest and < 110 bpm during moderate exercise, or to a lenient heart rate target of < 110 bpm. There was no difference in a composite of clinical events (14.9% in the strict rate control group, 12.9% in the lenient group),[560] NYHA class, or hospitalizations.[560, 561] Similar results were found in a pooled analysis of the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) and RACE trials (1091 participants), albeit with smaller heart rate differences and without randomization.[562] It is worthwhile to note that many 'adequately rate-controlled' patients (resting heart rate 60–100 bpm) are severely symptomatic, calling for additional management.[194] Nonetheless, lenient rate control is an acceptable initial approach, regardless of heart failure status, unless symptoms call for stricter rate control.

10.4. Atrioventricular node ablation and pacing

Ablation of the atrioventricular node/His bundle and implantation of a VVI pacemaker can control ventricular rate when medications fail to control rate and symptoms. It is a relatively simple procedure with a low complication rate and low long-term mortality risk,[563, 564] especially when the pacemaker is implanted a few weeks before the AV nodal ablation and the initial pacing rate after ablation is set at 70–90 bpm.[565, 566] The procedure does not worsen LV function[567] and may even improve LVEF in selected patients.[568-570] In some patients in heart failure treated with biventricular pacing (cardiac resynchronization therapy), AF can terminate,[571] although such a 'rhythm control' effect of cardiac resynchronization therapy is likely to be small and clearly needs confirmation.[572] AV nodal ablation renders patients pacemaker-dependent for the rest of their lives, limiting AV nodal ablation and pacing to patients whose symptoms cannot be managed by rate controlling medication or by reasonable rhythm control interventions. The choice of pacing therapy (right ventricular or biventricular pacing with or without an implantable defibrillator) will depend on individual patient characteristics, including LVEF.[573, 574]

Recommendations for rate control

Recommendations	Class [a]	Level [b]	Refs [c]
Beta-blocker, digoxin, diltiazem, or verapamil are recommended to control heart rate in AF patients with LVEF ≥ 40%	I	B	225, 526, 528, 531, 532, 541, 555, 575
Beta-blocker and/or digoxin are recommended to control heart rate in AF patients with LVEF < 40%	I	B	23, 225, 526, 533, 554, 575, 576
Combination therapy comprising different rate controlling agents should be considered if a single agent does not achieve the necessary heart rate target	IIa	C	23, 554, 577
In cases of haemodynamic instability or severe depression in LVEF, amiodarone may be considered for acute control of heart rate	IIb	B	536-538
In patients with permanent AF (i.e. where no attempt to restore sinus rhythm is planned), antiarrhythmic drugs should not routinely be used for rate control	III (harm)	A	41, 578, 579
A resting heart rate of < 110 bpm (i.e. lenient rate control) should be considered as the initial heart rate target for rate control therapy	IIa	B	560
Rhythm rather than rate control strategies should be considered as the preferred management in pre-excited AF and AF during pregnancy	IIa	C	
Atrioventricular node ablation should be considered to control heart rate in patients unresponsive or intolerant to intensive rate and rhythm control therapy, accepting that these patients will become pacemaker dependent	IIa	B	184, 564, 569

AF = atrial fibrillation; bpm = beats per minute; LVEF = left ventricular ejection fraction.
Digitoxin is a suitable alternative to digoxin, where available. In patients with heart failure with reduced ejection fraction (LVEF < 40%), recommended beta-blockers are bisoprolol, carvedilol, long-acting metoprolol, and nebivolol.
[a] Class of recommendation.

[b] Level of evidence.
[c] Reference(s) supporting recommendations.

Table 15 Rate control therapy in AF

Therapy	Acute intravenous rate control	Long-term oral rate control	Side-effect profile	Comments
Beta-blockers[a]				
Bisoprolol	Not available	1.25–20 mg once daily or split	Most common reported adverse symptoms are lethargy, headache, peripheral oedema, upper respiratory tract symptoms, gastrointestinal upset, and dizziness. Adverse effects include bradycardia, atrioventricular block, and hypotension	Bronchospasm is rare – in cases of asthma, recommend beta-1 selective agents (avoid carvedilol). Contraindicated in acute cardiac failure and a history of severe bronchospasm
Carvedilol	Not available	3.125–50 mg twice daily		
Metoprolol	2.5–10 mg intravenous bolus (repeated as required)	100–200 mg total daily dose (according to preparation)		
Nebivolol	N/A	2.5–10 mg once daily or split		
Esmolol	0.5 mg intravenous bolus over 1 min; then 0.05–0.25 mcg/kg/min			
Calcium-channel blockers				
Diltiazem	15–25 mg intravenous bolus (repeated as required)	60 mg three times daily up to 360 mg total daily dose (120–360 mg once daily modified release)	Most common reported adverse symptoms are dizziness, malaise, lethargy, headache, hot flushes, gastrointestinal upset, and oedema. Adverse effects include bradycardia, atrioventricular block, and hypotension (prolonged hypotension possible with verapamil)	Use with caution in combination with beta-blockers. Reduce dose with hepatic impairment and start with smaller dose in renal impairment. Contraindicated in LV failure with pulmonary congestion or LVEF < 40%
Verapamil	2.5–10 mg intravenous bolus (repeated as required)	40–120 mg three times daily (120–480 mg once daily modified release)		
Cardiac glycosides				
Digoxin	0.5 mg intravenous bolus (0.75–1.5 mg over 24 h in divided doses)	0.0625–0.25 mg daily dose	Most common reported adverse symptoms are gastrointestinal upset, dizziness, blurred vision, headache, and rash. In toxic states (serum levels > 2 ng/mL), digoxin is proarrhythmic and can aggravate heart failure, particularly with coexistent hypokalaemia	High plasma levels associated with increased risk of death. Check renal function before starting and adapt dose in patients with CKD. Contraindicated in accessory conducting pathways, ventricular tachycardia, and hypertrophic cardiomyopathy with outflow tract obstruction
Digitoxin	0.4–0.6 mg intravenous bolus	0.05–0.3 mg daily dose		
Specific indications				
Amiodarone	300 mg	200 mg daily	Hypotension,	Suggested as

	intravenously diluted in 250 mL 5% dextrose over 30–60 min (preferably via central venous cannula)[b]	bradycardia, nausea, QT prolongation, pulmonary toxicity, skin discolouration, thyroid dysfunction, corneal deposits, and cutaneous reaction with extravasation	adjunctive therapy in patients where heart rate control cannot be achieved using combination therapy

AF = atrial fibrillation; CKD = chronic kidney disease; LV = left ventricular; LVEF = left ventricular ejection fraction.

[a]A number of other beta-blockers are also available, but are not recommended as specific rate control therapy in AF. These include atenolol (25–100 mg once daily with a short biological half-life), propranolol (non-selective, 1 mg over 1 min and repeat up to 3 mg at 2-min intervals [acute] or 10–40 mg three times daily [long-term]), or labetalol (non-selective, 1–2 mg/min [acute]).

[b]If ongoing requirement for amiodarone, follow with 900 mg intravenous over 24 hours diluted in 500–1000 mL via a central venous cannula.

11 Rhythm control therapy in atrial fibrillation

Restoring and maintaining sinus rhythm is an integral part of AF management. Antiarrhythmic drugs approximately double the rate of sinus rhythm compared with placebo.[580-584] Catheter ablation or combination therapy is often effective when antiarrhythmic drugs fail.[226, 585-587] Although many clinicians believe that maintaining sinus rhythm can improve outcomes in AF patients,[588] all trials that have compared rhythm control to rate control (with appropriate anticoagulation) therapy have resulted in neutral outcomes.[41, 578, 579, 582, 589-593] Whether modern rhythm control management involving catheter ablation, combination therapy, and early therapy leads to a reduction in major cardiovascular events (e.g. stroke and cardiovascular death) is currently under investigation (e.g. in the EAST [Early treatment of Atrial fibrillation for Stroke prevention Trial] – AFNET 4[40] and CABANA [Catheter Ablation vs Anti-arrhythmic Drug Therapy for Atrial Fibrillation Trial][594] trials). For now, rhythm control therapy is indicated to improve symptoms in AF patients who remain symptomatic on adequate rate control therapy.

11.1. Acute restoration of sinus rhythm

11.1.1. Antiarrhythmic drugs for acute restoration of sinus rhythm ('pharmacological cardioversion')

Antiarrhythmic drug can restore sinus rhythm in patients with AF (pharmacological cardioversion) as shown in small controlled trials, meta-analyses,[41, 584, 595, 596] and in a few larger controlled trials.[597-605] Outside of Europe, dofetilide is available and can convert recent-onset AF.[606] Pharmacological cardioversion restores sinus rhythm in approximately 50% of patients with recent-onset AF (*Table 16*).[607-609] In the short term, electrical cardioversion restores sinus rhythm quicker and more effectively than pharmacological cardioversion and is associated with shorter hospitalization.[609-613] Pharmacological cardioversion, conversely, does not require sedation or fasting (*Figure 16*).

Flecainide and propafenone are effective for pharmacological cardioversion,[595, 602-605, 614, 615] but their use is restricted largely to patients without structural heart disease. Ibutilide is an alternative where available, but carries a risk of torsades de pointes.[615] Vernakalant[602-605] can be given to patients with mild heart failure (NYHA Class I or II), including those with ischaemic heart disease, provided they do not present with hypotension or severe aortic stenosis.[616-618] Amiodarone can be used in patients with heart failure and in patients with ischaemic heart disease (although patients with severe heart failure were excluded in most of the AF cardioversion trials).[596] Amiodarone also slows heart rate by 10–12 bpm after 8–12 hours when given intravenously.[596] Both amiodarone and flecainide appear more effective than sotalol in restoring sinus rhythm.[600, 601, 619]

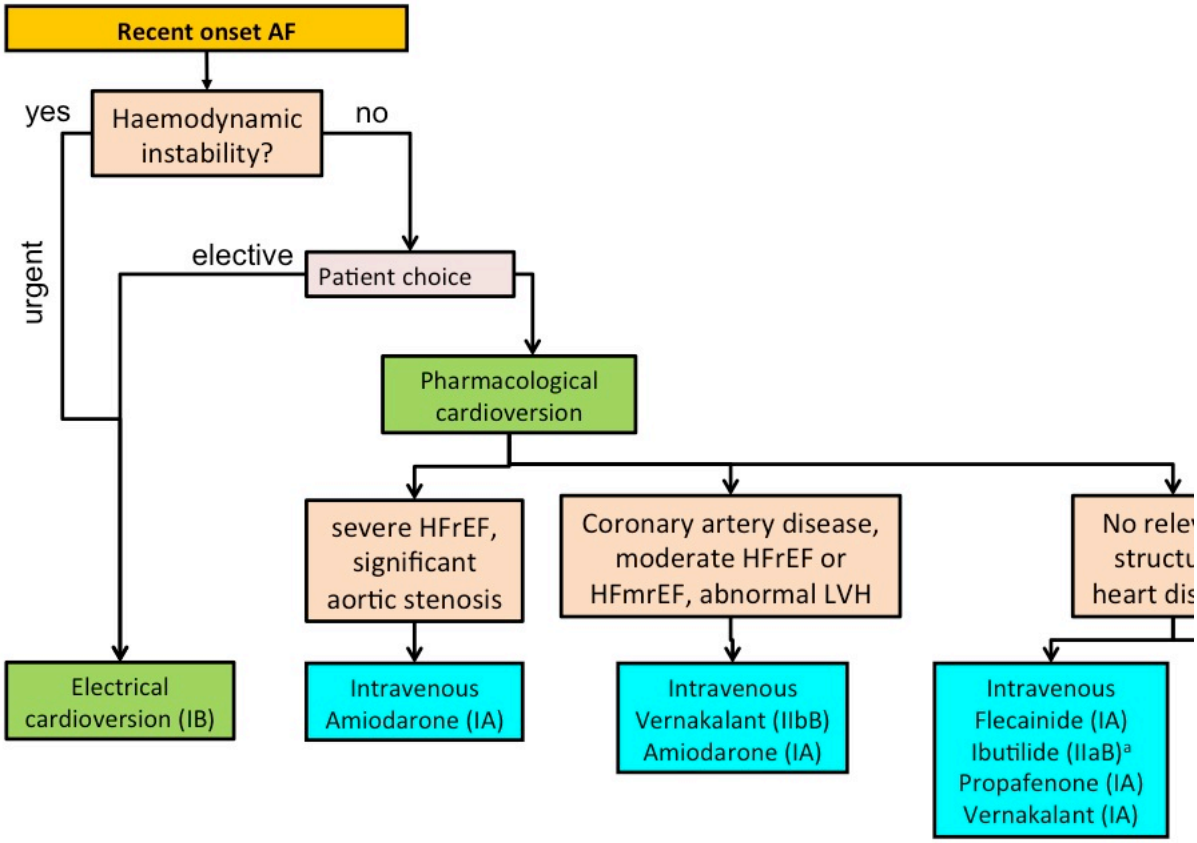


Figure 16 Rhythm control management of acute AF.
AF = atrial fibrillation; HFmrEF = heart failure with mid-range ejection fraction; HFrEF = heart failure with reduced ejection fraction.
[a]Ibutilide should not be used in patients with long QT interval.

11.1.2. 'Pill in the pocket' cardioversion performed by patients

In selected patients with infrequent symptomatic episodes of paroxysmal AF, a single bolus of oral flecainide (200–300 mg) or propafenone (450–600 mg) can be self-administered by the patient at home ('pill in the pocket' therapy) to restore sinus rhythm, after safety has been established in the hospital setting.[620] This approach seems marginally less effective than hospital-based cardioversion,[621] but is practical and provides control and reassurance to selected patients.

Table 16 Antiarrhythmic drugs for pharmacological cardioversion

Drug	Route	First dose	Follow-up dose	Risks	References
Flecainide	Oral	200–300 mg	N/A	Avoid in patients with IHD and/or significant structural heart disease. Hypotension, atrial flutter with 1:1 conduction, QT prolongation	595, 598
	IV	1.5–2 mg/kg over 10 min			
Amiodarone	IV[a]	5–7 mg/kg over 1–2 h	50 mg/h to a maximum of 1.0 g over 24 h	Phlebitis, hypotension, bradycardia/AV block. Will slow ventricular rate. Delayed conversion to sinus rhythm (8–12 h)	596-601
Propafenone	IV	1.5–2 mg/kg over 10 min		Avoid in patients with IHD and/or significant structural heart disease. Hypotension, atrial flutter with 1:1	622-625

	Oral	450–600 mg		conduction, QRS prolongation (mild)	
Ibutilide[b]	IV	1 mg over 10 min	1 mg over 10 min after waiting for 10 min	Avoid in patients with QT prolongation, hypokalemia, severe LVH, or low ejection fraction. QT prolongation, polymorphic ventricular tachycardia/torsades de pointes (3–4% of patients). Will slow ventricular rate	614, 615
Vernakalant	IV	3 mg/kg over 10 min	2 mg/kg over 10 min after waiting for 15 min	Avoid in patients with systolic blood pressure < 100 mmHg, recent (< 30 days) ACS, NYHA Class III and IV heart failure, QT interval prolongation (uncorrected QT > 440 ms), and severe aortic stenosis. Hypotension, non-sustained ventricular arrhythmias, QT and QRS prolongation	602-605, 618

ACS = acute coronary syndromes; IHD = ischaemic heart disease; IV = intravenous; LVH = left ventricular hypertrophy; NYHA = New York Heart Association.
[a]Use a large peripheral vessel and change to oral amiodarone within 24 h of IV (central line) administration.
[b]Ibutilide is only available in selected European countries.

11.1.3. Electrical cardioversion

Synchronized direct current electrical cardioversion quickly and effectively converts AF to sinus rhythm and is the method of choice in severely haemodynamically compromised patients with new-onset AF (*Figure 16*).[626-628] Electrical cardioversion can be performed safely in sedated patients treated with intravenous midazolam and/or propofol. Continuous monitoring of blood pressure and oximetry during the procedure is important.[629] Skin burns may occasionally be observed. Intravenous atropine or isoproterenol or temporary transcutaneous pacing should be available to mitigate post-cardioversion bradycardia. Biphasic defibrillators are more effective than monophasic waveforms, and have become industry standard.[626, 628] Anterior–posterior electrode positions generate a stronger shock field in the left atrium than anterolaterally positioned electrodes, and restore sinus rhythm more effectively. [626, 627, 630]

Pretreatment with amiodarone (requiring a few weeks of therapy),[631, 632] sotalol,[631] ibutilide,[633] or vernakalant[634] can improve efficacy of electrical cardioversion, and similar effects are likely for flecainide[584] and propafenone.[635] Beta-blockers,[636] verapamil, diltiazem,[637-639] and digoxin[640, 641] do not reliably terminate AF or facilitate electrical cardioversion. When antiarrhythmic drug therapy is planned to maintain sinus rhythm after cardioversion, it seems prudent to start therapy 1–3 days before cardioversion (amiodarone: a few weeks) to promote pharmacological conversion and to achieve effective drug levels.[584, 601]

11.1.4. Anticoagulation in patients undergoing cardioversion

Cardioversion carries an inherent risk of stroke in non-anticoagulated patients,[642] which is reduced substantially by the administration of anticoagulation.[643] Immediate initiation of anticoagulation is important in all patients scheduled for cardioversion.[644-646] Patients who have been in AF for longer than 48 hours should start OAC at least 3 weeks before cardioversion and continue it for 4 weeks afterwards (in patients without a need for long-term anticoagulation), and continue it indefinitely in patients at risk of stroke. This practice has never been evaluated in controlled trials, but seemed safe in a large observational data set from Finland.[647] When early cardioversion is desired, TOE can exclude the majority of left atrial thrombi, allowing immediate cardioversion.[648, 649] Ongoing studies will inform about the safety and efficacy of newly initiated anticoagulation using NOACs in patients scheduled for electrical cardioversion.

11.2. Long-term antiarrhythmic drug therapy

The aim of antiarrhythmic drug therapy is improvement in AF-related symptoms.[41, 580] Hence, the decision to initiate long-term antiarrhythmic drug therapy needs to balance symptom burden, possible adverse drug reactions, and patient preferences. The principles of antiarrhythmic drug therapy outlined in the 2010 ESC AF guidelines[369] are still relevant and should be observed:

1. Treatment is aimed at reducing AF-related symptoms;
2. Efficacy of antiarrhythmic drugs to maintain sinus rhythm is modest;

3. Clinically successful antiarrhythmic drug therapy may reduce rather than eliminate the recurrence of AF;
4. If one antiarrhythmic drug 'fails', a clinically acceptable response may be achieved with another agent;
5. Drug-induced proarrhythmia or extra-cardiac side-effects are frequent;
6. Safety rather than efficacy considerations should primarily guide the choice of antiarrhythmic drug.

Antiarrhythmic drug therapy approximately doubles sinus rhythm maintenance compared with no therapy.[580] There is no appreciable effect on mortality or cardiovascular complications, but rhythm control therapy can slightly increase the risk of hospitalizations (often for AF).[41, 578, 579, 582, 589-593] To reduce the risk of side-effects,[201, 580] a shorter duration of antiarrhythmic drug therapy seems desirable. As an example, short-term treatment (4 weeks) with flecainide for 4 weeks after cardioversion of AF was well-tolerated and prevented most (80%) AF recurrences when compared with long-term treatment.[584] Short-term antiarrhythmic drug therapy is also used to avoid early AF recurrences after catheter ablation[650] and may be reasonable in patients deemed at increased risk of antiarrhythmic drug side-effects or in those with a low perceived risk of recurrent AF.

In addition to antiarrhythmic drug therapy and catheter ablation (see Section 10.3), management of concomitant cardiovascular conditions can reduce symptom burden in AF and facilitate maintenance of sinus rhythm.[203, 204, 296, 312] This includes weight reduction, blood pressure control, heart failure treatment, increasing cardiorespiratory fitness, and other measures (see Chapter 6).

11.2.1. Selection of antiarrhythmic drugs for long-term therapy: Safety first!

Usually, the safety of antiarrhythmic drug therapy determines the initial choice of antiarrhythmic drugs (*Figure 17*). The following major antiarrhythmic drugs are available to prevent AF:

Amiodarone is an effective multichannel blocker, reduces ventricular rate, and is safe in patients with heart failure.[582, 651] Torsades de pointes proarrhythmia can occur, and QT interval and TU waves should be monitored on therapy (see *Table 17*).[652] Amiodarone often causes extracardiac side-effects, especially on long-term therapy,[653, 654] rendering it a second-line treatment in patients who are suitable for other antiarrhythmic drugs. Amiodarone appears less suitable to episodic short-term therapy (unless after catheter ablation),[655] probably because of its long biological half-life.

Dronedarone maintains sinus rhythm, reduces ventricular rate, and prevents cardiovascular hospitalizations (mostly due to AF) and cardiovascular death in patients with paroxysmal or persistent AF or flutter who had at least one relevant cardiovascular comorbidity.[583, 588, 656] Dronedarone increases mortality in patients with recently decompensated heart failure (with or without AF)[657] and in patients with permanent AF in whom sinus rhythm is not restored.[658] Dronedarone moderately increases serum creatinine, reflecting a reduction in creatinine excretion rather than a decline in kidney function.[659]

Flecainide and ***propafenone*** are effective in preventing recurrent AF.[581, 584, 620] They should only be used in patients without significant ischaemic heart disease or heart failure to avoid the risk of life-threatening ventricular arrhythmias.[660] High ventricular rates resulting from the conversion of AF into atrial flutter with 1:1 conduction by flecainide or propafenone can be prevented by preadministering a beta-blocker, verapamil, or diltiazem.

Quinidine and ***disopyramide*** have been associated with an increase in all-cause mortality (OR 2.39; 95% CI 1.03–5.59; number needed to harm 109; 95% CI 34–4985) at 1-year follow-up,[580, 661] likely due to ventricular arrhythmias (torsades de pointes).[580, 661] Although this proarrhythmic effect is more common at higher doses, they are less commonly used for rhythm control in AF. Disopyramide may be useful in 'vagally mediated' AF (e.g. AF occurring in athletes and/or during sleep[76]), and has been shown to reduce LV outflow gradient and improve symptoms in patients with hypertrophic cardiomyopathy.[662-664]

Sotalol has a relevant risk of torsades de pointes (1% in the Prevention of Atrial Fibrillation After Cardioversion [PAFAC] trial[118]). Its d-enantiomer is associated with an increased mortality compared to placebo in patients with LV dysfunction post-myocardial infarction,[665] probably due to ventricular arrhythmias (OR 2.47; 95% CI 1.2–5.05; number needed to harm 166; 95% CI 61–1159).[580, 665] On the other hand, d,l sotalol has been used in AF patients without safety signals in two controlled trials.[581, 601]

Dofetilide is another potassium channel blocker that is mainly available outside of Europe. Dofetilide restores and maintains sinus rhythm in heart failure patients[666] and occasionally in patients refractory to other antiarrhythmic drugs.[667]

Overall, it seems prudent to limit the use of quinidine, disopyramide, dofetilide, and sotalol to specific situations. Similarly, combinations of QT-prolonging antiarrhythmic drugs should generally be avoided (*Table 17*).

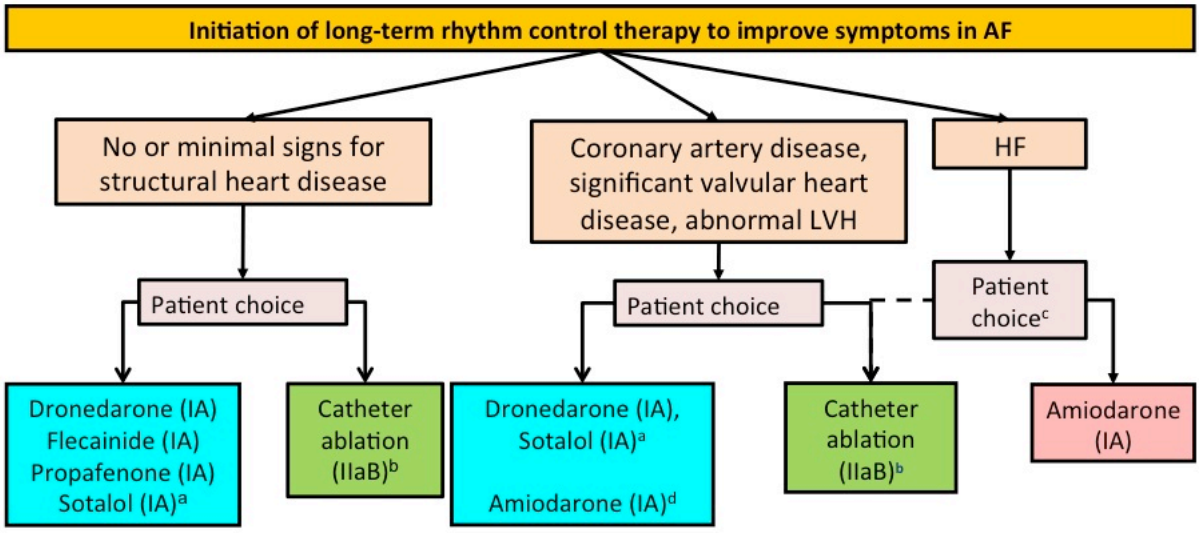


Figure 17 Initiation of rhythm control therapy in symptomatic patients.
AF = atrial fibrillation; HF = heart failure; LVH = left ventricular hypertrophy;
[a]Sotalol requires careful evaluation of proarrhythmic risk.
[b]Catheter ablation should isolate pulmonary veins and can be performed using radiofrequency or cryoballoon catheters.
[c]Catheter ablation as a first-line therapy is usually reserved for heart failure patients with tachycardiomyopathy.
[d]Amiodarone is a second-choice therapy in many patients because of its extracardiac side-effects.

11.2.2. Twelve-lead electrocardiogram as a tool to identify patients at risk of proarrhythmia

Identifying patients at risk of proarrhythmia can help to mitigate the proarrhythmic risk of antiarrhythmic drugs.[668] In addition to the clinical characteristics mentioned above, monitoring PR, QT, and QRS durations during initiation of antiarrhythmic drug therapy can identify patients at higher risk of drug-induced proarrhythmia on longer-term treatment.[669-671] In addition, the presence of 'abnormal TU waves' is a sign of imminent torsades de pointes.[652] Periodic ECG analysis for proarrhythmia signs has been used successfully in recent antiarrhythmic drug trials.[118, 584, 672] Specifically, ECG monitoring was used systematically on days 1–3 in patients receiving flecainide, propafenone, or sotalol to identify those at risk of proarrhythmia.[118, 584, 601] Based on this evaluated practice, we suggest to record an ECG in all patients before initiation of antiarrhythmic drugs. Scheduled ECGs during the initiation period seem reasonable (*Table 17*).

Table 17 Oral antiarrhythmic drugs used for maintaining sinus rhythm after cardioversion.

Drug	Dose	Main contraindications and precautions	Warning signs warranting discontinuation	Atrioventricular nodal slowing	Suggested ECG monitoring during initiation
Amiodarone	600 mg in divided doses for 4 weeks, 400 mg for 4 weeks, then 200 mg once daily	Caution when using concomitant therapy with QT-prolonging drugs and in patients with sinoatrial node or atrioventricular node and conduction disease. The dose of VKAs and of digitalis should be reduced. Increased risk of myopathy with statins. Caution in patients with pre-existing liver disease	QT prolongation > 500 ms	10–12 bpm in AF	Baseline, 1 week, 4 weeks
Dronedarone	400 mg twice daily	Contraindicated in NYHA class III or IV or unstable heart failure, during concomitant therapy with QT-prolonging drugs, or powerful CYP3A4 inhibitors (e.g. verapamil, diltiazem, azole antifungal agents), and when CrCl < 30 mg/mL. The dose of digitalis, beta-blockers, and of some statins should be reduced. Elevations in serum creatinine of 0.1–0.2 mg/dL are common and do not reflect a decline in renal function. Caution in patients with pre-existing liver disease	QT prolongation > 500 ms	10–12 bpm in AF	Baseline, 1 week, 4 weeks
Flecainide	100–150 mg twice daily	Contraindicated if CrCl < 50 mg/mL, liver disease, IHD, or reduced LVEF. Caution in the presence of sinoatrial node or atrioventricular node or conduction system disease. CYP2D6 inhibitors (e.g. fluoxetine, tricyclic) increase plasma concentration	QRS duration increases > 25% above baseline	None	Baseline, day 1, day 2–3
Flecainide slow release	200 mg once daily				
Propafenone	150–300 mg three times daily	Contraindicated in IHD or reduced LV ejection fraction. Caution in the presence of sinoatrial node or atrioventricular node and conduction system disease, renal or liver impairment, and asthma. Increases concentration of digitalis and warfarin	QRS duration increase > 25% above baseline	Slight	Baseline, day 1, day 2–3
Propafenone SR	225–425 mg twice daily				
d,l sotalol	80–160 mg twice daily	Contraindicated in the presence of significant LV hypertrophy, systolic heart failure, asthma, pre-existing QT prolongation, hypokalaemia, CrCl < 50 mg/mL. Moderate renal dysfunction requires careful adaptation of dose	QT interval > 500 ms, QT prolongation by > 60 ms upon therapy initiation	Similar to high-dose blockers	Baseline, day 1, day 2–3

AF = atrial fibrillation; bpm = beats per minute; CrCl = creatinine clearance; ECG = electrocardiogram; IHD = ischaemic heart disease; LV = left ventricular; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; VKA = vitamin K antagonist.

11.2.3. New antiarrhythmic drugs

Several compounds that inhibit the ultrarapid potassium current (I_{Kur}) and other inhibitors of atypical ion channels are in clinical development.[673-675] They are not available for clinical use at present. The antianginal compound ranolazine inhibits potassium and sodium currents and increases glucose metabolism at the expense of free fatty acid metabolism, thereby enhancing efficient use of oxygen.[676, 677] Ranolazine was safe in patients with non–ST-segment elevation myocardial infarction and unstable angina evaluated in the MERLIN (Metabolic Efficiency With Ranolazine for Less Ischemia in Non ST-Elevation Acute Coronary Syndrome) trial.[678] In a post-hoc analysis of continuous ECG recordings obtained during the first 7 days after randomization, patients assigned to ranolazine had a trend towards fewer episodes of AF than those on placebo (75 [2.4%] vs. 55 [1.7%] patients; $P = 0.08$).[679] In the HARMONY (A Study to Evaluate the Effect of Ranolazine and Dronedarone When Given Alone and in Combination in Patients With Paroxysmal Atrial Fibrillation) trial, the highest tested dose of a combination of ranolazine (750 mg twice daily) and dronedarone (225 mg twice daily) slightly reduced AF burden in 134 subjects with paroxysmal AF and dual-chamber pacemakers.[680] Small, open-label studies suggest that ranolazine might enhance the antiarrhythmic effect of amiodarone for cardioversion,[681-683] whereas the results from a controlled trial of ranolazine and the ranolazine–dronedarone combination to prevent AHRE in pacemaker patients were ambiguous.[684] At present, there is insufficient evidence to recommend ranolazine as an antiarrhythmic drug, alone or in combination with other antiarrhythmic drugs. Of note, the 'funny channel blocker' ivabradine, which is used for angina and heart failure, increases the risk of AF.[685]

11.2.4. Antiarrhythmic effects of non-antiarrhythmic drugs

ACE inhibitors or ARBs appear to prevent new-onset AF in patients with LV dysfunction and in hypertensive patients with LV hypertrophy.[219, 236, 237, 239, 246, 250, 686] Neprilysin inhibition needs to be studied further, but does not seem to enhance this effect.[224] A Danish cohort study also suggested that initial treatment of uncomplicated hypertension with ACE inhibitors or ARBs reduces incident AF compared with other hypertensive agents.[245] ARB therapy did not reduce the AF burden in patients with AF without structural heart disease.[241] Thus, ACE inhibitors or ARBs are unlikely to have a relevant direct antiarrhythmic effect. However, it might be justified to consider adding ACE inhibitors or ARB therapy to antiarrhythmic drugs to reduce AF recurrences after cardioversion.[248, 249, 687]

Compared with placebo, beta-blockers are associated with a reduced risk of new-onset AF in patients with reduced ejection fraction and sinus rhythm.[23] Beta-blockers have also been reported to reduce symptomatic AF recurrences,[580, 636, 688] but this finding may be driven by the beneficial effect of rate control, which will render AF more often asymptomatic.

Perioperative statin therapy appeared to reduce the risk of postoperative AF in a number of small RCTs[689, 690]; however, an adequately powered placebo-controlled trial has shown no effect of perioperative rosuvastatin therapy on postoperative AF.[691] Statin treatment does not prevent AF in other settings.[692, 693] Similarly, polyunsaturated fatty acids failed to show convincing benefit.[241, 694-698] The role of aldosterone antagonists in the management of AF has not been extensively investigated in humans; although preliminary evidence from trials of eplerenone is encouraging for primary prevention,[243] at present there is no robust evidence to make any recommendation for the use of aldosterone antagonists for secondary prevention of AF.[699-701]

Recommendations for rhythm control therapy

Recommendations	Class [a]	Level [b]	Refs [d]
General recommendations			
Management of cardiovascular risk factors and avoidance of AF triggers should be pursued in patients on rhythm control therapy to facilitate maintenance of sinus rhythm	IIa	B	203, 204, 296, 312
Rhythm control therapy is indicated for symptom improvement in patients with AF	I	B	120, 586, 601
With the exception of AF associated with haemodynamic instability, the choice between electrical and pharmacological cardioversion	IIa	C	

should be guided by patient and physician preferences			
Cardioversion of AF			
Electrical cardioversion of AF is recommended in patients with acute haemodynamic instability to acutely restore cardiac output	I	B	612, 702-704
Cardioversion of AF (either electrical or pharmacological) is recommended in symptomatic patients with persistent or long-standing persistent AF as part of rhythm control therapy	I	B	584, 601, 627, 628, 648, 705
Pretreatment with amiodarone, flecainide, ibutilide, or propafenone should be considered to enhance success of electrical cardioversion and prevent recurrent AF	IIa	B	248, 584, 633
In patients with no history of ischaemic or structural heart disease, flecainide, propafenone, or vernakalant are recommended for pharmacological cardioversion of new-onset AF	I	A	602-605, 614, 618, 622, 706, 707
In patients with no history of ischaemic or structural heart disease, ibutilide should be considered for pharmacological conversion of AF	IIa	B	
In selected patients with recent-onset AF and no significant structural or ischaemic heart disease, a single oral dose of flecainide or propafenone (the 'pill in the pocket' approach) should be considered for patient-led cardioversion, following safety assessment	IIa	B	620, 621
In patients with ischaemic and/or structural heart disease, amiodarone is recommended for cardioversion of AF	I	A	597-601
Vernakalant may be considered as an alternative to amiodarone for pharmacological conversion of AF in patients without hypotension, severe heart failure, or severe structural heart disease (especially aortic stenosis)	IIb	B	602-605, 616, 618
Stroke prevention in patients designated for cardioversion of AF			
Anticoagulation with heparin or a NOAC should be initiated as soon as possible before every cardioversion of AF or atrial flutter	IIa	B	708, 709
For cardioversion of AF/atrial flutter, effective anticoagulation is recommended for a minimum of 3 weeks before cardioversion	I	B	648, 708
Transoesophageal echocardiography (TOE) is recommended to exclude cardiac thrombus, as an alternative to preprocedural anticoagulation when early cardioversion is planned	I	B	648, 708
Early cardioversion can be performed without TOE in patients with a definite duration of AF < 48 hours	IIa	B	648
In patients at risk for stroke (e.g. presence of CHA_2DS_2-VASc factors), anticoagulant therapy should be continued long-term after cardioversion according to the long-term anticoagulation recommendations, irrespective of the method of cardioversion or the apparent maintenance of sinus rhythm. In patients without stroke risk factors, anticoagulation is recommended for 4 weeks after cardioversion	I	B	353, 710
In patients where thrombus is identified on TOE, effective anticoagulation is recommended for at least 3 weeks	I	C	
A repeat TOE to ensure thrombus resolution should be considered before cardioversion	IIa	C	
Antiarrhythmic drugs for the long-term maintenance of sinus rhythm/prevention of recurrent AF			

The choice of antiarrhythmic drug needs to be carefully evaluated, taking into account the presence of comorbidities, cardiovascular risk and potential for serious proarrhythmia, extracardiac toxic effects, patient preferences, and symptom burden	I	A	41, 580
Dronedarone, flecainide, propafenone, or sotalol are recommended for prevention of recurrent symptomatic AF in patients with normal left ventricular function and without pathological left ventricular hypertrophy.	I	A	581, 583, 584, 588, 601
Dronedarone is recommended for prevention of recurrent symptomatic AF in patients with stable coronary artery disease, and without heart failure	I	A	583, 588
Amiodarone is recommended for prevention of recurrent symptomatic AF in patients with heart failure	I	B	596-598
Amiodarone is more effective in preventing AF recurrences than other antiarrhythmic drugs but extracardiac toxic effects are common and increase with time. For this reason, other antiarrhythmic drugs should be considered first	IIa	C	596-598
Patients on antiarrhythmic drug therapy should be periodically evaluated to confirm their eligibility for treatment	IIa	C	583, 588, 657, 658, 660
ECG recording during the initiation of antiarrhythmic drug therapy should be considered to monitor heart rate, detect QRS and QT interval prolongation, and the occurrence of atrioventricular block	IIa	B	584 582, 583, 588, 601
Antiarrhythmic drug therapy is not recommended in patients with prolonged QT interval (> 0.5 s) or with significant sinoatrial node disease or atrioventricular node dysfunction who do not have a functioning permanent pacemaker	III (harm)	C	
Adding atrial-based bradycardia pacing to drug treatment that induces or exacerbates sinus node dysfunction should be considered to allow continuation of antiarrhythmic drug therapy in patients in whom AF ablation is declined or not indicated	IIa	B	711, 712
Continuation of antiarrhythmic drug therapy beyond the blanking period after AF ablation should be considered to maintain sinus rhythm when recurrences seem likely	IIa	B	713
Antiarrhythmic effects of non-antiarrhythmic drugs			
ACE inhibitors, ARBs, and beta-blockers should be considered for prevention of new-onset AF in patients with heart failure and reduced ejection fraction	IIa	A	23, 219, 236, 237, 239, 250, 714
ACE inhibitors and ARBs should be considered for prevention of new-onset AF in patients with hypertension, particularly with LV hypertrophy	IIa	B	238, 246, 686, 714
Pretreatment with ACE inhibitors or ARBs may be considered in patients with recurrent AF undergoing electrical cardioversion and receiving antiarrhythmic drug therapy	IIb	B	236, 237, 248, 249
ARBs or ACE inhibitors are not recommended for the secondary prevention of paroxysmal AF in patients with little or no underlying heart disease.	III (no benefit)	B	241, 697

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; CHA_2DS_2-VASc = Congestive Heart failure, hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female); ECG = electrocardiogram; NOAC = non-vitamin K antagonist oral anticoagulant; TOE = transoesophageal echocardiography.

[a]Class of recommendation.

[b]Level of evidence.

[c]Reference(s) supporting recommendations.

11.3. Catheter ablation

Since the initial description of triggers in the pulmonary veins that initiate paroxysmal AF,[108] catheter ablation of AF has developed from a specialized, experimental procedure into a common treatment to prevent recurrent AF.[587, 715] This is primarily achieved through isolation of the pulmonary veins, probably requiring complete isolation for full effectiveness,[716] and additional ablation in the posterior left atrial wall. AF ablation, when performed in experienced centres by adequately trained teams, is more effective than antiarrhythmic drug therapy in maintaining sinus rhythm, and the complication rate, though not negligible, is similar to the complication rate for antiarrhythmic drugs.[585, 717, 1042]

11.3.1. Indications

Catheter ablation of AF is effective in restoring and maintaining sinus rhythm in patients with symptomatic paroxysmal, persistent, and probably long-standing persistent AF – in general as second-line treatment after failure of or intolerance to antiarrhythmic drug therapy. In such patients, catheter ablation is more effective than antiarrhythmic drug therapy.[185, 586, 713, 717-720] As first-line treatment for paroxysmal AF, randomized trials showed only modestly improved rhythm outcome with catheter ablation compared to antiarrhythmic drug therapy.[585, 721-723] Complication rates were similar, but ablation was performed in expert centres, justifying catheter ablation as first-line therapy in selected patients with paroxysmal AF who ask for interventional therapy. Fewer data are available reporting the effectiveness and safety of catheter ablation in patients with persistent or long-standing persistent AF, but all point to lower recurrence rates after catheter ablation compared to antiarrhythmic drug therapy with or without cardioversion.[185, 717, 723-726, 1039] In patients who experience symptomatic recurrences of AF despite antiarrhythmic drug therapy, all RCTs showed better sinus rhythm maintenance with catheter ablation than on antiarrhythmic drugs.[586, 713, 727, 728] There is no current indication for catheter ablation to prevent cardiovascular outcomes (or desired withdrawal of anticoagulation), or to reduce hospitalization.[40, 594]

11.3.2. Techniques and technologies

Complete pulmonary vein isolation (PVI) on an atrial level is the best documented target for catheter ablation,[716, 729-731] achievable by point-by-point radiofrequency ablation, linear lesions encircling the pulmonary veins, or cryoballoon ablation, with similar outcomes.[732-734] Complete isolation of the pulmonary veins has better rhythm outcomes than incomplete isolation.[716] PVI was initially tested in patients with paroxysmal AF, but appears to be non-inferior to more extensive ablation in persistent AF as well.[729, 735] More extensive ablations have been used in patients with persistent AF, but there are insufficient data to guide the use of these at present.[117, 718, 719, 735-737] Extended ablation procedures (beyond PVI) consistently require longer procedures and more ionizing radiation, potentially creating risk for patients. Left atrial macro-reentrant tachycardia is relatively uncommon after PVI (≈ 5%). It also seems even less common after cryoballoon ablation,[734] but may occur in up to 25% of patients after left atrial substrate modification ablation, often due to incomplete ablation lines. Thus, for patients with persistent AF, ablation of complex fractionated electrograms, ablation of rotors, or routine deployment of linear lesions or other additional ablations does not seem justified in the first procedure.[735, 738, 739] However, additional ablation on top of complete PVI[716] may be considered in patients with recurrent AF after the initial ablation procedure.[719, 740, 741] In patients with documented right atrial isthmus-dependent flutter undergoing AF ablation, right atrial isthmus ablation is recommended. Adenosine testing to identify patients in need of additional ablation remains controversial after evaluation in several reports.[739, 742-744] Ablation of so-called ‘rotors’ guided by body surface mapping or endocardial mapping is under evaluation and cannot be recommended for routine clinical use at present.

11.3.3. Outcome and complications

The rhythm outcome after catheter ablation of AF is difficult to predict in individual patients.[173, 227, 713, 728] Most patients require more than one procedure to achieve symptom control.[713, 726, 728] In general, better rhythm outcome and lower procedure-related complications can be expected in younger patients with a short history of AF and frequent, short AF episodes in the absence of significant structural heart disease.[745] Catheter ablation is more effective than antiarrhythmic drug therapy in maintaining sinus rhythm (*Web Addenda Figure 2*).[746, 1039] Sinus rhythm without severely symptomatic recurrences of AF is found in up to 70% of patients with paroxysmal AF, and around 50% in persistent AF.[713, 728, 735, 1042] Very late recurrence of AF after years of sinus rhythm is not uncommon and may reflect disease progression, with important implications for continuation of AF therapies.[728] Multiple variables have been identified as risk factors for recurrence after catheter ablation of AF, but their predictive power is weak. The decision for catheter ablation thus should be based on a shared decision-making process[747] (see Chapter 7), following thorough explanation of the potential benefits and risks, and of the alternatives such as antiarrhythmic drug or acceptance of current symptoms without rhythm control therapy.[175]

Complications of catheter ablation for AF

There is a clear need to systematically capture complications in clinical practice to improve the quality of AF ablation procedures.[175] The median length of hospital stay in AF patients undergoing their first ablation as part of the EURObservational Research Programme (EORP) was 3 days (interquartile range 2–4 days), based on data from 1391 patients from hospitals performing at least 50 ablations per year. Five to seven per cent of patients will suffer severe complications after catheter ablation of AF, and 2–3% will experience life-threatening but usually manageable complications.[727, 748-750] Intraprocedural death has been reported, but is rare (< 0.2%).[751] The most important severe complications are stroke/TIA (< 1%), cardiac tamponade (1–2%), pulmonary vein stenosis, and severe oesophageal injury leading to atrio-oesophageal fistula weeks after ablation (*Table 18*). 'Silent strokes' (i.e. white matter lesions detectable by brain MRI), have been observed in around 10% of patients treated with radiofrequency and cryoballoon ablation.[752] The clinical relevance of this observation is unclear.[749] Post-procedure complications include stroke, with the highest risk within the first week,[753] late pericardial tamponade several days after catheter ablation,[751] and oesophageal fistulas, which usually become apparent 7–30 days after ablation. Timely detection of atrio-oesophageal fistulas can be life-saving and should be based on the typical triad of infection without a clear focus, retrosternal pain, and stroke or TIA.[748]

Table 18 Complications related to catheter ablation of AF

Complication severity	Complication type	Rate[727, 748, 750, 754-759]
Life-threatening complications	Periprocedural death	< 0.2%
	Oesophageal injury (perforation/fistula)[a]	< 0.5%
	Periprocedural stroke (including TIA/air embolism)	< 1%
	Cardiac tamponade	1–2%
Severe complications	Pulmonary vein stenosis	< 1%
	Persistent phrenic nerve palsy	1–2%
	Vascular complications	2–4%
	Other severe complications	≈ 1%
Other moderate or minor complications		1–2%
Unknown significance	Asymptomatic cerebral embolism (silent stroke)[b]	5–20%
	Radiation exposure	

AF = atrial fibrillation; TIA = transient ischaemic attack.

[a]Oesophageal fistula should be suspected in patients presenting with the triad of unspecific signs of infection, chest pain, and stroke or TIA in the first weeks after an ablation procedure. It requires immediate therapy.

[b]< 10% for cryoablation or radiofrequency ablation, > 20% for phased radiofrequency ablation

11.3.4. Anticoagulation – before, during, and after ablation

Patients anticoagulated with VKAs should continue therapy during ablation (with an INR of 2–3).[760] Anticoagulation with NOACs is an alternative to warfarin.[478, 761-765] There is no safety signal from observational cohorts treated with uninterrupted NOAC therapy undergoing catheter ablation in experienced centres.[761, 763, 766, 767] The first controlled trial, enrolling around 200 patients, has recently been published,[768] as well as several observational data sets.[761, 769, 770] Ongoing studies compare uninterrupted VKA with NOAC therapy in AF patients undergoing ablation (e.g. AXAFA – AFNET 5 [Apixaban During Atrial Fibrillation Catheter Ablation: Comparison to Vitamin K Antagonist Therapy – Anticoagulation using the direct factor Xa inhibitor apixaban during Atrial Fibrillation catheter Ablation: Comparison to vitamin K antagonist therapy; NCT02227550] and RE-CIRCUIT [Randomized Evaluation of dabigatran etexilate Compared to warfarin in pulmonaRy vein

ablation: assessment of different peri-proCedUral anticoagulation sTrategies; NCT02348723]). During ablation, heparin should be given to maintain an activated clotting time > 300 seconds. Anticoagulation should be maintained for at least 8 weeks after ablation for all patients. The true incidence of thromboembolic events after catheter ablation has never been systematically studied and the expected stroke risk has been adopted from non-ablation AF cohorts. Although observational studies suggest a relatively low stroke rate in the first few years after catheter ablation of AF,[737, 771-776] the long-term risk of recurrent AF and the safety profile of anticoagulation in ablated patients need to be considered. In the absence of controlled trial data, OAC after catheter ablation should follow general anticoagulation recommendations, regardless of the presumed rhythm outcome.

11.3.5. Ablation of atrial fibrillation in heart failure patients

Catheter ablation, compared with amiodarone therapy, significantly reduces recurrent AF in AF patients with HFrEF.[777] Selected patients with HFrEF and AF can achieve recovery of LV systolic function after catheter ablation (probably reflecting tachycardiomyopathy). Several smaller trials suggest improved LV function after catheter ablation in HFrEF patients[185, 226-228, 778, 779] and reduced hospitalizations,[720, 777] especially in patients without a previous myocardial infarction.[780] Larger trials are warranted to confirm these findings. Catheter ablation can be demanding in these patients. Thus, indications for catheter ablation in HFrEF patients should be carefully balanced, and the procedures performed in experienced centres.

11.3.6. Follow-up after catheter ablation

Patients and physicians involved in the follow-up after catheter ablation should know the signs and symptoms of late complications to allow swift referral for treatment. Patient should also be aware that symptomatic and asymptomatic AF recurrences are frequent after catheter ablation.[119, 781, 782] In line with the primary goal of rhythm control therapy, asymptomatic episodes should generally not trigger further rhythm control therapy. Patients should be seen at least once by a rhythm specialist in the first 12 months after ablation. Further rhythm control options should be considered in patients with symptomatic recurrences, including discussion in a Heart Team (*Figure 17*).

11.4. Atrial fibrillation surgery

11.4.1. Concomitant atrial fibrillation surgery

The Cox maze procedure was first performed 30 years ago as a ‘cut-and-sew’ technique, including isolation of the posterior left atrium, a connection to the posterior mitral annulus, a cavotricuspid connection, a cavocaval connection, and exclusion of the LAA (*Figure 18*).[783] Thereby, the Cox maze procedure creates an electrical labyrinth (maze) of passages through which the sinoatrial node impulse finds a route to the atrioventricular node while preventing fibrillatory conduction. The Cox maze procedure and other, often simpler, forms of AF surgery have mainly been used in patients undergoing other open heart surgical procedures.[461, 466, 784-798] In a systematic review commissioned for these guidelines, concomitant AF surgery resulted in greater freedom from AF, atrial flutter, and atrial tachycardia (RR 1.94, 95% CI 1.51–2.49; *n* = 554 from seven RCTs) (*Web Addenda Figure 3*).[1040] Patients undergoing the Cox maze procedure required pacemaker implantation more often (RR 1.69, 95% CI 1.12–2.54; *n* = 1631 from 17 RCTs), without a detectable difference in other outcomes or complications. These findings are underpinned by an analysis of Society of Thoracic Surgeons database comprising 67,389 patients in AF: mortality or major morbidity was not affected by concomitant AF surgery (adjusted OR 1.00; 95% CI 0.83–1.20), but pacemaker implantation was more frequent (adjusted OR 1.26; 95% CI 1.07–1.49).[799] Predictors of AF recurrence after surgery include left atrial dilatation, older age, > 10-year history of AF, and non-paroxysmal AF.[800-804] Regarding AF type, surgical PVI seems effective in paroxysmal AF.[805] Biatrial lesion patterns may be more effective in persistent and long-standing persistent AF.[797, 803, 806] The suggested management of patients with AF-related symptoms undergoing cardiac surgery is displayed in *Figure 19*, with an important contribution of the AF Heart Team to advise and inform patient choice.

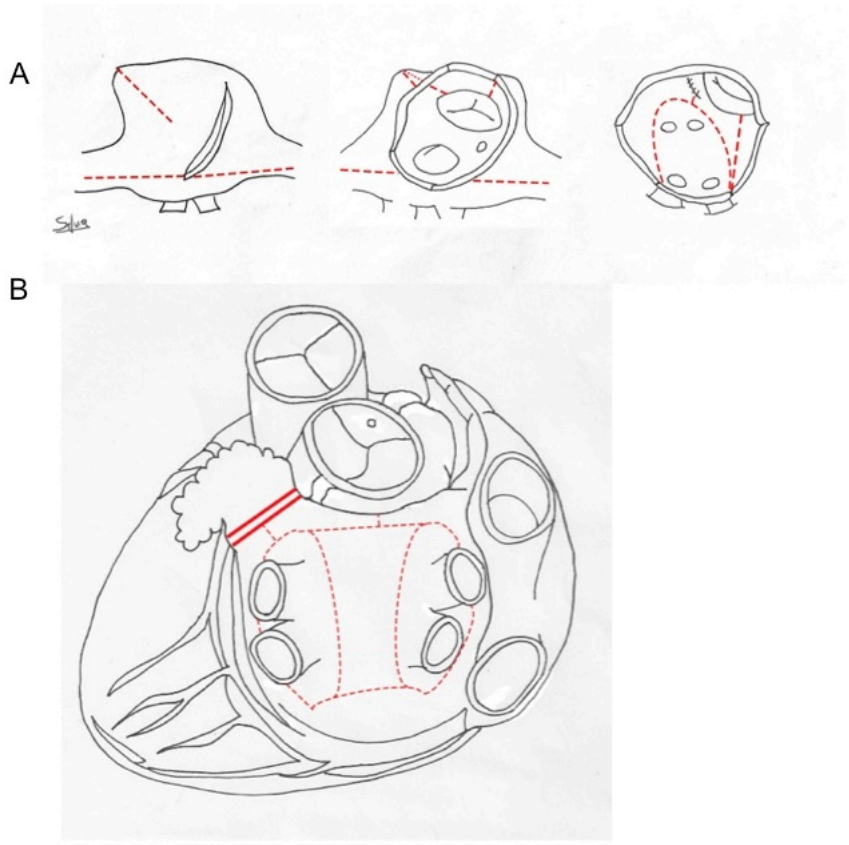


Figure 18 A. Surgical lesion sets for the biatrial Cox maze procedure. Left and middle panel: right atrial lesions. Right panel: left atrial lesions.
B: Left atrial lesions in a thoracoscopic minimally invasive surgical procedure (dashed lines), including left appendage exclusion (double line).

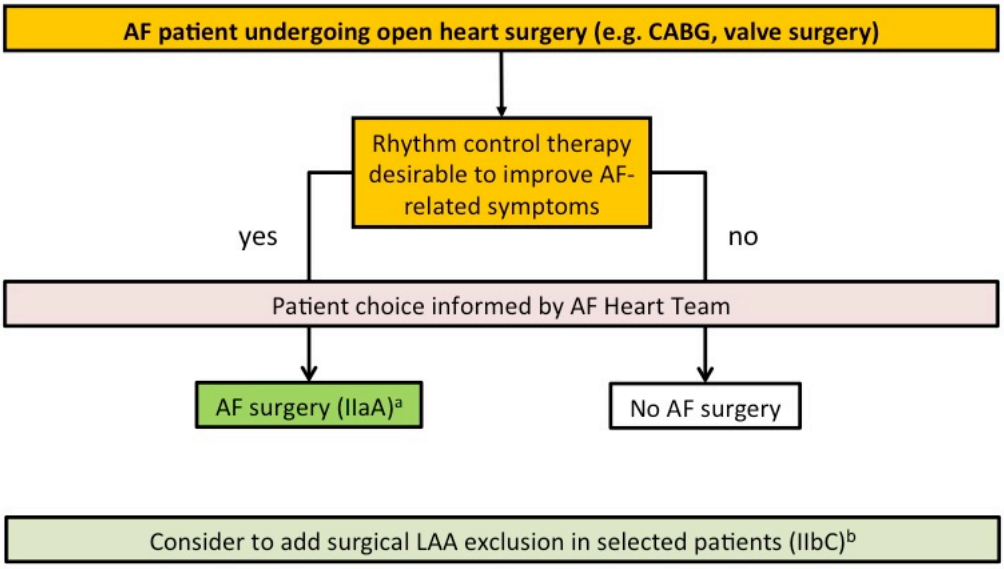


Figure 19 Surgical rhythm control in patients undergoing cardiac surgery.
AF = atrial fibrillation; CABG = coronary artery bypass graft; LAA = left atrial appendage; PVI = pulmonary vein isolation.
[a]AF surgery may be PVI in paroxysmal AF and biatrial maze in persistent or long-standing persistent AF.
[b]Oral anticoagulation should be continued in patients at risk of stroke irrespective of AF surgery or LAA exclusion.

11.4.2. Stand-alone rhythm control surgery

Current technology (e.g. bipolar radiofrequency or cryothermy) renders the procedure easier and more reproducible and feasible via a mini-thoracotomy.[786, 807, 808] Thoracoscopic PVI with bipolar radiofrequency prevents recurrence of paroxysmal AF (69–91% freedom from arrhythmias at 1 year, see *Figure 18B* for lesion set),[468, 809, 810] and seems effective in patients refractory to catheter ablation.[811] The average length of hospital stay for thoracoscopic ablation varies from 3.6 to 6.0 days.[468, 812, 813] The FAST (Atrial Fibrillation Catheter Ablation vs Surgical Ablation Treatment) trial,[468] and another smaller trial,[814] suggested that thoracoscopic AF surgery could be more effective than catheter ablation for the maintenance of sinus rhythm,[468, 814] while also causing more complications (*Table 19*).[815] To improve results,[468, 816-818] more extensive lesion sets have been performed, connecting lines between the PVI encircling and towards the mitral annulus.[812, 819-822] To improve the generation of transmural lesions,[716] endo-epicardial ablation strategies have recently been proposed.[812, 823-825] Although preliminary experience with hybrid simultaneous ablation shows promise, procedural time and rates of bleeding complications are higher.[812, 823]

Table 19 Complications of thoracoscopic AF surgery

Complication	Rate[468, 815, 822, 826]
Conversion to sternotomy	0–1.6%
Pacemaker implantation	0–3.3%
Drainage for pneumothorax	0–3.3%
Pericardial tamponade	0–6.0%
Transient ischaemic attack [a]	0–3.0%

AF = atrial fibrillation.
[a]The rate of asymptomatic cerebral embolism is unknown

11.5. Choice of rhythm control following treatment failure

There is insufficient evidence on which to base clear recommendations on how to treat patients with recurrent AF after catheter ablation. Early recurrences of AF or atrial tachycardias after ablation (occurring within 8 weeks) may be treated with cardioversion. Many of the published series of patients undergoing AF ablation included those who failed antiarrhythmic drug therapy. Thus, considering ablation therapy in patients who have symptomatic recurrences on antiarrhythmic drug therapy is often reasonable. Alternatively, trialling another antiarrhythmic drug can be considered. Combining antiarrhythmic drug with ablation ('hybrid therapy', see Section 11) should be considered based on the different and possibly synergistic effects of these drugs with AF ablation, possibly benefitting patients in whom either treatment alone was previously ineffective. Rate control without rhythm control, surgical ablation, or repeat catheter ablation should be considered as well as third-line options (*Figure 20*). Patient preferences and local access to therapy are important considerations to inform the therapy choice in patients who are in need of further rhythm control therapy after an initial therapy failure.

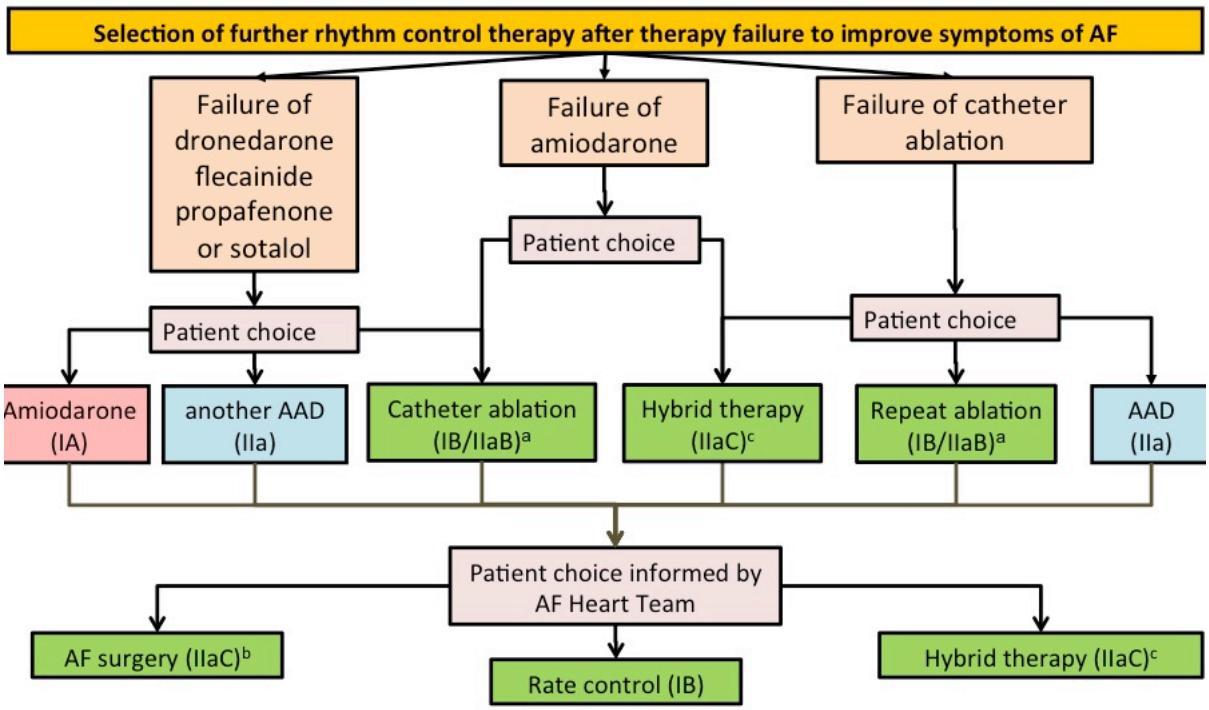


Figure 20 Choice of rhythm control approaches following treatment failure.
AAD = antiarrhythmic drug; AF = atrial fibrillation; PVI = pulmonary vein isolation.
[a] catheter ablation should target PVI. Class I level B for paroxysmal AF and Class IIa level B for persistent AF.
[b] AF surgery may be PVI (e.g. in paroxysmal AF) or maze surgery (e.g. in therapy-refractory or long-standing persistent AF).
[c] Hybrid therapy involves combination of antiarrhythmic drugs, catheter ablation, and/or AF surgery.

11.6. The atrial fibrillation Heart Team

In view of the complexity of the different treatment options in patients with failed rhythm control therapy but who still require or demand further rhythm control therapy, this Task Force proposes that decisions involving AF surgery or extensive AF ablation should be based on advice from an AF Heart Team. This will also apply to reversal to a rate control strategy in patients with severe (EHRA III or IV) AF symptoms. An AF Heart Team should consist of a cardiologist with expertise in antiarrhythmic drug therapy, an interventional electrophysiologist, and a cardiac surgeon with expertise in appropriate patient selection, techniques, and

technologies for interventional or surgical AF ablation. Such AF Heart Teams – and a collaborative infrastructure supporting a continued interaction between physicians delivering continued care, AF cardiologists, interventional electrophysiologists, and AF surgeons – should be established to provide optimal advice and ultimately to improve rhythm outcomes for patients in need of advanced and complex rhythm control interventions.

Recommendations for catheter ablation of AF and AF surgery

Recommendations	Class [a]	Level [b]	Refs [c]
Catheter ablation of symptomatic paroxysmal AF is recommended to improve AF symptoms in patients who have symptomatic recurrences of AF on antiarrhythmic drug therapy (amiodarone, dronedarone, flecainide, propafenone, sotalol) and who prefer further rhythm control therapy, when performed by an electrophysiologist who has received appropriate training and is performing the procedure in an experienced centre	I	A	585-587, 713, 727
Ablation of common atrial flutter should be considered to prevent recurrent flutter as part of an AF-ablation procedure if previously documented or occurring during the AF ablation	IIa	B	827
Catheter ablation of AF should be considered as first-line therapy to prevent recurrent AF and to improve symptoms in selected patients with symptomatic paroxysmal AF as an alternative to antiarrhythmic drug therapy, considering patient choice, benefit, and risk	IIa	B	585
All patients should receive oral anticoagulation for stroke prevention for at least 8 weeks after catheter (IIaB) or surgical (IIaC) ablation.	IIa	B/C	727
Anticoagulation for stroke prevention should be continued indefinitely after apparently successful catheter or surgical ablation of AF in patients at high risk of stroke	IIa	C	
When catheter ablation of AF is planned, continuation of oral anticoagulation with VKA (IIaB) or NOAC (IIaC) should be considered during the procedure, maintaining effective anticoagulation	IIa	B/C	760, 768
Catheter ablation should target complete isolation of the pulmonary veins using radiofrequency ablation or cryothermy balloon catheters	IIa	B	585, 715, 716, 734, 735
AF ablation should be considered in symptomatic patients with AF and heart failure with reduced ejection fraction to improve symptoms and cardiac function when tachycardiomyopathy is suspected	IIa	C	185, 226-228, 720, 777-779, 828
AF ablation should be considered as a strategy to avoid pacemaker implantation in patients with AF-related bradycardia	IIa	C	829, 830
Catheter or surgical ablation should be considered in patients with symptomatic persistent or long-standing persistent AF refractory to antiarrhythmic drug therapy to improve symptoms, considering patient choice, benefit and risk, supported by an AF Heart Team	IIa	C	468, 735, 777, 831, 832, 1040
Minimally invasive surgery with epicardial pulmonary vein isolation should be considered in patients with symptomatic AF when catheter ablation has failed. Decisions on such patients should be supported by an AF Heart Team	IIa	B	468 812, 819, 823
Maze surgery, possibly via a minimally invasive approach, performed by an adequately trained operator in an experienced centre, should be considered by an AF Heart Team as a treatment option for patients with symptomatic refractory persistent AF or post-ablation AF to improve symptoms	IIa	C	808, 832

Maze surgery, preferably biatrial, should be considered in patients undergoing cardiac surgery to improve symptoms attributable to AF, balancing the added risk of the procedure and the benefit of rhythm control therapy	IIa	A	461, 466, 790, 791, 796, 797
Concomitant biatrial maze or pulmonary vein isolation surgery may be considered in asymptomatic AF patients undergoing cardiac surgery	IIb	C	796, 797, 833

AF = atrial fibrillation; NOAC = non-vitamin K antagonist oral anticoagulant; VKA = vitamin K antagonist.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

12 Hybrid rhythm control therapy

AF has many different drivers, which are only partially targeted by antiarrhythmic drug or catheter ablation.[96] Hence, combination or 'hybrid' rhythm control therapy seems reasonable, although there is little evidence supporting its use.

12.1. Combining antiarrhythmic drugs and catheter ablation

Antiarrhythmic drug therapy is commonly given for 8–12 weeks after ablation to reduce early recurrences of AF after catheter ablation, supported by a recent controlled trial where amiodarone halved early AF recurrences compared with placebo.[650] Prospective studies have not been done, but a meta-analysis of the available (weak) evidence suggests slightly better prevention of recurrent AF in patients treated with antiarrhythmic drugs after catheter ablation.[713] Many patients are treated with antiarrhythmic drug therapy after catheter ablation (most often amiodarone or flecainide),[587] and this seems a reasonable option in patients with recurrent AF after ablation. It seems common sense to consider antiarrhythmic drug therapy in patients who are in need of further rhythm control therapy after catheter ablation, but controlled trials to confirm this are desirable.

Combining cavotricuspid isthmus ablation and antiarrhythmic drugs may lead to improved rhythm control without the need for left atrial ablation in patients who develop 'drug-induced atrial flutter' on therapy with flecainide, propafenone, or amiodarone,[834-836] although recurrent AF is a concern in the long term.[837, 838]

12.2. Combining antiarrhythmic drugs and pacemakers

In selected patients with sick sinus syndrome and fast ventricular response during AF paroxysms requiring rate control therapy, the addition of a pacemaker not only optimizes rate control but may also help to control rhythm.[711, 712] Moreover, when antiarrhythmic drug treatment leads to sinus node dysfunction and bradycardia, pacing may permit uptitration of the antiarrhythmic drug dose. Such strategies have never been prospectively investigated and the existing populations studied are highly selected.[839, 840] Some patients with AF-induced bradycardia may benefit from catheter ablation of AF, obviating the need for antiarrhythmic drugs and pacemaker implantation.[829, 830]

13 Specific situations

13.1. Frail and 'elderly' patients

Many AF patients present at an older age (e.g. > 75 or > 80 years). There are no studies suggesting that cardiovascular risk reduction is less effective in these 'elderly' AF patients than in younger patients. Rather, age is one of the strongest predictors/risk factors for ischaemic stroke in AF (*Table 11*).[382] Good data are available to support the use of anticoagulants in older patients from BAFTA (Birmingham Atrial Fibrillation Treatment of the Aged Study),[362] the NOAC trials,[39] and from analyses in elderly Americans (Medicare).[396] Elderly AF patients are at higher risk of stroke and thus are more likely to benefit from OAC than younger patients,[841] and yet OAC is still underutilized in the elderly.[220, 842] Although the evidence base is smaller for other treatment options in AF, the available data support the use of available rate and rhythm control interventions, including pacemakers and catheter ablation, without justification to discriminate by age group. Individual patients at older age may present with multiple comorbidities including dementia, a tendency to falls, CKD, anaemia, hypertension, diabetes, and cognitive dysfunction. Such conditions may limit quality of life more than AF-related symptoms. Impairment of renal and hepatic function and multiple simultaneous medications make drug interactions and adverse drug reactions more likely. Integrated AF management and careful adaptation of drug dosing seem reasonable to reduce complications of AF therapy in such patients.[843]

13.2. Inherited cardiomyopathies, channelopathies, and accessory pathways

Several inherited cardiac conditions are associated with early-onset AF (*Table 20*). Treatment of the underlying cardiac condition is an important contribution to AF management in these young patients (see also ESC guidelines on the sudden cardiac death[844] and hypertrophic cardiomyopathy[845]).

Table 20 Inherited cardiomyopathies, channelopathies, and pathways associated with AF

Syndrome	Gene	Functional alteration	AF prevalence	References
Long QT syndrome	KCNQ1 KCNH2 SCN5A ANK2 others	IKs ↓ IKr ↓ INa ↓ INa,K ↓ Various effects	5–10%	846-850
Brugada syndrome	SCN5A GPDIL SCN1B CACNA1C CACNB2b others	INa ↓ INa ↓ INa ↓ ICa ↓ ICa ↓ others	10–20%	851-855
Short QT syndrome	KCNH2 KCNQ1 KCNJ2 CACNA1C CACNB2b	IKr ↑ IKs ↑ IK1 ↑ ICa ↑ ICa ↑	Up to 70%	853, 856-858
Catecholaminergic ventricular tachycardia	RYR2 CASQ2	Abnormal Ca^{2+} release from sarcoplasmic reticulum	Variable but significant	859-861
Hypertrophic cardiomyopathy	Sarcomeric genes		5–15%	862-864
Wolff–Parkinson–White syndrome	PRKAG		Variable	865
Holt–Oram syndrome	TBX5		Variable	866
Arrhythmogenic right ventricular cardiomyopathy	Several desmosomal genes, unknown gene loci		>40% in patients with VTs	867, 868

AF = atrial fibrillation.

13.2.1. Wolff–Parkinson–White syndrome

Patients with pre-excitation and AF are at risk of rapid conduction across the accessory pathway, resulting in a fast ventricular rate, possibly ventricular fibrillation, and sudden death. In AF patients with evidence of an antegrade accessory pathway, catheter ablation of the pathway is recommended.[869, 870] This procedure is safe and effective and may be considered as a prophylactic treatment strategy.[871, 872] In AF patients surviving a sudden death event with evidence of an accessory pathway, urgent catheter ablation of the pathway is recommended.[869] A documented short pre-excited RR interval (< 250 ms) during spontaneous or induced AF is one of the risk markers for sudden death in Wolff–Parkinson–White syndrome (WPW) syndrome, in addition to a history of symptomatic tachycardia, the presence of multiple accessory pathways, and Ebstein's anomaly. Intravenous procainamide, propafenone, or ajmaline can be used to acutely slow ventricular rate,[873, 874] whereas digoxin, verapamil, and diltiazem are contraindicated.[875] Intravenous amiodarone should be used with caution, as there are case reports of accelerated ventricular rhythms and ventricular fibrillation in patients with pre-excited AF receiving intravenous amiodarone infusion.[876]

13.2.2. Hypertrophic cardiomyopathy

AF is the most common arrhythmia in patients with hypertrophic cardiomyopathy, affecting approximately one-quarter of this population.[877] Observational data highlight a high stroke risk in hypertrophic cardiomyopathy

patients with AF, confirming the need for OAC.[878] While there is more experience with VKAs, there are no data to suggest that NOACs cannot be used in these patients.[845] Studies of rate or rhythm control medications in patients with hypertrophic cardiomyopathy are relatively scarce. Beta-blockers and diltiazem or verapamil seem reasonable treatment options for rate control in these patients. In the absence of significant LV outflow tract obstruction, digoxin can be used alone or in combination with beta-blockers.[845] Amiodarone seems a safe antiarrhythmic drug in AF patients with hypertrophic cardiomyopathy,[879] and expert opinion suggests that disopyramide may be beneficial in those with outflow tract obstruction. AF ablation is effective to suppress symptomatic AF recurrences.[880-884] Surgical treatment of AF may be appropriate in patients with hypertrophic cardiomyopathy undergoing surgery (e.g. for LV outflow tract obstruction or mitral valve surgery), but experience is limited.

13.2.3. Channelopathies and arrhythmogenic right ventricular cardiomyopathy

Many channelopathies and inherited cardiomyopathies are associated with AF. AF prevalence ranges from 5% to 20% in patients with long QT syndrome or Brugada syndrome, and is up to 70% in short QT syndrome (*Table 20*).[853, 856-858] Penetrance of disease phenotype including AF is variable.[61, 852, 885, 886] Both shortening as well as prolongation of the atrial action potential have been demonstrated as likely mechanisms underlying AF in these diseases. It seems reasonable to consider antiarrhythmic drugs that reverse the suspected channel defect in AF patients with inherited cardiomyopathies (e.g. a sodium channel blocker in LQT3[852] and quinidine in Brugada syndrome[887]). More importantly, new-onset AF in young, otherwise healthy individuals should trigger a careful search for such inherited conditions, including clinical history, family history, ECG phenotype, and echocardiography and/or other cardiac imaging.

Monogenic defects only account for 3–5% of all patients with AF, even in younger populations.[846, 848, 888-890] Furthermore, there is no clear link between detected mutations and specific outcomes or therapeutic needs. For these reasons, genetic testing is not recommended in the general AF population.[77] Other guidelines have described the indications for genetic testing in patients with inherited arrhythmogenic diseases.[844, 891]

Recommendations for inherited cardiomyopathies

Recommendations	Class [a]	Level [b]	Refs [c]
WPW syndrome			
Catheter ablation of the accessory pathway in WPW patients with AF and rapid conduction over the accessory pathway is recommended to prevent sudden cardiac death	I	B	892-894
Catheter ablation of the accessory pathway is recommended without delay in WPW patients who survive sudden cardiac death	I	C	869
Asymptomatic patients with overt pre-excitation and AF should be considered for accessory pathway ablation after careful counselling	IIa	B	872, 895
Hypertrophic cardiomyopathy			
Lifelong oral anticoagulation to prevent stroke is recommended in hypertrophic cardiomyopathy patients who develop AF	I	B	878
Restoration of sinus rhythm by electrical or pharmacological cardioversion to improve symptoms is recommended in hypertrophic cardiomyopathy patients with symptomatic new-onset AF	I	B	845
In haemodynamically stable hypertrophic cardiomyopathy patients with AF, ventricular rate control using beta-blockers and diltiazem/verapamil is recommended	I	C	845
Treatment of LV outflow tract obstruction should be considered in AF patients with hypertrophic cardiomyopathy to improve symptoms	IIa	B	896
Amiodarone should be considered to achieve rhythm control and maintain sinus rhythm in hypertrophic cardiomyopathy patients	IIa	C	845, 897
Inherited cardiomyopathies and channelopathies			
Targeted genetic testing should be considered in patients with AF and a suspicion of inherited cardiomyopathies or channelopathies based on clinical history, family history, or electrocardiographic phenotype	IIa	A	852

AF = atrial fibrillation; LV = left ventricular; WPW = Wolff–Parkinson–White syndrome.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

13.3. Sports and atrial fibrillation

Physical activity improves cardiovascular health, which translates into a lower risk of AF.[898] Therefore, physical activity is a cornerstone of preventing AF. Intensive sports practice, especially endurance sports (> 1500 h of endurance sports practice),[899] increases the risk of AF later in life,[900-902] probably mediated by altered autonomic tone, volume load during exercise, atrial hypertrophy, and dilatation.[903, 904] This results in a U-shaped relationship of physical activity and incident AF.[214, 898, 902, 905, 906] Detraining can reduce AF in models[904] and reduces ventricular arrhythmias in athletes,[907] but the role of detraining for AF in human athletes is unknown. The management of athletes with AF is similar to general AF management, but requires a few special considerations. Clinical risk factors will determine the need for anticoagulation. Sports with direct bodily contact or prone to trauma should be avoided in patients on OAC. Beta-blockers are not well tolerated and at times prohibited, and digoxin, verapamil, and diltiazem are often not potent enough to slow heart rate during exertional AF. Catheter ablation for AF probably has similar outcomes in athletes as in non-athletes,[908, 909] but further data are needed. Pill-in-the-pocket therapy has been used as well.[620] After ingestion of flecainide or propafenone as pill-in-the-pocket, patients should refrain from sports as long as AF persists and until two half-lives of the antiarrhythmic drug have elapsed. Prophylactic ablation of the flutter circuit may be considered in athletes treated with sodium channel blockers.[910]

Recommendations for physical activity in patients with AF

Recommendations	Class [a]	Level [b]	Refs[c]
Moderate regular physical activity is recommended to prevent AF, while athletes should be counselled that long-lasting, more intense sports participation can promote AF	I	A	214, 898, 900-902, 905, 906
AF ablation should be considered to prevent recurrent AF in athletes	IIa	B	908, 909
The ventricular rate while exercising with AF should be evaluated in every athlete (by symptoms and/or by monitoring), and titrated rate control should be instituted	IIa	C	
After ingestion of pill-in-the-pocket Class I antiarrhythmic drugs, patients should refrain from sports as long as AF persists and until two half-lives of the antiarrhythmic drug have elapsed	IIa	C	620

AF = atrial fibrillation.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

13.4. Pregnancy

AF in pregnant women is rare and is usually associated with pre-existing heart disease. AF is associated with increased complications for the mother and foetus.[911, 912] Better treatment of congenital heart diseases will probably increase the incidence of AF during pregnancy in the future.[913] Pregnant women with AF should be managed as high-risk pregnancies in close collaboration with cardiologists, obstetricians, and neonatologists.

13.4.1. Rate control

Owing to a lack of specific data, beta-blockers, verapamil, diltiazem, and digoxin all carry a US Food and Drug Administration pregnancy safety category of C (benefits may outweigh risk), except for atenolol (category D: positive evidence of risk). Their use should be at the lowest dose and for the shortest time required. None of the agents are teratogenic, but they readily cross the placenta.[914] Beta-blockers are commonly used in clinical practice (e.g. for management of gestational hypertension and pre-eclampsia), but may be associated with intrauterine growth retardation,[915] and hence growth scans after 20 weeks gestation are recommended. Digoxin is considered safe for maternal and foetal arrhythmias.[916] There are insufficient data to comment on verapamil or diltiazem, hence rate control using beta-blockers and/or digoxin is recommended.[917] With regards to breastfeeding, all rate control agents are present in breast milk, although levels of beta-blockers, digoxin, and verapamil are too low to be considered harmful. Diltiazem will be present at high levels and should be considered second-line treatment.[918]

13.4.2. Rhythm control

Rhythm control therapy in pregnant patients with AF has only been reported in case studies. Amiodarone is associated with severe adverse foetal side-effects and should only be considered for emergency situations.[919] Flecainide and sotalol can both be used for conversion of foetal arrhythmias without major adverse effects,[920] and thus are likely to be safe to treat maternal symptomatic AF. Electrical cardioversion can be effective for restoration of sinus rhythm when tachyarrhythmia is causing haemodynamic instability, with low rates of adverse outcomes for both mother and foetus.[921] However, in view of the risk of foetal distress, electrical cardioversion should only be carried out where facilities are available for foetal monitoring and emergency caesarean section. As with other emergencies during pregnancy, patients should receive 100% oxygen, intravenous access should be established early, and the mother should be positioned in the left lateral position to improve venous return.[922]

13.4.3. Anticoagulation

VKAs should be avoided in the first trimester because of teratogenic effects, and in the 2–4 weeks preceding delivery to avoid foetal bleeding. Low-molecular-weight heparins are a safe substitute, as they do not cross the placenta.[923] In the third trimester, frequent laboratory checks for adequate anticoagulation (e.g. every 10–14 days) and corresponding dose adjustments are advised, given that in some women high doses of both VKA and heparin may be needed to maintain adequate anticoagulation. Pregnant patients with AF and mechanical prosthetic valves who elect to stop VKA treatment in consultation with their specialist team between 6 and 12 weeks of gestation, should receive continuous, dose-adjusted unfractionated heparin or dose-adjusted subcutaneous low-molecular-weight heparin. As only limited data are available about teratogenesis for NOACs, these drugs should be avoided during pregnancy.

Recommendations during pregnancy

Recommendations	Class [a]	Level [b]	Refs [c]
Electrical cardioversion can be performed safely at all stages of pregnancy, and is recommended in patients who are haemodynamically unstable due to AF, and whenever the risk of ongoing AF is considered high, for the mother or the foetus	I	C	
Anticoagulation is recommended in pregnant patients with AF at risk of stroke. To minimize teratogenic risk and intrauterine bleeding, dose-adjusted heparins are recommended during the first trimester of pregnancy and in the 2–4 weeks before delivery. Vitamin K antagonists or heparin can be used in the remaining parts of the pregnancy	I	B	923
NOACs should be avoided in pregnancy and in women planning a pregnancy	III (harm)	C	

NOAC = non-vitamin K antagonist oral anticoagulants
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

13.5. Postoperative atrial fibrillation

AF is common after cardiac surgery (occurring in 15–45% of patients),[924-926] and is associated with increased length of hospital stay and higher rates of complications and mortality.[927] Postoperative AF is also not uncommon after other major surgery, especially in elderly patients. The treatment of postoperative AF is mainly based on studies of patients undergoing cardiac surgery, with much less evidence in the non-cardiac surgery setting.

13.5.1. Prevention of postoperative atrial fibrillation

Beta-blockers reduce postoperative AF and supraventricular tachycardias, albeit with high heterogeneity and moderate risk of bias in a systematic review of published studies (the most commonly studied drug was propranolol, with AF in 16.3% of the treatment group vs. 31.7% in the control group).[925] In the majority of these studies, beta-blockers were administered postoperatively, a regimen supported in a recent meta-analysis.[928] Amiodarone reduced the incidence of postoperative AF compared to a beta-blocker regimen in several meta-analyses, also reducing hospital stay.[925, 929-931]

Despite initial reports from meta-analyses,[689, 932, 933] preoperative treatment with statins did not prevent postoperative AF in a prospective controlled trial.[934] Other therapies have also been studied in small, hypothesis-generating trials, but have not demonstrated clear beneficial effects. These include magnesium,[925, 935, 936] n-3 polyunsaturated fatty acids,[937-945] colchicine,[946] corticosteroids,[947, 948] and posterior pericardectomy.[949] Postoperative overdrive biatrial pacing has not gained widespread use despite some suggestion of prophylactic effects.[925, 950]

13.5.2. Anticoagulation

Postoperative AF is associated with an increased early stroke risk, increased morbidity, and 30-day mortality.[927, 951, 952] In the long term, patients with an episode of postoperative AF have a twofold increase in cardiovascular mortality and a substantially increased risk of future AF and ischaemic stroke compared with patients that remain in sinus rhythm after surgery.[952-958] OAC at discharge has been associated with a reduced long-term mortality in patients with postoperative AF,[959] without evidence from controlled trials. Good quality data are needed to determine whether long-term anticoagulation can prevent strokes in patients with postoperative AF at high stroke risk,[368, 386] and to assess whether short episodes of postoperative AF (e.g. < 48 h) carry a similar risk as longer episodes.[960] The indication and timing of OAC in postoperative AF patients should take into consideration the risk of postoperative bleeding.

13.5.3. Rhythm control therapy in postoperative atrial fibrillation

In haemodynamically unstable patients, cardioversion and consideration of antiarrhythmic drugs is recommended. Amiodarone or vernakalant have been efficient in converting postoperative AF to sinus rhythm.[603, 950, 961] A recent medium-sized trial randomizing patients with postoperative AF to either rhythm control therapy with amiodarone or to rate control did not find a difference in hospital admissions during a 60-day follow-up,[962] underpinning that the aim of rhythm control therapy should be to improve AF-related symptoms in postoperative AF. In asymptomatic patients and in those with acceptable symptoms, rate control or deferred cardioversion preceded by anticoagulation is a reasonable approach.

Recommendations for preventing postoperative AF

Recommendations	Class [a]	Level [b]	Refs [c]
Perioperative oral beta-blocker therapy is recommended for the prevention of postoperative AF after cardiac surgery	I	B	925, 928
Restoration of sinus rhythm by electrical cardioversion or antiarrhythmic drugs is recommended in postoperative AF with haemodynamic instability	I	C	
Long-term anticoagulation should be considered in patients with AF after cardiac surgery at risk for stroke, considering individual stroke and bleeding risk	IIa	B	368, 386
Antiarrhythmic drugs should be considered for recurrent or symptomatic postoperative AF after cardiac surgery in an attempt to restore sinus rhythm	IIa	C	
Perioperative amiodarone should be considered for prophylactic therapy to prevent AF after cardiac surgery	IIa	A	925
Intravenous vernakalant may be considered for cardioversion of postoperative AF in patients without severe heart failure, hypotension, or severe structural heart disease (especially aortic stenosis)	IIb	B	603
Asymptomatic postoperative AF should initially be managed with rate control and anticoagulation	IIa	B	962

AF = atrial fibrillation.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

13.6. Atrial arrhythmias in grown-up patients with congenital heart disease

Atrial arrhythmias (AF, atrial flutter, atrial tachycardias) often occur late after surgical repair of congenital heart defects, occurring in 15–40% of grown-up patients with congenital heart disease (GUCH). They are associated with heart failure, syncope, thromboembolic events, and sudden death.[963-967] The pathophysiological substrate is complex, associated with hypertrophy, fibrosis, hypoxaemia, chronic haemodynamic overload, and surgical scars and patches. Additionally, related primary anomalies in the conduction pathways can lead to reentrant atrial and ventricular tachycardia, heart block, and sinus node dysfunction.[963] Macro-reentrant atrial tachycardia or atypical atrial flutter may be seen after nearly any surgical procedure involving atriotomy or atrial patches.

13.6.1. General management of atrial arrhythmias in grown-up patients with congenital heart disease

The conventional stroke risk factors should be used to inform decisions on long-term anticoagulation in GUCH patients with AF. In addition, anticoagulation should be considered in GUCH patients with atrial arrhythmias when they present with intracardial repair, cyanosis, Fontan palliation, or systemic right ventricle, in addition to those with conventional stroke risk factors.[968] Beta-blockers, verapamil, diltiazem, and digitalis can be used. Care should be taken to avoid bradycardia and hypotension.

Sodium channel blockers suppress approximately half of atrial arrhythmias in Fontan patients.[969] Amiodarone is more effective, but long-term treatment with an antiarrhythmic drugs carries a high risk of extracardiac side-effects in this relatively young population. Intracardiac thrombi are common in GUCH patients undergoing cardioversion for AF, but also in patients with atrial tachycardias or atrial flutter.[970] Therefore, both a TOE and anticoagulation for a few weeks before the planned cardioversion should be considered.[964] Radiofrequency ablation may be a good option for symptomatic GUCH patients with atrial arrhythmias, especially in those with atrial flutter and other macro-reentrant tachycardias. Interventions should be performed in adequately qualified centres by specialized teams.

13.6.2. Atrial tachyarrhythmias and atrial septal defects

Atrial flutter and fibrillation occur in 14–22% of adults with unoperated atrial septal defects, especially in older patients,[971] and can lead to heart failure.[972] Early repair can reduce but not eliminate the risk of AF.[973] Biatrial volume overload,[974] pulmonary hypertension,[975] and possibly the arrhythmogenic effect of atrial patches can contribute to these arrhythmias.[976] Anticoagulation should be decided based on stroke risk factors. In patients with a history of paroxysmal or persistent AF, AF surgery could be considered at the time of surgical closure, or catheter ablation in patients undergoing interventional atrial septal defect closure. Catheter ablation of late atrial arrhythmias has shown to be effective in 46 consecutive patients after surgical atrial septal defect.[977]

13.6.3. Atrial tachyarrhythmias after Fontan operation

Atrial arrhythmias occur in up to 40% of patients with a Fontan circulation, and can manifest as atrial flutter, primary atrial tachycardia, AF, and accelerated junctional rhythm or junctional tachycardia[978] with or without sinoatrial node dysfunction.[979] Patients with atriopulmonary anastomoses (possibly due to higher atrial volume and pressure load) and those with early postoperative atrial arrhythmias are more likely to develop long-term atrial arrhythmias.[980] Atrial arrhythmias can also be the first manifestation of obstruction of the atriopulmonary anastomosis, a complication that must be identified. Right atrial thrombus formation is common in Fontan patients with atrial arrhythmias and requires oral anticoagulation.[981] Operative conversion to total cavopulmonary artery connection with concomitant arrhythmia surgery can in some patients improve heart failure symptoms and reduce recurrent arrhythmias,[969, 982] with low recurrence rates of clinically apparent atrial arrhythmias in the first few years after repeat surgery.[983-985] Catheter ablation of atrial arrhythmia in Fontan patients has been successful in selected patients.[986]

13.6.4. Atrial tachyarrhythmias after tetralogy of Fallot correction

Approximately one-third of patients after repair of tetralogy of Fallot develop atrial arrhythmias, including intra-atrial reentrant tachycardia, focal atrial tachycardia, and AF.[987] Circuits involving the cavotricuspid isthmus and areas of presumed surgical right atrial scaring have been described as responsible for atrial arrhythmias.

Recommendations in patients with GUCH

Recommendations	Class [a]	Level [b]	Refs [c]
Atrial septal defect closure should be considered before the fourth decade of life to diminish the chance of atrial flutter and fibrillation	IIa	C	971, 972, 974

In patients who need surgical closure of an atrial septal defect and who have a history of symptomatic atrial arrhythmia, atrial ablation should be considered at the time of surgical closure	IIa	C	204, 988, 989
Cox maze surgery should be considered in patients with symptomatic AF and an indication for corrective repair of congenital heart defects. All such surgery should be done in experienced centres	IIa	C	988, 990
Oral anticoagualtion should be considered in all adult patients with intracardiac repair, cyanosis, Fontan palliation, or systemic right ventricle and a history of AF, atrial flutter, or intra-atrial reentrant tachycardia. In all other congenital heart disease patients with AF, anticoagulation should be considered if the CHA_2DS_2-VAS_C score is ≥ 1	IIa	C	**968**
Catheter ablation of atrial arrhythmias associated with congenital heart defects may be considered when performed in experienced centres	IIb	C	991
In patients with congenital heart disease, transoesophageal echocardiography may be considered together with 3-week anticoagulation therapy before cardioversion	IIb	C	964, 970, 988, 990

AF = atrial fibrillation; CHA_2DS_2-VASc = Congestive Heart failure, hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female); GUCH = grown-up patients with congenital heart disease; OAC = oral anticoagulation; TOE = transoesophageal echocardiography.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

13.7. Management of atrial flutter

The goals for the management of atrial flutter are similar to those for AF.[992] Based on the available evidence, the stroke risk in patients with atrial flutter is not much different from that in AF.[827] Furthermore, many patients diagnosed with atrial flutter develop AF.[993-995] Thus, anticoagulation should be used in patients with atrial flutter similar to that in patients with AF. Rate control in atrial flutter is achieved with the same medications as in AF, but is often more difficult to achieve. Flecainide, propafenone, dofetilide, and intravenous ibutilide are useful for cardioversion of atrial flutter. They should be combined with a rate-controlling agent to avoid 1:1 conduction of slowing flutter waves to the ventricles. Ibutilide is more effective for conversion of atrial flutter than AF, whereas vernakalant is less effective in converting typical atrial flutter.[996, 997] Electrical cardioversion of atrial flutter can be performed using lower energies (50–100 J) than for AF.[998, 999] Atrial overdrive pacing through pacemaker leads or endocardial or transesophageal catheters can convert atrial flutter to sinus rhythm.[1000, 1001] Anticoagulation and transoesophageal echocardiography around cardioversion or overdrive pacing should be used similar to that in AF.

Ablation of the cavotricuspid isthmus for isthmus-dependent right atrial flutter (either the common counter-clockwise atrial flutter or the less-common clockwise atrial flutter) restores and maintains sinus rhythm with a success rate of 90–95%.[1002] It may also reduce AF recurrences in selected patients,[1003, 1004] and help to prevent hospitalizations.[1004, 1005] Isthmus ablation is comparably safe and more effective than antiarrhythmic drug therapy, and is recommended for recurrent atrial flutter.[585-587, 713] Catheter ablation of left atrial macro-reentrant tachycardia is more complex, with lower success rates and higher recurrence rates.[1006, 1007]

Recommendations for management of atrial flutter

Recommendations	Class [a]	Level [b]	Refs [c]
For patients with atrial flutter, antithrombotic therapy is recommended according to the same risk profile used for AF	I	B	827
Overdrive atrial pacing of atrial flutter should be considered as an alternative to electrical cardioversion, depending on local availability and experience	IIa	B	1000, 1001

Management of typical atrial flutter with ablation of the cavotricuspid isthmus is recommended for patients failing antiarrhythmic drug therapy or as first-line treatment considering patient preference	I	B	[158]
If atrial flutter has been documented before AF ablation, ablation of the cavotricuspid isthmus should be considered as part of the AF ablation procedure	IIa	C	

AF = atrial fibrillation.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

14 Patient involvement, education and self-management

A fundamental aspect of a structured AF management programme is the focus on patient-centred care.

14.1. Patient-centred care

Autonomous, informed patients are better placed to adhere to long-term therapy, and it is very likely that long-term management of chronic conditions such as AF will benefit from informed patients involved in the disease management who are aware of their own responsibilities.[328] Shared decision-making[747] and patient-centred organization of care can help to ensure adherence to management and empower patients, and respect individual patient preferences, needs, and values (see Chapter 7.2).[326, 1008, 1009] Patients in an active role tend to have better health outcomes and care experiences, and engagement itself can be considered as an intermediate outcome, particularly where related to improved clinical outcomes.[1010]

14.2. Integrated patient education

Education is a prerequisite for informed, involved patients and patient-centred care. However, lack of AF-related knowledge in patients is common, even in those who have received verbal and written information,[32, 1011, 1012] indicating the need to further develop structured patient education. Several patient-information tools have been developed, largely focusing on oral anticoagulation.[1013-1016] Understanding patients' perceptions and attitudes towards AF and its management can improve AF management and related outcomes.[1017] This includes tailored patient education focusing on the disease, symptom recognition, therapy, modifiable risk factors for AF, and self-management activities.[1018, 1019]

14.3. Self-management and shared decision-making

Self-management is primarily focused on tasks to manage the condition, such as adhering to a therapeutic regimen or modifying behaviour (e.g. resulting in smoking cessation or weight loss).[1020] It requires understanding of the treatment modalities and goals.[350] Within a multidisciplinary team, allied health professionals can guide this interactive process in which communication, trust, and reciprocal respect foster patient engagement.[1021] Shared decision-making should be considered as a routine part of the decision-making process,[747] supported by decision aids where applicable.[1022] Models of care that integrate education, engagement, and shared decision making are now available,[1023] and may be of particular value in the management of AF.

Recommendations for patient involvement, education, and self-management

Recommendations	Class [a]	Level [b]	Refs [c]
Tailored patient education is recommended in all phases of AF management to support patients' perception of AF and to improve management	I	C	1014, 1017
Patient involvement in the care process should be considered to encourage self-management and responsibility for lifestyle changes	IIa	C	328, 1010
Shared decision-making should be considered to ensure that care is based on the best available evidence and fits the needs, values, and preferences of the patient	IIa	C	747

AF = atrial fibrillation.
[a]Class of recommendation.
[b]Level of evidence.

[c]Reference(s) supporting recommendations.

15 Gaps in evidence

There are some areas of AF management that are supported by excellent evidence from multiple, adequately powered randomized trials (e.g. oral anticoagulation. Other areas, such as rhythm control therapy, integrated AF management, and lifestyle modifications are clearly developing the required evidence, while areas such as rate control are in dire need of better studies to underpin future guidelines. Here we identify areas in need of further research.

15.1. Major health modifiers causing atrial fibrillation

Atrial fibrillation has different causes in different patients. More research is needed into the major causes (and electrophysiological mechanisms) of AF in different patient groups.[176, 1024] Such research should consider the major comorbidities associated with AF, and characterize the response to AF therapy in patients with different, pathophysiologically distinct types of AF.

15.2. How much atrial fibrillation constitutes a mandate for therapy?

Technological advances allow screening for an irregular pulse using patient-operated ECG devices, smartphones, and a variety of other technologies. These may be very useful to detect silent, undiagnosed AF.[157] Adequately powered studies evaluating the diagnostic accuracy of such technologies, the diagnostic yield in different populations, the shortest duration of atrial arrhythmias conveying a stroke risk, and ideally the effect of ECG screening on outcomes are needed.

15.3. Atrial high-rate episodes and need for anticoagulation

All of the information on the benefit of OAC has been in patients with AF diagnosed by ECG. Technological advances allow ready detection of AHRE in patients with implanted devices and an atrial lead. Such patients are at increased stroke risk, but it is unclear whether they benefit from OAC. Controlled trials evaluating OAC in AHRE patients are ongoing and will provide evidence on the best antithrombotic therapy in these patients.

15.4. Stroke risk in specific populations

Several specific AF groups should be studied to better characterize their risk for AF, stroke, and other AF-related complications (e.g. patients with one stroke risk factor, and non-Caucasian patients). Confounding factors (e.g. different therapy of concomitant cardiovascular diseases) may help to explain the variability in the reported rates of incident AF, prevalent AF, and AF complications. This also applies to the effect of gender in AF patients.[47]

15.5. Anticoagulation in patients with severe chronic kidney disease

The use of NOACs has not been tested in patients with creatinine clearance < 30 mL/min, and there is very little evidence on the effects of OAC in patients on haemodialysis or on other forms of renal-replacement therapy. Studies evaluating OAC in patients with severe chronic kidney disease are needed to inform the best management in this patient group at high risk for stroke and bleeding.

15.6. Left atrial appendage occlusion for stroke prevention

The most common justification for LAA occlusion devices in clinical practice is a perceived high bleeding risk and, less often, contraindications for OAC.[459] Unfortunately, LAA occluders have not been tested in such populations. Furthermore, LAA occluders have not been compared with NOAC therapy in patients at risk for bleeding, or with thoracoscopic LAA clipping. There is a clear need to conduct adequately designed and powered trials to define the clinical role of LAA occluders compared with NOAC therapy in patients with relative or absolute contraindications for anticoagulation, and/or in those suffering from an ischaemic stroke on anticoagulant therapy.

15.7. Anticoagulation in atrial fibrillation patients after a bleeding or stroke event

At least 2% of anticoagulated patients with AF will experience a serious bleeding event per year. Observational data suggest that OAC can be reinitiated even after an intracerebral bleeding event.[460, 484] Controlled studies evaluating different anticoagulation and stroke prevention interventions are urgently needed to provide evidence on the best management of patients who have suffered a bleeding event that would usually lead to withholding

OAC. Some studies (e.g. APACHE II[1025]) are ongoing, but adequately powered trials are needed. Similarly, prospectively collected data are needed on the efficacy and bleeding risk following (re-)initiation of OAC after stroke or intracranial bleeding.

15.8. Anticoagulation and optimal timing of non-acute cardioversion

Based on retrospective data, previous recommendations on the safe time-window in which a cardioversion can be performed in new-onset AF used ≤ 48 hours as the 'gold standard' for non-protected cardioversion. However, new evidence has emerged that initiating precardioversion anticoagulation in patients with AF episodes of < 24 hours or even < 12 hours would provide even better safety.[642, 647, 1026-1028] Further research is needed to establish a clear safety margin in this clinical situation.

15.9. Competing causes of stroke or transient ischaemic attack in atrial fibrillation patients

Prospective RCTs have demonstrated the superiority of carotid endarterectomy compared to stenting in patients with symptomatic high-degree stenosis of the internal carotid artery.[1029] As endartectomy minimizes the need for combination therapy with OAC and antiplatelets,[1030] this approach has appeal in patients with AF to reduce bleeding risk. However, few of these studies included patients with AF. In a large observational study, the composite of in-hospital mortality, post-procedural stroke, and cardiac complications was higher in AF patients undergoing carotid stenting (457/7668; 6.0%) compared with endarterectomy (4438/51320; 8.6%; $P <$ 0.0001).[1031] Despite adjustment for baseline risk, this may just reflect the type of patients referred for each procedure, and further randomized studies are needed to confirm the optimal treatment strategy in AF patients with carotid disease.

15.10. Anticoagulation in patients with biological heart valves (including transcatheter aortic valve implantation) and non-rheumatic valve disease

The optimal antithrombotic therapy in the first months after biological valve replacement (including after catheter-based valve replacement) is not known. VKAs remain the mainstay during the initial postoperative period; NOACs probably deliver the same protection. In patients without AF, many centres use platelet inhibitors only. NOACs appear to be equally effective as VKAs in patients with moderate aortic stenosis, based on a subanalysis from the ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial[1032] as well as the Loire Valley AF project.[1033] Further data would be helpful to confirm these observations.[1034] The safety and efficacy of NOACs in patients with rheumatic mitral valve disease has not been evaluated and should be studied.

15.11. Anticoagulation after 'successful' catheter ablation

In view of the long-term recurrence rates of AF, this Task Force recommends to continue OAC in AF patients after 'successful' catheter ablation. Nonetheless, observational data suggest that the stroke risk may be lower after catheter ablation of AF compared with other AF patients. The ongoing EAST (Early treatment of Atrial fibrillation for Stroke prevention Trial) trial will inform in a more general way whether rhythm control therapy can reduce stroke rates in anticoagulated AF patients. If confirmed, there may be a place for a controlled trial evaluating the termination of OAC therapy at an interval after 'successful' catheter ablation.

15.12. Comparison of rate control agents

Although the use of rate control therapy is very common in AF patients, robust data comparing rate control therapies are scant, with the majority of studies being small uncontrolled trials over short periods of follow-up. Some studies are funded (e.g. RATE-AF [Rate Control Therapy Evaluation in Permanent Atrial Fibrillation][559]) and will investigate the potential benefits of different rate controlling agents, characteristics, or biomarkers that can help to personalize the use of rate control, and the adverse-event profile of specific drugs in defined groups of patients (e.g. AF with HFrEF).

15.13. Catheter ablation in persistent and long-standing persistent AF

While a few recent randomized studies support the use of catheter or surgical ablation in patients with persistent AF and long-standing persistent AF, there is a clear need for more data evaluating this intervention in adequately powered randomized trials.

15.14. Optimal technique for repeat catheter ablation

PVI emerges as the most important target for catheter ablation of AF. Although a plethora of different additional ablation techniques have been published, their added value is questionable in patients undergoing a first catheter ablation, including those with persistent AF.[735] Many patients are in need of multiple catheter-ablation procedures, and such interventions often follow local or operator-specific protocols without clear evidence to support the choice of ablation target or intervention. There is a clear clinical need to define the best approach in patients who are in need of a second ablation procedure.

15.15. Combination therapy for maintenance of sinus rhythm

In the follow-up after initially successful catheter ablation, even when done in experienced centres, many patients will experience symptomatic recurrences of AF. These patients are often managed with antiarrhythmic drugs. There is a surprising paucity of data evaluating different rhythm control interventions in patients with recurrent AF after catheter ablation. Such studies seem reasonable and feasible.

15.16. Can rhythm control therapy convey a prognostic benefit in atrial fibrillation patients?

The progress in rhythm control therapy (catheter ablation, new antiarrhythmic drugs) and observational long-term analyses suggest that rhythm control therapy may have a prognostic benefit. Ongoing trials such as CABANA and EAST – AFNET 4 will provide initial answers to this important question, but more data are needed, in addition to trials of surgical ablation techniques.

15.17. Thoracoscopic ‘stand-alone’ atrial fibrillation surgery

Minimally invasive epicardial ablation surgery for the treatment of stand-alone AF was reported a decade ago.[1035] The procedure has since evolved towards a totally thoracoscopic procedure,[1036] and lesion sets were extended to a complete left atrial maze.[822] With such rapid development and the coexistence of different techniques and lesion sets, scientific evidence on long-term results is still limited. Randomized trials using a standardized procedure are urgently needed to clearly define the benefits and risks of thoracoscopic AF ablation, and to further support decisions of the AF Heart Team.

15.18. Surgical exclusion of the left atrial appendage

Exclusion of the LAA has been performed by cardiothoracic surgeons for decades, but prospective randomized studies comparing the rate of ischaemic stroke with or without left appendage exclusion are presently lacking. The LAAOS (Left Atrial Appendage Occlusion Study) III is currently randomizing cardiac surgery patients with AF to undergo concomitant occlusion or no occlusion of the appendage.[467] More data are also needed to confirm the safety and efficacy of thoracoscopic exclusion, following early positive observational data.[1037]

15.19. Concomitant atrial fibrillation surgery

Adequately powered randomized trials are needed, employing systematic follow-up, uniform lesion sets and energy sources to evaluate the benefits and risks of concomitant AF surgery in symptomatic AF patients. An RCT on non-uniform lesion sets with long-term follow-up is due to publish shortly.[1038] These will assist the AF Heart Team to decide on optimal therapy for individual patients, including the full repertoire of medical and surgical options for the treatment of AF.

16 To do and not to do messages from the Guidelines

Recommendations for diagnosis and screening of AF	Class	Level
ECG documentation is required to establish the diagnosis of AF	I	B
Opportunistic screening for AF is recommended by pulse taking or ECG rhythm strip in patients > 65 years of age	I	B
In patients with TIA or ischaemic stroke, screening for AF is recommended by short-term ECG recording followed by continuous ECG monitoring for at least 72 hours	I	B
It is recommended to interrogate pacemakers and ICDs on a regular basis for atrial high rate episodes (AHRE). Patients with AHRE should undergo further ECG monitoring to document AF before initiating AF therapy	I	B
Recommendations for general management of AF	**Class**	**Level**
Tailored patient education is recommended in all phases of AF management to support patients' perception of AF and to improve management	I	C
A full cardiovascular evaluation, including an accurate history, careful clinical examination, and assessment of concomitant conditions, is recommended in all AF patients	I	C
Use of the modified EHRA symptom scale is recommended in clinical practice and research studies to quantify AF-related symptoms	I	C
Transthoracic echocardiography is recommended in all AF patients to guide management	I	C
The assessment of kidney function by serum creatinine or creatinine clearance is recommended in all AF patients to detect kidney disease and to support correct dosing of AF therapy	I	A
Recommendations for stroke prevention in AF	**Class**	**Level**
The CHA_2DS_2-VASc score is recommended for stroke risk prediction in patients with AF	I	A
Oral anticoagulation therapy to prevent thromboembolism is recommended for all male AF patients with a CHA_2DS_2-VASc score of 2 or more	I	A
Oral anticoagulation therapy to prevent thromboembolism is recommended in all female AF patients with a CHA_2DS_2-VASc score of 3 or more	I	A
When oral anticoagulation is initiated in a patient with AF who is eligible for a non vitamin-K-antagonist oral anticoagulant (NOAC, apixaban, dabigatran, edoxaban, or rivaroxaban), a NOAC is recommended in preference to a Vitamin K antagonist	I	A
Vitamin K antagonist therapy (INR 2.0–3.0 or higher) is recommended for stroke prevention in AF patients with moderate-to-severe mitral stenosis or mechanical heart valves	I	B
NOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) are not recommended in patients with mechanical heart valves (Level of evidence B) or moderate-to-severe mitral stenosis (Level of evidence C)	III (harm)	B/C
When patients are treated with a vitamin K antagonist, time in therapeutic range (TTR) should be kept as high as possible and closely monitored	I	A
Combinations of oral anticoagulants and platelet inhibitors increase bleeding risk and should be avoided in AF patients without another indication for platelet	III (harm)	B

inhibition		
In male or female AF patients without additional stroke risk factors, anticoagulant or antiplatelet therapy is not recommended for stroke prevention	III (harm)	B
Antiplatelet monotherapy is not recommended for stroke prevention in AF patients, regardless of stroke risk	III (harm)	A
After surgical occlusion or exclusion of the left atrial appendage, it is recommended to continue anticoagulation in at-risk patients with AF for stroke prevention	I	B
Genetic testing before the initiation of vitamin K antagonist therapy is not recommended.	III (no benefit)	B
In AF patients with severe active bleeding events, it is recommended to interrupt oral anticoagulation therapy until the underlying cause is resolved	I	C
NOACs should be avoided in pregnancy and in women planning a pregnancy	III (harm)	C
For patients with atrial flutter, antithrombotic therapy is recommended according to the same risk profile used for AF	I	B
Management of typical atrial flutter with ablation of the cavotricuspid isthmus is recommended for patients failing antiarrhythmic drug therapy or as first-line treatment considering patient preference	I	B
Lifelong oral anticoagulation to prevent stroke is recommended in hypertrophic cardiomyopathy patients who develop AF	I	B
Anticoagulation with heparin or low-molecular-weight heparin immediately after ischaemic stroke is not recommended in AF patients	III (harm)	A
Systemic thrombolysis with a recombinant tissue plasminogen activator is not recommended if the INR is above 1.7 (or, for patients on dabigatran, if activated partial thromboplastin time is outside the normal range)	III (harm)	C
After TIA or stroke, combination therapy of OAC and an antiplatelet is not recommended	III (harm)	B
Recommendations for rate control of AF	Class	Level
Beta-blocker, digoxin, diltiazem, or verapamil is recommended to control heart rate in AF patients with LVEF ≥ 40%	I	B
Beta-blocker and/or digoxin is recommended to control heart rate in AF patients with LVEF < 40%	I	B
In patients with permanent AF (i.e. where no attempt to restore sinus rhythm is planned), antiarrhythmic drugs should not routinely be used for rate control	III (harm)	A
Recommendations for rhythm control of AF	Class	Level
Rhythm control therapy is indicated for symptom improvement in patients with AF	I	B
Cardioversion of AF (either electrical or pharmacological) is recommended in symptomatic patients with persistent or long-standing persistent AF as part of rhythm control therapy	I	B
In patients with no history of ischaemic or structural heart disease, flecainide, propafenone, or vernakalant is recommended for pharmacological cardioversion of new-onset AF	I	A

In patients with ischaemic and/or structural heart disease, amiodarone is recommended for cardioversion of AF	I	A
For cardioversion of AF/atrial flutter, effective anticoagulation is recommended for a minimum of 3 weeks before cardioversion	I	B
Transoesophageal echocardiography (TOE) is recommended to exclude cardiac thrombus, as an alternative to preprocedural anticoagulation when early cardioversion is planned	I	B
The choice of antiarrhythmic drug needs to be carefully evaluated, taking into account the presence of comorbidities, cardiovascular risk and potential for serious proarrhythmia, extracardiac toxic effects, patient preferences, and symptom burden	I	A
Dronedarone, flecainide, propafenone, or sotalol is recommended for prevention of recurrent symptomatic AF in patients with normal left ventricular function and without pathological left ventricular hypertrophy.	I	A
Dronedarone is recommended for prevention of recurrent symptomatic AF in patients with stable coronary artery disease, and without heart failure	I	A
Amiodarone is recommended for prevention of recurrent symptomatic AF in patients with heart failure	I	B
Antiarrhythmic drug therapy is not recommended in patients with prolonged QT interval (> 0.5 s) or with significant sinoatrial node disease or atrioventricular node dysfunction who do not have a functioning permanent pacemaker	III (harm)	C
Catheter ablation of symptomatic paroxysmal AF is recommended to improve AF symptoms in patients who have symptomatic recurrences of AF on antiarrhythmic drug therapy (amiodarone, dronedarone, flecainide, propafenone, sotalol) and who prefer further rhythm control therapy, when performed by an electrophysiologist who has received appropriate training and is performing the procedure in an experienced centre	I	A
ARBs or ACE inhibitors are not recommended for the secondary prevention of paroxysmal AF in patients with little or no underlying heart disease.	III (no benefit)	B
Moderate regular physical activity is recommended to prevent AF, while athletes should be counselled that long-lasting, more intense sports participation can promote AF	I	A

17 A short summary of the management of AF patients

Here, we provide 17 simple rules to guide diagnosis and management of AF patients according to the 2016 ESC/EACTS/ESO Guidelines for the management of atrial fibrillation

1. Use ECG screening in at risk populations for atrial fibrillation, especially stroke survivors and the Elderly.
2. Document AF by ECG before starting treatment.
3. Evaluate all AF patients by clinical evaluation, ECG, and echocardiogram for underlying cardiovascular conditions such as hypertension, heart failure, valvular heart disease, and others.
4. Provide tailored information and education to AF patients to empower them to support AF management.
5. Propose life style changes to all suitable AF patients to make their management more effective.
6. Treat underlying cardiovascular conditions adequately, e.g. valve repair or replacement in AF patients with significant valvular heart disease, treatment of heart failure, or management of hypertension, among others.
7. Use oral anticoagulation in all AF patients unless they are at low risk for stroke based on the CHA_2DS_2VASc score or have true contraindications for anticoagulant therapy.
8. Anticoagulate patients with atrial flutter similar to atrial fibrillation. Offer isthmus ablation to symptomatic flutter patients.
9. Reduce all modifiable bleeding risk factors in all AF patients on oral anticoagulation, e.g. by treating hypertension, minimising the duration and intensity of concomitant antiplatelet and NSAID therapy , treating anaemia and eliminating causes for blood loss, maintaining stable INR values in patients on vitamin K antagonists, and moderating alcohol intake
10. Check ventricular rate in all AF patients and use rate control medications to achieve lenient rate control.
11. Evaluate AF-related symptoms in all AF patients using the modified EHRA score. Whenever patients have AF-related symptoms, aim to improve symptoms by adjustment of rate control therapy and by offering antiarrhythmic drugs, cardioversion, or catheter or surgical ablation.
12. Select antiarrhythmic drugs based on their safety profile and consider catheter or surgical ablation when antiarrhythmic drugs fail.
13. Do not offer routine genetic testing in AF patients unless there is a suspicion for an inherited cardiac condition.
14. Do not use antiplatelet therapy for stroke prevention in AF.
15. Do not permanently discontinue oral anticoagulation in AF patients at increased risk of stroke unless such a decision is taken by a multidisciplinary team.
16. Do neither use rhythm control therapy in asymptomatic AF patients, nor in patients with permanent AF.
17. Do not perform cardioversion or catheter ablation without anticoagulation unless an atrial thrombus has been ruled out by transesophageal echocardiogram.

18 Web Addenda

All Web figures and Web tables are available in the Web addenda, available at European Heart Journal online and also via the ESC Website (www.escardio.org/guidelines).

19 Appendix

ESC Committee for Practice Guidelines (CPG): Jose Luis Zamorano (Chairperson) (Spain), Victor Aboyans (France), Stephan Achenbach (Germany), Stefan Agewall (Norway), Lina Badimon (Spain), Gonzalo Barón-Esquivias (Spain), Helmut Baumgartner (Germany), Jeroen J. Bax (The Netherlands), Héctor Bueno (Spain), Scipione Carerj (Italy), Veronica Dean (France), Çetin Erol (Turkey), Donna Fitzsimons (UK), Oliver Gaemperli (Switzerland), Paulus Kirchhof (UK/Germany), Philippe Kolh (Belgium), Patrizio Lancellotti (Belgium), Gregory Y. H. Lip (UK), Petros Nihoyannopoulos (UK), Massimo F. Piepoli (Italy), Piotr Ponikowski (Poland), Marco Roffi (Switzerland), Adam Torbicki (Poland), António Vaz Carneiro (Portugal), Stephan Windecker (Switzerland).

ESC National Cardiac Societies actively involved in the review process of the 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

Armenia: Armenian Cardiologists Association, Hamlet G. Hayrapetyan; **Austria:** Austrian Society of Cardiology, Franz Xaver Roithinger; **Azerbaijan:** Azerbaijan Society of Cardiology, Farid Aliyev; **Belarus:** Belorussian Scientific Society of Cardiologists, Alexandr Chasnoits; **Belgium:** Belgian Society of Cardiology, Georges H. Mairesse; **Bosnia and Herzegovina:** Association of Cardiologists of Bosnia and Herzegovina, Daniela Loncar Matičević; **Bulgaria:** Bulgarian Society of Cardiology, Tchavdar Shalganov; **Croatia:** Croatian Cardiac Society, Boško Skorić; **Cyprus:** Cyprus Society of Cardiology, Loizos Antoniades; **Czech Republic:** Czech Society of Cardiology, Milos Taborsky; **Denmark:** Danish Society of Cardiology, Steen Pehrson; **Egypt:** Egyptian Society of Cardiology, Said Khaled; **Estonia:** Estonian Society of Cardiology, Priit Kampus; **Finland:** Finnish Cardiac Society, Antti Hedman; **The Former Yugoslav Republic of Macedonia:** Macedonian FYR Society of Cardiology, Lidija Poposka; **France:** French Society of Cardiology, Jean-Yves Le Heuzey; **Georgia:** Georgian Society of Cardiology, Kakhaber Estadashvili; **Germany:** German Cardiac Society, Dietmar Bänsch; **Hungary:** Hungarian Society of Cardiology, Zoltán Csanádi; **Iceland:** Icelandic Society of Cardiology, David O. Arnar; **Ireland:** Irish Cardiac Society, David Keane; **Israel:** Israel Heart Society, Roy Beinart; **Italy:** Italian Federation of Cardiology, Francesco Romeo; **Kazakhstan:** Association of Cardiologists of Kazakhstan, Kulzida Koshumbayeva; **Kosovo:** Kosovo Society of Cardiology, Gani Bajraktari; **Kyrgyzstan:** Kyrgyz Society of Cardiology, Aibek Mirrakhimov, **Latvia:** Latvian Society of Cardiology, Oskars Kalejs; **Lebanon:** Lebanese Society of Cardiology, Samer Nasr; **Lithuania:** Lithuanian Society of Cardiology, Germanas Marinskis; **Luxembourg:** Luxembourg Society of Cardiology, Carlo Dimmer; **Malta:** Maltese Cardiac Society, Mark Sammut; **Moldova:** Moldavian Society of Cardiology, Aurel Grosu; **Morocco:** Moroccan Society of Cardiology, Salima Abdelali; **The Netherlands:** Netherlands Society of Cardiology, Martin E. W. Hemels; **Norway:** Norwegian Society of Cardiology, Ole-Gunnar Anfinsen; **Poland:** Polish Cardiac Society, Beata Średniawa; **Portugal:** Portuguese Society of Cardiology, Pedro Adragao; **Romania:** Romanian Society of Cardiology, Gheorghe-Andrei Dan; **Russian Federation:** Russian Society of Cardiology, Evgeny N. Mikhaylov; **San Marino:** San Marino Society of Cardiology, Marco Zavatta; **Serbia:** Cardiology Society of Serbia, Tatjana Potpara; **Slovakia:** Slovak Society of Cardiology, Peter Hlivak **Slovenia:** Slovenian Society of Cardiology, Igor Zupan; **Spain:** Spanish Society of Cardiology, Angel Arenal; **Sweden:** Swedish Society of Cardiology, Frieder Braunschweig; **Switzerland:** Swiss Society of Cardiology, Dipen Shah; **Tunisia:** Tunisian Society of Cardiology and Cardio-Vascular Surgery, Ag Sana Ouali; **Turkey:** Turkish Society of Cardiology, Mesut Demir; **Ukraine:** Ukrainian Association of Cardiology, Oleg Sychov; **United Kingdom:** British Cardiovascular Society, Ed Duncan.

20 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. Colilla S, Crow A, Petkun W, Singer DE, Simon T, Liu X. Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. *Am J Cardiol* 2013;**112**:1142-1147.
3. Heeringa J, van der Kuip DA, Hofman A, Kors JA, van Herpen G, Stricker BH, Stijnen T, Lip GY, Witteman JC. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart J* 2006;**27**:949-953.
4. Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, D'Agostino RB, Massaro JM, Beiser A, Wolf PA, Benjamin EJ. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation* 2004;**110**:1042-1046.
5. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA* 2001;**285**:2370-2375.
6. Krijthe BP, Kunst A, Benjamin EJ, Lip GY, Franco OH, Hofman A, Witteman JC, Stricker BH, Heeringa J. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *Eur Heart J* 2013;**34**:2746-2751.
7. Zoni-Berisso M, Lercari F, Carazza T, Domenicucci S. Epidemiology of atrial fibrillation: European perspective. *Clin Epidemiol* 2014;**6**:213-220.
8. Bjorck S, Palaszewski B, Friberg L, Bergfeldt L. Atrial fibrillation, stroke risk, and warfarin therapy revisited: a population-based study. *Stroke* 2013;**44**:3103-3108.
9. Haim M, Hoshen M, Reges O, Rabi Y, Balicer R, Leibowitz M. Prospective national study of the prevalence, incidence, management and outcome of a large contemporary cohort of patients with incident non-valvular atrial fibrillation. *J Am Heart Assoc* 2015;**4**:e001486.
10. McManus DD, Rienstra M, Benjamin EJ. An update on the prognosis of patients with atrial fibrillation. *Circulation* 2012;**126**:e143-146.
11. Ball J, Carrington MJ, McMurray JJ, Stewart S. Atrial fibrillation: profile and burden of an evolving epidemic in the 21st century. *Int J Cardiol* 2013;**167**:1807-1824.
12. Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. *Am J Cardiol* 1998;**82**:2N-9N.
13. Nguyen TN, Hilmer SN, Cumming RG. Review of epidemiology and management of atrial fibrillation in developing countries. *Int J Cardiol* 2013;**167**:2412-2420.
14. 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, RE-LY Atrial Fibrillation Registry Investigators. 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.
15. Chiang CE, Naditch-Brule L, Murin J, Goethals M, Inoue H, O'Neill J, Silva-Cardoso J, Zharinov O, Gamra H, Alam S, Ponikowski P, Lewalter T, Rosenqvist M, Steg PG. Distribution and risk profile of paroxysmal, persistent, and permanent atrial fibrillation in routine clinical practice: insight from the real-life global survey evaluating patients with atrial fibrillation international registry. *Circ Arrhythm Electrophysiol* 2012;**5**:632-639.
16. Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, D'Agostino RB, Murabito JM, Kannel WB, Benjamin EJ. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation* 2003;**107**:2920-2925.
17. 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.
18. 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, CRYSTAL AF Investigators. Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med* 2014;**370**:2478-2486.

19. Schnabel RB, Yin X, Gona P, Larson MG, Beiser AS, McManus DD, Newton-Cheh C, Lubitz SA, Magnani JW, Ellinor PT, Seshadri S, Wolf PA, Vasan RS, Benjamin EJ, Levy D. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet* 2015;**386**:154-162.
20. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation* 1998;**98**:946-952.
21. Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med* 2002;**113**:359-364.
22. Andersson T, Magnuson A, Bryngelsson IL, Frobert O, Henriksson KM, Edvardsson N, Poci D. All-cause mortality in 272,186 patients hospitalized with incident atrial fibrillation 1995-2008: a Swedish nationwide long-term case-control study. *Eur Heart J* 2013;**34**:1061-1067.
23. 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.
24. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991;**22**:983-988.
25. Krahn AD, Manfreda J, Tate RB, Mathewson FA, Cuddy TE. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. *Am J Med* 1995;**98**:476-484.
26. Henriksson KM, Farahmand B, Asberg S, Edvardsson N, Terent A. Comparison of cardiovascular risk factors and survival in patients with ischemic or hemorrhagic stroke. *Int J Stroke* 2012;**7**:276-281.
27. 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.
28. Ott A, Breteler MM, de Bruyne MC, van Harskamp F, Grobbee DE, Hofman A. Atrial fibrillation and dementia in a population-based study. The Rotterdam Study. *Stroke* 1997;**28**:316-321.
29. Knecht S, Oelschlager C, Duning T, Lohmann H, Albers J, Stehling C, Heindel W, Breithardt G, Berger K, Ringelstein EB, Kirchhof P, Wersching H. Atrial fibrillation in stroke-free patients is associated with memory impairment and hippocampal atrophy. *Eur Heart J* 2008;**29**:2125-2132.
30. Ball J, Carrington MJ, Stewart S, SAFETY investigators. Mild cognitive impairment in high-risk patients with chronic atrial fibrillation: a forgotten component of clinical management? *Heart* 2013;**99**:542-547.
31. Marzona I, O'Donnell M, Teo K, Gao P, Anderson C, Bosch J, Yusuf S. Increased risk of cognitive and functional decline in patients with atrial fibrillation: results of the ONTARGET and TRANSCEND studies. *CMAJ* 2012;**184**:E329-336.
32. Thrall G, Lane D, Carroll D, Lip GY. Quality of life in patients with atrial fibrillation: a systematic review. *Am J Med* 2006;**119**:448 e441-419.
33. von Eisenhart Rothe A, Hutt F, Baumert J, Breithardt G, Goette A, Kirchhof P, Ladwig KH. Depressed mood amplifies heart-related symptoms in persistent and paroxysmal atrial fibrillation patients: a longitudinal analysis - data from the German Competence Network on Atrial Fibrillation. *Europace* 2015;**17**:1354-1362.
34. Steinberg BA, Kim S, Fonarow GC, Thomas L, Ansell J, Kowey PR, Mahaffey KW, Gersh BJ, Hylek E, Naccarelli G, Go AS, Reiffel J, Chang P, Peterson ED, Piccini JP. Drivers of hospitalization for patients with atrial fibrillation: Results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *Am Heart J* 2014;**167**:735-742 e732.
35. Kirchhof P, Schmalowsky J, Pittrow D, Rosin L, Kirch W, Wegscheider K, Meinertz T. Management of patients wtih atrial fibrillation by primary care physicians in Germany: 1-year results of the ATRIUM registry. *Clin Cardiol* 2014;**37**:277-284.
36. Stewart S, Murphy N, Walker A, McGuire A, McMurray JJV. Cost of an emerging epidemic: an economic analysis of atrial fibrillation in the UK. *Heart* 2004;**90**:286-292.
37. Kim MH, Johnston SS, Chu BC, Dalal MR, Schulman KL. Estimation of total incremental health care costs in patients with atrial fibrillation in the United States. *Circ Cardiovasc Qual Outcomes* 2011;**4**:313-320.
38. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;**146**:857-867.

39. 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.
40. 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.
41. Al-Khatib SM, Allen LaPointe NM, Chatterjee R, Crowley MJ, Dupre ME, Kong DF, Lopes RD, Povsic TJ, Raju SS, Shah B, Kosinski AS, McBroom AJ, Sanders GD. Rate- and rhythm-control therapies in patients with atrial fibrillation: a systematic review. *Ann Intern Med* 2014;**160**:760-773.
42. 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;**35**:3365-3376.
43. Marijon E, Le Heuzey JY, Connolly S, Yang S, Pogue J, Brueckmann M, Eikelboom J, Themeles E, Ezekowitz M, Wallentin L, Yusuf S, RE-LY Investigators. 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.
44. Senoo K, Lip GY, Lane DA, Buller HR, Kotecha D. Residual risk of stroke and death in anticoagulated patients according to the type of atrial fibrillation: AMADEUS Trial. *Stroke* 2015;**46**:2523-2528.
45. Soliman EZ, Safford MM, Muntner P, Khodneva Y, Dawood FZ, Zakai NA, Thacker EL, Judd S, Howard VJ, Howard G, Herrington DM, Cushman M. Atrial fibrillation and the risk of myocardial infarction. *JAMA Intern Med* 2014;**174**:107-114.
46. Emdin CA, Wong CX, Hsiao AJ, Altman DG, Peters SA, Woodward M, Odutayo AA. Atrial fibrillation as risk factor for cardiovascular disease and death in women compared with men: systematic review and meta-analysis of cohort studies. *BMJ* 2016;**532**:h7013.
47. Ko D, Rahman F, Schnabel RB, Yin X, Benjamin EJ, Christophersen IE. Atrial fibrillation in women: epidemiology, pathophysiology, presentation, and prognosis. *Nat Rev Cardiol* 2016:[Epub ahead of print].
48. Andersson T, Magnuson A, Bryngelsson IL, Frobert O, Henriksson KM, Edvardsson N, Poci D. Gender-related differences in risk of cardiovascular morbidity and all-cause mortality in patients hospitalized with incident atrial fibrillation without concomitant diseases: A nationwide cohort study of 9519 patients. *Int J Cardiol* 2014;**177**:91-99.
49. Fang MC, Singer DE, Chang Y, Hylek EM, Henault LE, Jensvold NG, Go AS. Gender differences in the risk of ischemic stroke and peripheral embolism in atrial fibrillation: the AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) study. *Circulation* 2005;**112**:1687-1691.
50. Pancholy SB, Sharma PS, Pancholy DS, Patel TM, Callans DJ, Marchlinski FE. Meta-analysis of gender differences in residual stroke risk and major bleeding in patients with nonvalvular atrial fibrillation treated with oral anticoagulants. *Am J Cardiol* 2014;**113**:485-490.
51. Potpara TS, Marinkovic JM, Polovina MM, Stankovic GR, Seferovic PM, Ostojic MC, Lip GY. Gender-related differences in presentation, treatment and long-term outcome in patients with first-diagnosed atrial fibrillation and structurally normal heart: the Belgrade atrial fibrillation study. *Int J Cardiol* 2012;**161**:39-44.
52. Ball J, Carrington MJ, Wood KA, Stewart S, SAFETY Investigators. Women versus men with chronic atrial fibrillation: insights from the Standard versus Atrial Fibrillation spEcific managemenT studY (SAFETY). *PLoS One* 2013;**8**:e65795.
53. Hughes M, Lip GY. Risk factors for anticoagulation-related bleeding complications in patients with atrial fibrillation: a systematic review. *Qjm* 2007;**100**:599-607.
54. Roten L, Rimoldi SF, Schwick N, Sakata T, Heimgartner C, Fuhrer J, Delacretaz E, Tanner H. Gender differences in patients referred for atrial fibrillation management to a tertiary center. *Pacing Clin Electrophysiol* 2009;**32**:622-626.
55. Forleo GB, Tondo C, De Luca L, Dello Russo A, Casella M, De Sanctis V, Clementi F, Fagundes RL, Leo R, Romeo F, Mantica M. Gender-related differences in catheter ablation of atrial fibrillation. *Europace* 2007;**9**:613-620.
56. Henry L, Hunt S, Holmes SD, Martin LM, Ad N. Are there gender differences in outcomes after the Cox-Maze procedure for atrial fibrillation? *Innovations (Phila)* 2013;**8**:190-198.
57. Michelena HI, Powell BD, Brady PA, Friedman PA, Ezekowitz MD. Gender in atrial fibrillation: Ten years later. *Gend Med* 2010;**7**:206-217.

58. Fox CS, Parise H, D'Agostino RB, Sr., Lloyd-Jones DM, Vasan RS, Wang TJ, Levy D, Wolf PA, Benjamin EJ. Parental atrial fibrillation as a risk factor for atrial fibrillation in offspring. *JAMA* 2004;**291**:2851-2855.
59. Oyen N, Ranthe MF, Carstensen L, Boyd HA, Olesen MS, Olesen SP, Wohlfahrt J, Melbye M. Familial aggregation of lone atrial fibrillation in young persons. *J Am Coll Cardiol* 2012;**60**:917-921.
60. Ellinor PT, Lunetta KL, Albert CM, Glazer NL, Ritchie MD, Smith AV, Arking DE, Muller-Nurasyid M, Krijthe BP, Lubitz SA, Bis JC, Chung MK, Dorr M, Ozaki K, Roberts JD, Smith JG, Pfeufer A, Sinner MF, Lohman K, Ding J, Smith NL, Smith JD, Rienstra M, Rice KM, Van Wagoner DR, Magnani JW, Wakili R, Clauss S, Rotter JI, Steinbeck G, Launer LJ, Davies RW, Borkovich M, Harris TB, Lin H, Volker U, Volzke H, Milan DJ, Hofman A, Boerwinkle E, Chen LY, Soliman EZ, Voight BF, Li G, Chakravarti A, Kubo M, Tedrow UB, Rose LM, Ridker PM, Conen D, Tsunoda T, Furukawa T, Sotoodehnia N, Xu S, Kamatani N, Levy D, Nakamura Y, Parvez B, Mahida S, Furie KL, Rosand J, Muhammad R, Psaty BM, Meitinger T, Perz S, Wichmann HE, Witteman JC, Kao WH, Kathiresan S, Roden DM, Uitterlinden AG, Rivadeneira F, McKnight B, Sjogren M, Newman AB, Liu Y, Gollob MH, Melander O, Tanaka T, Stricker BH, Felix SB, Alonso A, Darbar D, Barnard J, Chasman DI, Heckbert SR, Benjamin EJ, Gudnason V, Kaab S. Meta-analysis identifies six new susceptibility loci for atrial fibrillation. *Nat Genet* 2012;**44**:670-675.
61. Olesen MS, Nielsen MW, Haunso S, Svendsen JH. Atrial fibrillation: the role of common and rare genetic variants. *Eur J Hum Genet* 2014;**22**:297-306.
62. 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, METASTROKE Consortium, AFGen Consortium, 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.
63. 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.
64. 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.
65. Lemmens R, Buysschaert I, Geelen V, Fernandez-Cadenas I, Montaner J, Schmidt H, Schmidt R, Attia J, Maguire J, Levi C, Jood K, Blomstrand C, Jern C, Wnuk M, Slowik A, Lambrechts D, Thijs V, International Stroke Genetics Consortium. The association of the 4q25 susceptibility variant for atrial fibrillation with stroke is limited to stroke of cardioembolic etiology. *Stroke* 2010;**41**:1850-1857.
66. 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.
67. Wang J, Klysik E, Sood S, Johnson RL, Wehrens XH, Martin JF. Pitx2 prevents susceptibility to atrial arrhythmias by inhibiting left-sided pacemaker specification. *Proc Natl Acad Sci U S A* 2010;**107**:9753-9758.
68. Franco D, Chinchilla A, Daimi H, Dominguez JN, Aranega A. Modulation of conductive elements by Pitx2 and their impact on atrial arrhythmogenesis. *Cardiovasc Res* 2011;**91**:223-231.
69. Kirchhof P, Kahr PC, Kaese S, Piccini I, Vokshi I, Scheld HH, Rotering H, Fortmueller L, Laakmann S, Verheule S, Schotten U, Fabritz L, Brown NA. PITX2c is expressed in the adult left

2957 atrium, and reducing Pitx2c expression promotes atrial fibrillation inducibility and complex changes in
2958 gene expression. *Circ Cardiovasc Genet* 2011;**4**:123-133.
2959 70. Wang J, Bai Y, Li N, Ye W, Zhang M, Greene SB, Tao Y, Chen Y, Wehrens XH, Martin JF.
2960 Pitx2-microRNA pathway that delimits sinoatrial node development and inhibits predisposition to atrial
2961 fibrillation. *Proc Natl Acad Sci U S A* 2014.
2962 71. Husser D, Adams V, Piorkowski C, Hindricks G, Bollmann A. Chromosome 4q25 variants and
2963 atrial fibrillation recurrence after catheter ablation. *J Am Coll Cardiol* 2010;**55**:747-753.
2964 72. Parvez B, Shoemaker MB, Muhammad R, Richardson R, Jiang L, Blair MA, Roden DM,
2965 Darbar D. Common genetic polymorphism at 4q25 locus predicts atrial fibrillation recurrence after
2966 successful cardioversion. *Heart Rhythm* 2013;**10**:849-855.
2967 73. Benjamin Shoemaker M, Muhammad R, Parvez B, White BW, Streur M, Song Y, Stubblefield
2968 T, Kucera G, Blair M, Rytlewski J, Parvathaneni S, Nagarakanti R, Saavedra P, Ellis CR, Patrick
2969 Whalen S, Roden DM, Darbar RD. Common atrial fibrillation risk alleles at 4q25 predict recurrence
2970 after catheter-based atrial fibrillation ablation. *Heart Rhythm* 2013;**10**:394-400.
2971 74. Parvez B, Vaglio J, Rowan S, Muhammad R, Kucera G, Stubblefield T, Carter S, Roden D,
2972 Darbar D. Symptomatic response to antiarrhythmic drug therapy is modulated by a common single
2973 nucleotide polymorphism in atrial fibrillation. *J Am Coll Cardiol* 2012;**60**:539-545.
2974 75. Kirchhof P, Sipido KR, Cowie MR, Eschenhagen T, Fox KA, Katus H, Schroeder S, Schunkert
2975 H, Priori S, ESC CRT R&D and European Affairs Work Shop on Personalized Medicine. The
2976 continuum of personalized cardiovascular medicine: a position paper of the European Society of
2977 Cardiology. *Eur Heart J* 2014;**35**:3250-3257.
2978 76. Kirchhof P, Breithardt G, Aliot E, Al Khatib S, Apostolakis S, Auricchio A, Bailleul C, Bax J,
2979 Benninger G, Blomstrom-Lundqvist C, Boersma L, Boriani G, Brandes A, Brown H, Brueckmann M,
2980 Calkins H, Casadei B, Clemens A, Crijns H, Derwand R, Dobrev D, Ezekowitz M, Fetsch T, Gerth A,
2981 Gillis A, Gulizia M, Hack G, Haegeli L, Hatem S, Georg Hausler K, Heidbuchel H, Hernandez-Brichis
2982 J, Jais P, Kappenberger L, Kautzner J, Kim S, Kuck KH, Lane D, Leute A, Lewalter T, Meyer R, Mont
2983 L, Moses G, Mueller M, Munzel F, Nabauer M, Nielsen JC, Oeff M, Oto A, Pieske B, Pisters R,
2984 Potpara T, Rasmussen L, Ravens U, Reiffel J, Richard-Lordereau I, Schafer H, Schotten U, Stegink
2985 W, Stein K, Steinbeck G, Szumowski L, Tavazzi L, Themistoclakis S, Thomitzek K, Van Gelder IC,
2986 von Stritzky B, Vincent A, Werring D, Willems S, Lip GY, Camm AJ. Personalized management of
2987 atrial fibrillation: Proceedings from the fourth Atrial Fibrillation competence NETwork/European Heart
2988 Rhythm Association consensus conference. *Europace* 2013;**15**:1540-1556.
2989 77. Ackerman MJ, Priori SG, Willems S, Berul C, Brugada R, Calkins H, Camm AJ, Ellinor PT,
2990 Gollob M, Hamilton R, Hershberger RE, Judge DP, Le Marec H, McKenna WJ, Schulze-Bahr E,
2991 Semsarian C, Towbin JA, Watkins H, Wilde A, Wolpert C, Zipes DP, Heart Rhythm Society, European
2992 Heart Rhythm Association. HRS/EHRA expert consensus statement on the state of genetic testing for
2993 the channelopathies and cardiomyopathies: this document was developed as a partnership between
2994 the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). *Europace*
2995 2011;**13**:1077-1109.
2996 78. Anne W, Willems R, Roskams T, Sergeant P, Herijgers P, Holemans P, Ector H, Heidbuchel
2997 H. Matrix metalloproteinases and atrial remodeling in patients with mitral valve disease and atrial
2998 fibrillation. *Cardiovasc Res* 2005;**67**:655-666.
2999 79. Chimenti C, Russo MA, Carpi A, Frustaci A. Histological substrate of human atrial fibrillation.
3000 *Biomed Pharmacother* 2010;**64**:177-183.
3001 80. Nguyen BL, Fishbein MC, Chen LS, Chen PS, Masroor S. Histopathological substrate for
3002 chronic atrial fibrillation in humans. *Heart Rhythm* 2009;**6**:454-460.
3003 81. Frustaci A, Chimenti C, Bellocci F, Morgante E, Russo MA, Maseri A. Histological substrate of
3004 atrial biopsies in patients with lone atrial fibrillation. *Circulation* 1997;**96**:1180-1184.
3005 82. Venteclef N, Guglielmi V, Balse E, Gaborit B, Cotillard A, Atassi F, Amour J, Leprince P,
3006 Dutour A, Clement K, Hatem SN. Human epicardial adipose tissue induces fibrosis of the atrial
3007 myocardium through the secretion of adipo-fibrokines. *Eur Heart J* 2013.
3008 83. Rocken C, Peters B, Juenemann G, Saeger W, Klein HU, Huth C, Roessner A, Goette A.
3009 Atrial amyloidosis: an arrhythmogenic substrate for persistent atrial fibrillation. *Circulation*
3010 2002;**106**:2091-2097.
3011 84. Schotten U, Ausma J, Stellbrink C, Sabatschus I, Vogel M, Frechen D, Schoendube F,
3012 Hanrath P, Allessie MA. Cellular mechanisms of depressed atrial contractility in patients with chronic
3013 atrial fibrillation. *Circulation* 2001;**103**:691-698.
3014 85. Allessie MA, de Groot NM, Houben RP, Schotten U, Boersma E, Smeets JL, Crijns HJ.
3015 Electropathological substrate of long-standing persistent atrial fibrillation in patients with structural
3016 heart disease: longitudinal dissociation. *Circ Arrhythm Electrophysiol* 2010;**3**:606-615.

86. Spach MS, Josephson ME. Initiating reentry: the role of nonuniform anisotropy in small circuits. *J Cardiovasc Electrophysiol* 1994;**5**:182-209.
87. Shinagawa K, Shi YF, Tardif JC, Leung TK, Nattel S. Dynamic nature of atrial fibrillation substrate during development and reversal of heart failure in dogs. *Circulation* 2002;**105**:2672-2678.
88. Lim HS, Willoughby SR, Schultz C, Gan C, Alasady M, Lau DH, Leong DP, Brooks AG, Young GD, Kistler PM, Kalman JM, Worthley MI, Sanders P. Effect of atrial fibrillation on atrial thrombogenesis in humans: impact of rate and rhythm. *J Am Coll Cardiol* 2013;**61**:852-860.
89. Hijazi Z, Oldgren J, Siegbahn A, Granger CB, Wallentin L. Biomarkers in atrial fibrillation: a clinical review. *Eur Heart J* 2013;**34**:1475-1480.
90. Xu J, Cui G, Esmailian F, Plunkett M, Marelli D, Ardehali A, Odim J, Laks H, Sen L. Atrial extracellular matrix remodeling and the maintenance of atrial fibrillation. *Circulation* 2004;**109**:363-368.
91. Gramley F, Lorenzen J, Plisiene J, Rakauskas M, Benetis R, Schmid M, Autschbach R, Knackstedt C, Schimpf T, Mischke K, Gressner A, Hanrath P, Kelm M, Schauerte P. Decreased plasminogen activator inhibitor and tissue metalloproteinase inhibitor expression may promote increased metalloproteinase activity with increasing duration of human atrial fibrillation. *J Cardiovasc Electrophysiol* 2007;**18**:1076-1082.
92. Hatem SN, Sanders P. Epicardial adipose tissue and atrial fibrillation. *Cardiovasc Res* 2014;**102**:205-213.
93. Leone O, Boriani G, Chiappini B, Pacini D, Cenacchi G, Martin Suarez S, Rapezzi C, Bacchi Reggiani ML, Marinelli G. Amyloid deposition as a cause of atrial remodelling in persistent valvular atrial fibrillation. *Eur Heart J* 2004;**25**:1237-1241.
94. Dobrev D, Friedrich A, Voigt N, Jost N, Wettwer E, Christ T, Knaut M, Ravens U. The G protein-gated potassium current I(K,ACh) is constitutively active in patients with chronic atrial fibrillation. *Circulation* 2005;**112**:3697-3706.
95. Van Wagoner DR, Pond AL, Lamorgese M, Rossie SS, McCarthy PM, Nerbonne JM. Atrial L-type Ca2+ currents and human atrial fibrillation. *Circ Res* 1999;**85**:428-436.
96. Schotten U, Verheule S, Kirchhof P, Goette A. Pathophysiological mechanisms of atrial fibrillation: a translational appraisal. *Physiol Rev* 2011;**91**:265-325.
97. Voigt N, Heijman J, Wang Q, Chiang DY, Li N, Karck M, Wehrens XH, Nattel S, Dobrev D. Cellular and molecular mechanisms of atrial arrhythmogenesis in patients with paroxysmal atrial fibrillation. *Circulation* 2014;**129**:145-156.
98. Voigt N, Li N, Wang Q, Wang W, Trafford AW, Abu-Taha I, Sun Q, Wieland T, Ravens U, Nattel S, Wehrens XH, Dobrev D. Enhanced sarcoplasmic reticulum Ca2+ leak and increased Na+-Ca2+ exchanger function underlie delayed afterdepolarizations in patients with chronic atrial fibrillation. *Circulation* 2012;**125**:2059-2070.
99. Polontchouk L, Haefliger JA, Ebelt B, Schaefer T, Stuhlmann D, Mehlhorn U, Kuhn-Regnier F, De Vivie ER, Dhein S. Effects of chronic atrial fibrillation on gap junction distribution in human and rat atria. *J Am Coll Cardiol* 2001;**38**:883-891.
100. Aime-Sempe C, Folliguet T, Rucker-Martin C, Krajewska M, Krajewska S, Heimburger M, Aubier M, Mercadier JJ, Reed JC, Hatem SN. Myocardial cell death in fibrillating and dilated human right atria. *J Am Coll Cardiol* 1999;**34**:1577-1586.
101. Spach MS, Heidlage JF, Barr RC, Dolber PC. Cell size and communication: role in structural and electrical development and remodeling of the heart. *Heart Rhythm* 2004;**1**:500-515.
102. Skalidis EI, Hamilos MI, Karalis IK, Chlouverakis G, Kochiadakis GE, Vardas PE. Isolated atrial microvascular dysfunction in patients with lone recurrent atrial fibrillation. *J Am Coll Cardiol* 2008;**51**:2053-2057.
103. Barretto AC, Mady C, Nussbacher A, Ianni BM, Oliveira SA, Jatene A, Ramires JA. Atrial fibrillation in endomyocardial fibrosis is a marker of worse prognosis. *Int J Cardiol* 1998;**67**:19-25.
104. Levy S. Factors predisposing to the development of atrial fibrillation. *Pacing Clin Electrophysiol* 1997;**20**:2670-2674.
105. Chen PS, Chen LS, Fishbein MC, Lin SF, Nattel S. Role of the autonomic nervous system in atrial fibrillation: pathophysiology and therapy. *Circ Res* 2014;**114**:1500-1515.
106. Christ T, Rozmaritsa N, Engel A, Berk E, Knaut M, Metzner K, Canteras M, Ravens U, Kaumann A. Arrhythmias, elicited by catecholamines and serotonin, vanish in human chronic atrial fibrillation. *Proc Natl Acad Sci U S A* 2014;**111**:11193-11198.
107. Greiser M, Kerfant BG, Williams GS, Voigt N, Harks E, Dibb KM, Giese A, Meszaros J, Verheule S, Ravens U, Allessie MA, Gammie JS, van der Velden J, Lederer WJ, Dobrev D, Schotten U. Tachycardia-induced silencing of subcellular Ca2+ signaling in atrial myocytes. *J Clin Invest* 2014;**124**:4759-4772.

108. Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, Le Metayer P, Clementy J. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med* 1998;**339**:659-666.
109. Patterson E, Jackman WM, Beckman KJ, Lazzara R, Lockwood D, Scherlag BJ, Wu R, Po S. Spontaneous pulmonary vein firing in man: relationship to tachycardia-pause early afterdepolarizations and triggered arrhythmia in canine pulmonary veins in vitro. *J Cardiovasc Electrophysiol* 2007;**18**:1067-1075.
110. Atienza F, Almendral J, Moreno J, Vaidyanathan R, Talkachou A, Kalifa J, Arenal A, Villacastin JP, Torrecilla EG, Sanchez A, Ploutz-Snyder R, Jalife J, Berenfeld O. Activation of inward rectifier potassium channels accelerates atrial fibrillation in humans: evidence for a reentrant mechanism. *Circulation* 2006;**114**:2434-2442.
111. Mandapati R, Skanes A, Chen J, Berenfeld O, Jalife J. Stable microreentrant sources as a mechanism of atrial fibrillation in the isolated sheep heart. *Circulation* 2000;**101**:194-199.
112. Sahadevan J, Ryu K, Peltz L, Khrestian CM, Stewart RW, Markowitz AH, Waldo AL. Epicardial mapping of chronic atrial fibrillation in patients: preliminary observations. *Circulation* 2004;**110**:3293-3299.
113. Sanders P, Nalliah CJ, Dubois R, Takahashi Y, Hocini M, Rotter M, Rostock T, Sacher F, Hsu LF, Jonsson A, O'Neill MD, Jais P, Haissaguerre M. Frequency mapping of the pulmonary veins in paroxysmal versus permanent atrial fibrillation. *J Cardiovasc Electrophysiol* 2006;**17**:965-972.
114. Moe GK, Abildskov JA. Atrial fibrillation as a self-sustaining arrhythmia independent of focal discharge. *Am Heart J* 1959;**58**:59-70.
115. Cox JL, Canavan TE, Schuessler RB, Cain ME, Lindsay BD, Stone C, Smith PK, Corr PB, Boineau JP. The surgical treatment of atrial fibrillation. II. Intraoperative electrophysiologic mapping and description of the electrophysiologic basis of atrial flutter and atrial fibrillation. *J Thorac Cardiovasc Surg* 1991;**101**:406-426.
116. Narayan SM, Krummen DE, Shivkumar K, Clopton P, Rappel WJ, Miller JM. Treatment of atrial fibrillation by the ablation of localized sources: CONFIRM (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation) trial. *J Am Coll Cardiol* 2012;**60**:628-636.
117. Haissaguerre M, Hocini M, Denis A, Shah AJ, Komatsu Y, Yamashita S, Daly M, Amraoui S, Zellerhoff S, Picat MQ, Quotb A, Jesel L, Lim H, Ploux S, Bordachar P, Attuel G, Meillet V, Ritter P, Derval N, Sacher F, Bernus O, Cochet H, Jais P, Dubois R. Driver domains in persistent atrial fibrillation. *Circulation* 2014;**130**:530-538.
118. Fetsch T, Bauer P, Engberding R, Koch HP, Lukl J, Meinertz T, Oeff M, Seipel L, Trappe HJ, Treese N, Breithardt G. Prevention of atrial fibrillation after cardioversion: results of the PAFAC trial. *Eur Heart J* 2004;**25**:1385-1394.
119. Hindricks G, Piorkowski C, Tanner H, Kobza R, Gerds-Li JH, Carbucicchio C, Kottkamp H. Perception of atrial fibrillation before and after radiofrequency catheter ablation: relevance of asymptomatic arrhythmia recurrence. *Circulation* 2005;**112**:307-313.
120. Kirchhof P, Bax J, Blomstrom-Lundquist C, Calkins H, Camm AJ, Cappato R, Cosio F, Crijns H, Diener HC, Goette A, Israel CW, Kuck KH, Lip GY, Nattel S, Page RL, Ravens U, Schotten U, Steinbeck G, Vardas P, Waldo A, Wegscheider K, Willems S, Breithardt G. Early and comprehensive management of atrial fibrillation: executive summary of the proceedings from the 2nd AFNET-EHRA consensus conference 'research perspectives in AF'. *Eur Heart J* 2009;**30**:2969-2977c.
121. Xiong Q, Proietti M, Senoo K, Lip GY. Asymptomatic versus symptomatic atrial fibrillation: A systematic review of age/gender differences and cardiovascular outcomes. *Int J Cardiol* 2015;**191**:172-177.
122. Savelieva I, Camm AJ. Clinical relevance of silent atrial fibrillation: prevalence, prognosis, quality of life, and management. *J Interv Card Electrophysiol* 2000;**4**:369-382.
123. Friberg L, Hammar N, Rosenqvist M. Stroke in paroxysmal atrial fibrillation: report from the Stockholm Cohort of Atrial Fibrillation. *Eur Heart J* 2010;**31**:967-975.
124. Vanassche T, Lauw MN, Eikelboom JW, Healey JS, Hart RG, Alings M, Avezum A, Diaz R, Hohnloser SH, Lewis BS, Shestakovska O, Wang J, Connolly SJ. Risk of ischaemic stroke according to pattern of atrial fibrillation: analysis of 6563 aspirin-treated patients in ACTIVE-A and AVERROES. *Eur Heart J* 2015;**36**:281-287a.
125. Steinberg BA, Hellkamp AS, Lokhnygina Y, Patel MR, Breithardt G, Hankey GJ, Becker RC, Singer DE, Halperin JL, Hacke W, Nessel CC, Berkowitz SD, Mahaffey KW, Fox KA, Califf RM, Piccini JP. Higher risk of death and stroke in patients with persistent vs. paroxysmal atrial fibrillation: results from the ROCKET-AF Trial. *Eur Heart J* 2015;**36**:288-296.

126. Fitzmaurice DA, Hobbs FD, Jowett S, Mant J, Murray ET, Holder R, Raftery JP, Bryan S, Davies M, Lip GY, Allan TF. Screening versus routine practice in detection of atrial fibrillation in patients aged 65 or over: cluster randomised controlled trial. *BMJ* 2007;**335**:383.
127. Rizos T, Guntner J, Jenetzky E, Marquardt L, Reichardt C, Becker R, Reinhardt R, Hepp T, Kirchhof P, Aleynichenko E, Ringleb P, Hacke W, Veltkamp R. Continuous stroke unit electrocardiographic monitoring versus 24-hour Holter electrocardiography for detection of paroxysmal atrial fibrillation after stroke. *Stroke* 2012;**43**:2689-2694.
128. 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, EMBRACE Investigators and Coordinators. Atrial fibrillation in patients with cryptogenic stroke. *N Engl J Med* 2014;**370**:2467-2477.
129. Friberg L, Engdahl J, Frykman V, Svennberg E, Levin LA, Rosenqvist M. Population screening of 75- and 76-year-old men and women for silent atrial fibrillation (STROKESTOP). *Europace* 2013;**15**:135-140.
130. Davis RC, Hobbs FD, Kenkre JE, Roalfe AK, Iles R, Lip GY, Davies MK. Prevalence of atrial fibrillation in the general population and in high-risk groups: the ECHOES study. *Europace* 2012;**14**:1553-1559.
131. Hobbs FD, 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 Technol Assess* 2005;**9**:iii-iv, ix-x, 1-74.
132. Aronsson M, Svennberg E, Rosenqvist M, Engdahl J, Al-Khalili F, Friberg L, Frykman-Kull V, Levin LA. Cost-effectiveness of mass screening for untreated atrial fibrillation using intermittent ECG recording. *Europace* 2015;**17**:1023-1029.
133. Levin LA, Husberg M, Sobocinski PD, Kull VF, Friberg L, Rosenqvist M, Davidson T. A cost-effectiveness analysis of screening for silent atrial fibrillation after ischaemic stroke. *Europace* 2015;**17**:207-214.
134. Lowres N, Neubeck L, Redfern J, Freedman SB. Screening to identify unknown atrial fibrillation. A systematic review. *Thromb Haemost* 2013;**110**:213-222.
135. 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.
136. 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.
137. 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.
138. Barrett PM, Komatireddy R, Haaser S, Topol S, Sheard J, Encinas J, Fought AJ, Topol EJ. Comparison of 24-hour Holter monitoring with 14-day novel adhesive patch electrocardiographic monitoring. *Am J Med* 2014;**127**:95 e11-97.
139. 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**:1167-1176.
140. Quinn FR, Gladstone D. Screening for undiagnosed atrial fibrillation in the community. *Curr Opin Cardiol* 2014;**29**:28-35.
141. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, Lau CP, Fain E, Yang S, Bailleul C, Morillo CA, Carlson M, Themeles E, Kaufman ES, Hohnloser SH, ASSERT Investigators. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med* 2012;**366**:120-129.
142. Hindricks G, Pokushalov E, Urban L, Taborsky M, Kuck KH, Lebedev D, Rieger G, Purerfellner H. Performance of a new leadless implantable cardiac monitor in detecting and quantifying atrial fibrillation - results of the XPECT trial. *Circ Arrhythm Electrophysiol* 2010;**3**:141-147.
143. Brambatti M, Connolly SJ, Gold MR, Morillo CA, Capucci A, Muto C, Lau CP, Van Gelder IC, Hohnloser SH, Carlson M, Fain E, Nakamya J, Mairesse GH, Halytska M, Deng WQ, Israel CW, Healey JS, ASSERT Investigators. Temporal relationship between subclinical atrial fibrillation and embolic events. *Circulation* 2014;**129**:2094-2099.
144. Boriani G, Glotzer TV, Santini M, West TM, De Melis M, Sepsi M, Gasparini M, Lewalter T, Camm JA, Singer DE. Device-detected atrial fibrillation and risk for stroke: an analysis of >10,000

patients from the SOS AF project (Stroke preventiOn Strategies based on Atrial Fibrillation information from implanted devices). *Eur Heart J* 2014;**35**:508-516.
145. Santini M, Gasparini M, Landolina M, Lunati M, Proclemer A, Padeletti L, Catanzariti D, Molon G, Botto GL, La Rocca L, Grammatico A, Boriani G. Device-detected atrial tachyarrhythmias predict adverse outcome in real-world patients with implantable biventricular defibrillators. *J Am Coll Cardiol* 2011;**57**:167-172.
146. Daoud EG, Glotzer TV, Wyse DG, Ezekowitz MD, Hilker C, Koehler J, Ziegler PD. Temporal relationship of atrial tachyarrhythmias, cerebrovascular events, and systemic emboli based on stored device data: a subgroup analysis of TRENDS. *Heart Rhythm* 2011;**8**:1416-1423.
147. Glotzer TV, Daoud EG, Wyse DG, Singer DE, Ezekowitz MD, Hilker C, Miller C, Qi D, Ziegler PD. The relationship between daily atrial tachyarrhythmia burden from implantable device diagnostics and stroke risk: the TRENDS study. *Circ Arrhythm Electrophysiol* 2009;**2**:474-480.
148. Lamas G. How much atrial fibrillation is too much atrial fibrillation? *N Engl J Med* 2012;**366**:178-180.
149. Kirchhof P, Lip GY, Van Gelder IC, Bax J, Hylek E, Kaab S, Schotten U, Wegscheider K, Boriani G, Brandes A, Ezekowitz M, Diener H, Haegeli L, Heidbuchel H, Lane D, Mont L, Willems S, Dorian P, Aunes-Jansson M, Blomstrom-Lundqvist C, Borentain M, Breitenstein S, Brueckmann M, Cater N, Clemens A, Dobrev D, Dubner S, Edvardsson NG, Friberg L, Goette A, Gulizia M, Hatala R, Horwood J, Szumowski L, Kappenberger L, Kautzner J, Leute A, Lobban T, Meyer R, Millerhagen J, Morgan J, Muenzel F, Nabauer M, Baertels C, Oeff M, Paar D, Polifka J, Ravens U, Rosin L, Stegink W, Steinbeck G, Vardas P, Vincent A, Walter M, Breithardt G, Camm AJ. Comprehensive risk reduction in patients with atrial fibrillation: emerging diagnostic and therapeutic options--a report from the 3rd Atrial Fibrillation Competence NETwork/European Heart Rhythm Association consensus conference. *Europace* 2012;**14**:8-27.
150. Kirchhof P, Lip GY, Van Gelder IC, Bax J, Hylek E, Kaab S, Schotten U, Wegscheider K, Boriani G, Ezekowitz M, Diener H, Heidbuchel H, Lane D, Mont L, Willems S, Dorian P, Vardas P, Breithardt G, Camm AJ. Comprehensive risk reduction in patients with atrial fibrillation: Emerging diagnostic and therapeutic options. Executive summary of the report from the 3rd AFNET/EHRA consensus conference. *Thromb Haemost* 2011;**106**:1012-1019.
151. Sposato LA, Cipriano LE, Saposnik G, Ruiz Vargas E, 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.
152. Thijs VN, Brachmann J, Morillo CA, Passman RS, Sanna T, Bernstein RA, Diener HC, Di Lazzaro V, Rymer MM, Hogge L, Rogers TB, Ziegler PD, Assar MD. Predictors for atrial fibrillation detection after cryptogenic stroke: Results from CRYSTAL AF. *Neurology* 2016;**86**:261-269.
153. Adams HP, Jr., Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE, 3rd. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993;**24**:35-41.
154. Hart RG, Diener HC, Coutts SB, Easton JD, Granger CB, O'Donnell MJ, Sacco RL, Connolly SJ, Cryptogenic Stroke/ESUS International Working Group. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol* 2014;**13**:429-438.
155. Mant J, Fitzmaurice DA, Hobbs FD, Jowett S, Murray ET, Holder R, Davies M, Lip GY. Accuracy of diagnosing atrial fibrillation on electrocardiogram by primary care practitioners and interpretative diagnostic software: analysis of data from screening for atrial fibrillation in the elderly (SAFE) trial. *BMJ* 2007;**335**:380.
156. Israel CW, Gronefeld G, Ehrlich JR, Li YG, Hohnloser SH. Long-term risk of recurrent atrial fibrillation as documented by an implantable monitoring device: implications for optimal patient care. *J Am Coll Cardiol* 2004;**43**:47-52.
157. Svennberg E, Engdahl J, Al-Khalili F, Friberg L, Frykman V, Rosenqvist M. Mass Screening for Untreated Atrial Fibrillation: The STROKESTOP Study. *Circulation* 2015;**131**:2176-2184.
158. Bun SS, Latcu DG, Marchlinski F, Saoudi N. Atrial flutter: more than just one of a kind. *Eur Heart J* 2015;**36**:2356-2363.
159. Granada J, Uribe W, Chyou PH, Maassen K, Vierkant R, Smith PN, Hayes J, Eaker E, Vidaillet H. Incidence and predictors of atrial flutter in the general population. *J Am Coll Cardiol* 2000;**36**:2242-2246.
160. Halligan SC, Gersh BJ, Brown RD, Jr., Rosales AG, Munger TM, Shen WK, Hammill SC, Friedman PA. The natural history of lone atrial flutter. *Ann Intern Med* 2004;**140**:265-268.
161. Jahangir A, Lee V, Friedman PA, Trusty JM, Hodge DO, Kopecky SL, Packer DL, Hammill SC, Shen WK, Gersh BJ. Long-term progression and outcomes with aging in patients with lone atrial fibrillation: a 30-year follow-up study. *Circulation* 2007;**115**:3050-3056.

162. Gillis AM, Rose MS. Temporal patterns of paroxysmal atrial fibrillation following DDDR pacemaker implantation. *Am J Cardiol* 2000;**85**:1445-1450.
163. 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.
164. Banerjee A, Taillandier S, Olesen JB, Lane DA, Lallemand B, Lip GY, Fauchier L. Pattern of atrial fibrillation and risk of outcomes: the Loire Valley Atrial Fibrillation Project. *Int J Cardiol* 2013;**167**:2682-2687.
165. Lee G, Sanders P, Kalman JM. Catheter ablation of atrial arrhythmias: state of the art. *Lancet* 2012;**380**:1509-1519.
166. Wyse DG, Van Gelder IC, Ellinor PT, Go AS, Kalman JM, Narayan SM, Nattel S, Schotten U, Rienstra M. Lone atrial fibrillation: does it exist? *J Am Coll Cardiol* 2014;**63**:1715-1723.
167. Andrade J, Khairy P, Dobrev D, Nattel S. The clinical profile and pathophysiology of atrial fibrillation: relationships among clinical features, epidemiology, and mechanisms. *Circ Res* 2014;**114**:1453-1468.
168. Chao TF, Suenari K, Chang SL, Lin YJ, Lo LW, Hu YF, Tuan TC, Tai CT, Tsao HM, Li CH, Ueng KC, Wu TJ, Chen SA. Atrial substrate properties and outcome of catheter ablation in patients with paroxysmal atrial fibrillation associated with diabetes mellitus or impaired fasting glucose. *Am J Cardiol* 2010;**106**:1615-1620.
169. Albertsen IE, Rasmussen LH, Lane DA, Overvad TF, Skjoth F, Overvad K, Lip GY, Larsen TB. The impact of smoking on thromboembolism and mortality in patients with incident atrial fibrillation: insights from the Danish Diet, Cancer, and Health study. *Chest* 2014;**145**:559-566.
170. Overvad TF, Rasmussen LH, Skjoth F, Overvad K, Albertsen IE, Lane DA, Lip GY, Larsen TB. Alcohol intake and prognosis of atrial fibrillation. *Heart* 2013;**99**:1093-1099.
171. Daccarett M, Badger TJ, Akoum N, Burgon NS, Mahnkopf C, Vergara G, Kholmovski E, McGann CJ, Parker D, Brachmann J, Macleod RS, Marrouche NF. Association of left atrial fibrosis detected by delayed-enhancement magnetic resonance imaging and the risk of stroke in patients with atrial fibrillation. *J Am Coll Cardiol* 2011;**57**:831-838.
172. Neilan TG, Shah RV, Abbasi SA, Farhad H, Groarke JD, Dodson JA, Coelho-Filho O, McMullan CJ, Heydari B, Michaud GF, John RM, van der Geest R, Steigner ML, Blankstein R, Jerosch-Herold M, Kwong RY. The incidence, pattern, and prognostic value of left ventricular myocardial scar by late gadolinium enhancement in patients with atrial fibrillation. *J Am Coll Cardiol* 2013;**62**:2205-2214.
173. Marrouche NF, Wilber D, Hindricks G, Jais P, Akoum N, Marchlinski F, Kholmovski E, Burgon N, Hu N, Mont L, Deneke T, Duytschaever M, Neumann T, Mansour M, Mahnkopf C, Herweg B, Daoud E, Wissner E, Bansmann P, Brachmann J. Association of atrial tissue fibrosis identified by delayed enhancement MRI and atrial fibrillation catheter ablation: the DECAAF study. *JAMA* 2014;**311**:498-506.
174. Bonizzi P, Zeemering S, Karel JM, Di Marco LY, Uldry L, Van Zaen J, Vesin JM, Schotten U. Systematic comparison of non-invasive measures for the assessment of atrial fibrillation complexity: a step forward towards standardization of atrial fibrillation electrogram analysis. *Europace* 2014.
175. Kirchhof P, Breithardt G, Bax J, Benninger G, Blomstrom-Lundqvist C, Boriani G, Brandes A, Brown H, Brueckmann M, Calkins H, Calvert M, Christoffels V, Crijns H, Dobrev D, Ellinor P, Fabritz L, Fetsch T, Freedman SB, Gerth A, Goette A, Guasch E, Hack G, Haegeli L, Hatem S, Haeusler KG, Heidbuchel H, Heinrich-Nols J, Hidden-Lucet F, Hindricks G, Juul-Moller S, Kaab S, Kappenberger L, Kespohl S, Kotecha D, Lane DA, Leute A, Lewalter T, Meyer R, Mont L, Munzel F, Nabauer M, Nielsen JC, Oeff M, Oldgren J, Oto A, Piccini JP, Pilmeyer A, Potpara T, Ravens U, Reinecke H, Rostock T, Rustige J, Savelieva I, Schnabel R, Schotten U, Schwichtenberg L, Sinner MF, Steinbeck G, Stoll M, Tavazzi L, Themistoclakis S, Tse HF, Van Gelder IC, Vardas PE, Varpula T, Vincent A, Werring D, Willems S, Ziegler A, Lip GY, Camm AJ. A roadmap to improve the quality of atrial fibrillation management: proceedings from the fifth Atrial Fibrillation Network/European Heart Rhythm Association consensus conference. *Europace* 2016;**18**:37-50.
176. Fabritz L, Guasch E, Antoniades C, Bardinet I, Benninger G, Betts TR, Brand E, Breithardt G, Bucklar-Suchankova G, Camm AJ, Cartlidge D, Casadei B, Chua WW, Crijns HJ, Deeks J, Hatem S, Hidden-Lucet F, Kaab S, Maniadakis N, Martin S, Mont L, Reinecke H, Sinner MF, Schotten U, Southwood T, Stoll M, Vardas P, Wakili R, West A, Ziegler A, Kirchhof P. Expert consensus document: Defining the major health modifiers causing atrial fibrillation: a roadmap to underpin personalized prevention and treatment. *Nat Rev Cardiol* 2016;**13**:230-237.

177. Dorian P, Jung W, Newman D, Paquette M, Wood K, Ayers GM, Camm J, Akhtar M, Luderitz B. The impairment of health-related quality of life in patients with intermittent atrial fibrillation: implications for the assessment of investigational therapy. *J Am Coll Cardiol* 2000;**36**:1303-1309.
178. Sears SF, Serber ER, Alvarez LG, Schwartzman DS, Hoyt RH, Ujhelyi MR. Understanding atrial symptom reports: objective versus subjective predictors. *Pacing Clin Electrophysiol* 2005;**28**:801-807.
179. Peinado R, Arribas F, Ormaetxe JM, Badia X. Variation in quality of life with type of atrial fibrillation. *Rev Esp Cardiol* 2010;**63**:1402-1409.
180. Steg PG, Alam S, Chiang CE, Gamra H, Goethals M, Inoue H, Krapf L, Lewalter T, Merioua I, Murin J, Naditch-Brule L, Ponikowski P, Rosenqvist M, Silva-Cardoso J, Zharinov O, Brette S, Neill JO, RealiseAF investigators. Symptoms, functional status and quality of life in patients with controlled and uncontrolled atrial fibrillation: data from the RealiseAF cross-sectional international registry. *Heart* 2012;**98**:195-201.
181. Gronefeld GC, Lilienthal J, Kuck KH, Hohnloser SH, Pharmacological Intervention in Atrial Fibrillation (PIAF) Study investigators. Impact of rate versus rhythm control on quality of life in patients with persistent atrial fibrillation. Results from a prospective randomized study. *Eur Heart J* 2003;**24**:1430-1436.
182. Pepine CJ. Effects of pharmacologic therapy on health-related quality of life in elderly patients with atrial fibrillation: a systematic review of randomized and nonrandomized trials. *Clin Med Insights Cardiol* 2013;**7**:1-20.
183. Hagens VE, Ranchor AV, Van Sonderen E, Bosker HA, Kamp O, Tijssen JG, Kingma JH, Crijns HJ, Van Gelder IC, RACE Study Group. Effect of rate or rhythm control on quality of life in persistent atrial fibrillation. Results from the Rate Control Versus Electrical Cardioversion (RACE) Study. *J Am Coll Cardiol* 2004;**43**:241-247.
184. Weerasooriya R, Davis M, Powell A, Szili-Torok T, Shah C, Whalley D, Kanagaratnam L, Heddle W, Leitch J, Perks A, Ferguson L, Bulsara M. The Australian intervention randomized control of rate in atrial fibrillation trial (AIRCRAFT). *J Am Coll Cardiol* 2003;**41**:1697-1702.
185. Jones DG, Haldar SK, Hussain W, Sharma R, Francis DP, Rahman-Haley SL, McDonagh TA, Underwood SR, Markides V, Wong T. A randomized trial to assess catheter ablation versus rate control in the management of persistent atrial fibrillation in heart failure. *J Am Coll Cardiol* 2013;**61**:1894-1903.
186. Rienstra M, Lubitz SA, Mahida S, Magnani JW, Fontes JD, Sinner MF, Van Gelder IC, Ellinor PT, Benjamin EJ. Symptoms and functional status of patients with atrial fibrillation: state of the art and future research opportunities. *Circulation* 2012;**125**:2933-2943.
187. Arribas F, Ormaetxe JM, Peinado R, Perulero N, Ramirez P, Badia X. Validation of the AF-QoL, a disease-specific quality of life questionnaire for patients with atrial fibrillation. *Europace* 2010;**12**:364-370.
188. Spertus J, Dorian P, Bubien R, Lewis S, Godejohn D, Reynolds MR, Lakkireddy DR, Wimmer AP, Bhandari A, Burk C. Development and validation of the Atrial Fibrillation Effect on QualiTy-of-Life (AFEQT) Questionnaire in patients with atrial fibrillation. *Circ Arrhythm Electrophysiol* 2011;**4**:15-25.
189. Dorian P, Burk C, Mullin CM, Bubien R, Godejohn D, Reynolds MR, Lakkireddy DR, Wimmer AP, Bhandari A, Spertus J. Interpreting changes in quality of life in atrial fibrillation: How much change is meaningful? *Am Heart J* 2013;**166**:381-387.e388.
190. Ware JE, Jr., Gandek B. Overview of the SF-36 Health Survey and the International Quality of Life Assessment (IQOLA) Project. *J Clin Epidemiol* 1998;**51**:903-912.
191. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, Bonsel G, Badia X. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;**20**:1727-1736.
192. Kirchhof P, Auricchio A, Bax J, Crijns H, Camm J, Diener HC, Goette A, Hindricks G, Hohnloser S, Kappenberger L, Kuck KH, Lip GY, Olsson B, Meinertz T, Priori S, Ravens U, Steinbeck G, Svernhage E, Tijssen J, Vincent A, Breithardt G. Outcome parameters for trials in atrial fibrillation: executive summary. *Eur Heart J* 2007;**28**:2803-2817.
193. Dorian P, Cvitkovic SS, Kerr CR, Crystal E, Gillis AM, Guerra PG, Mitchell LB, Roy D, Skanes AC, Wyse DG. A novel, simple scale for assessing the symptom severity of atrial fibrillation at the bedside: the CCS-SAF scale. *Can J Cardiol* 2006;**22**:383-386.
194. 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.

195. Lip GY, Laroche C, Popescu MI, Rasmussen LH, Vitali-Serdoz L, Dan GA, Kalarus Z, Crijns HJ, Oliveira MM, Tavazzi L, Maggioni AP, Boriani G. Improved outcomes with European Society of Cardiology guideline-adherent antithrombotic treatment in high-risk patients with atrial fibrillation: a report from the EORP-AF General Pilot Registry. *Europace* 2015;**17**:1777-1786.
196. Freeman JV, Simon DN, Go AS, Spertus J, Fonarow GC, Gersh BJ, Hylek EM, Kowey PR, Mahaffey KW, Thomas LE, Chang P, Peterson ED, Piccini JP, Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) Investigators and Patients. Association Between Atrial Fibrillation Symptoms, Quality of Life, and Patient Outcomes: Results From the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *Circ Cardiovasc Qual Outcomes* 2015;**8**:393-402.
197. Boriani G, Laroche C, Diemberger I, Fantecchi E, Popescu MI, Rasmussen LH, Sinagra G, Petrescu L, Tavazzi L, Maggioni AP, Lip GY. Asymptomatic atrial fibrillation: clinical correlates, management, and outcomes in the EORP-AF Pilot General Registry. *Am J Med* 2015;**128**:509-518 e502.
198. Szymanski FM, Filipiak KJ, Karpinski G, Platek AE, Opolski G. Occurrence of poor sleep quality in atrial fibrillation patients according to the EHRA score. *Acta Cardiol* 2014;**69**:291-296.
199. 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.
200. Meinertz T, Kirch W, Rosin L, Pittrow D, Willich SN, Kirchhof P, ATRIUM investigators. Management of atrial fibrillation by primary care physicians in Germany: baseline results of the ATRIUM registry. *Clin Res Cardiol* 2011;**100**:897-905.
201. 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.
202. von Eisenhart Rothe AF, Goette A, Kirchhof P, Breithardt G, Limbourg T, Calvert M, Baumert J, Ladwig KH. Depression in paroxysmal and persistent atrial fibrillation patients: a cross-sectional comparison of patients enroled in two large clinical trials. *Europace* 2014;**16**:812-819.
203. 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.
204. 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.
205. Psaty BM, Manolio TA, Kuller LH, Kronmal RA, Cushman M, Fried LP, White R, Furberg CD, Rautaharju PM. Incidence of and risk factors for atrial fibrillation in older adults. *Circulation* 1997;**96**:2455-2461.
206. Selmer C, Olesen JB, Hansen ML, Lindhardsen J, Olsen AM, Madsen JC, Faber J, Hansen PR, Pedersen OD, Torp-Pedersen C, Gislason GH. The spectrum of thyroid disease and risk of new onset atrial fibrillation: a large population cohort study. *BMJ* 2012;**345**:e7895.
207. Kim EJ, Lyass A, Wang N, Massaro JM, Fox CS, Benjamin EJ, Magnani JW. Relation of hypothyroidism and incident atrial fibrillation (from the Framingham Heart Study). *Am Heart J* 2014;**167**:123-126.
208. Vermond RA, Geelhoed B, Verweij N, Tieleman RG, Van der Harst P, Hillege HL, Van Gilst WH, Van Gelder IC, Rienstra M. Incidence of atrial fibrillation and relationship with cardiovascular events, heart failure, and mortality: A community-based study from the netherlands. *J Am Coll Cardiol* 2015;**66**:1000-1007.
209. Buch P, Friberg J, Scharling H, Lange P, Prescott E. Reduced lung function and risk of atrial fibrillation in the Copenhagen City Heart Study. *Eur Respir J* 2003;**21**:1012-1016.
210. Gami AS, Hodge DO, Herges RM, Olson EJ, Nykodym J, Kara T, Somers VK. Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation. *J Am Coll Cardiol* 2007;**49**:565-571.
211. Baber U, Howard VJ, Halperin JL, Soliman EZ, Zhang X, McClellan W, Warnock DG, Muntner P. Association of chronic kidney disease with atrial fibrillation among adults in the United States: REasons for Geographic and Racial Differences in Stroke (REGARDS) Study. *Circ Arrhythm Electrophysiol* 2011;**4**:26-32.
212. Chamberlain AM, Agarwal SK, Folsom AR, Duval S, Soliman EZ, Ambrose M, Eberly LE, Alonso A. Smoking and incidence of atrial fibrillation: results from the Atherosclerosis Risk in Communities (ARIC) study. *Heart Rhythm* 2011;**8**:1160-1166.

213. Larsson SC, Drca N, Wolk A. Alcohol consumption and risk of atrial fibrillation: a prospective study and dose-response meta-analysis. *J Am Coll Cardiol* 2014;**64**:281-289.
214. Aizer A, Gaziano JM, Cook NR, Manson JE, Buring JE, Albert CM. Relation of vigorous exercise to risk of atrial fibrillation. *Am J Cardiol* 2009;**103**:1572-1577.
215. Guha K, McDonagh T. Heart failure epidemiology: European perspective. *Curr Cardiol Rev* 2013;**9**:123-127.
216. Braunschweig F, Cowie MR, Auricchio A. What are the costs of heart failure? *Europace* 2011;**13 Suppl 2**:ii13-17.
217. Wodchis WP, Bhatia RS, Leblanc K, Meshkat N, Morra D. A review of the cost of atrial fibrillation. *Value Health* 2012;**15**:240-248.
218. Kotecha D, Piccini JP. Atrial fibrillation in heart failure: what should we do? *Eur Heart J* 2015;**36**:3250-3257.
219. Olsson LG, Swedberg K, Ducharme A, Granger CB, Michelson EL, McMurray JJ, Puu M, Yusuf S, Pfeffer MA. Atrial fibrillation and risk of clinical events in chronic heart failure with and without left ventricular systolic dysfunction: results from the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) program. *J Am Coll Cardiol* 2006;**47**:1997-2004.
220. Kotecha D, Chudasama R, Lane DA, Kirchhof P, Lip GY. Atrial fibrillation and heart failure due to reduced versus preserved ejection fraction: A systematic review and meta-analysis of death and adverse outcomes. *Int J Cardiol* 2016;**203**:660-666.
221. Mamas MA, Caldwell JC, Chacko S, Garratt CJ, Fath-Ordoubadi F, Neyses L. A meta-analysis of the prognostic significance of atrial fibrillation in chronic heart failure. *Eur J Heart Fail* 2009;**11**:676-683.
222. AUTHORS TO BE ADDED, The Task Force for the diagnosis and teatment of acute and chronic heart failure of the European Society of Cardiology (ESC). 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2016.
223. Lip GY, Heinzel FR, Gaita F, Juanatey JR, Le Heuzey JY, Potpara T, Svendsen JH, Vos MA, Anker SD, Coats AJ, Haverkamp W, Manolis AS, Chung MK, Sanders P, Pieske B, Gorenek B, Lane D, Boriani G, Linde C, Hindricks G, Tsutsui H, Homma S, Brownstein S, Nielsen JC, Lainscak M, Crespo-Leiro M, Piepoli M, Seferovic P, Savelieva I. European Heart Rhythm Association/Heart Failure Association joint consensus document on arrhythmias in heart failure, endorsed by the Heart Rhythm Society and the Asia Pacific Heart Rhythm Society. *Europace* 2016;**18**:12-36.
224. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;**371**:993-1004.
225. Ziff OJ, Lane DA, Samra M, Griffith M, Kirchhof P, Lip GY, Steeds RP, Townend J, Kotecha D. Safety and efficacy of digoxin: systematic review and meta-analysis of observational and controlled trial data. *BMJ* 2015;**351**:h4451.
226. Anselmino M, Matta M, D'Ascenzo F, Bunch TJ, Schilling RJ, Hunter RJ, Pappone C, Neumann T, Noelker G, Fiala M, Bertaglia E, Frontera A, Duncan E, Nalliah C, Jais P, Weerasooriya R, Kalman JM, Gaita F. Catheter ablation of atrial fibrillation in patients with left ventricular systolic dysfunction: a systematic review and meta-analysis. *Circ Arrhythm Electrophysiol* 2014;**7**:1011-1018.
227. Ganesan AN, Nandal S, Luker J, Pathak RK, Mahajan R, Twomey D, Lau DH, Sanders P. Catheter ablation of atrial fibrillation in patients with concomitant left ventricular impairment: a systematic review of efficacy and effect on ejection fraction. *Heart Lung Circ* 2015;**24**:270-280.
228. Khan MN, Jais P, Cummings J, Di Biase L, Sanders P, Martin DO, Kautzner J, Hao S, Themistoclakis S, Fanelli R, Potenza D, Massaro R, Wazni O, Schweikert R, Saliba W, Wang P, Al-Ahmad A, Beheiry S, Santarelli P, Starling RC, Dello Russo A, Pelargonio G, Brachmann J, Schibgilla V, Bonso A, Casella M, Raviele A, Haissaguerre M, Natale A, PABA-CHF Investigators. Pulmonary-vein isolation for atrial fibrillation in patients with heart failure. *N Engl J Med* 2008;**359**:1778-1785.
229. Gupta S, Figueredo VM. Tachycardia mediated cardiomyopathy: pathophysiology, mechanisms, clinical features and management. *Int J Cardiol* 2014;**172**:40-46.
230. Kusunose K, Yamada H, Nishio S, Tomita N, Niki T, Yamaguchi K, Koshiba K, Yagi S, Taketani Y, Iwase T, Soeki T, Wakatsuki T, Akaike M, Sata M. Clinical utility of single-beat E/e' obtained by simultaneous recording of flow and tissue Doppler velocities in atrial fibrillation with preserved systolic function. *JACC Cardiovasc Imaging* 2009;**2**:1147-1156.
231. Li C, Zhang J, Zhou C, Huang L, Tang H, Rao L. Will simultaneous measurement of E/e' index facilitate the non-invasive assessment of left ventricular filling pressure in patients with non-valvular atrial fibrillation? *Eur J Echocardiogr* 2010;**11**:296-301.

232. Senechal M, O'Connor K, Deblois J, Magne J, Dumesnil JG, Pibarot P, Bergeron S, Poirier P. A simple Doppler echocardiography method to evaluate pulmonary capillary wedge pressure in patients with atrial fibrillation. *Echocardiography* 2008;**25**:57-63.
233. Sohn DW, Song JM, Zo JH, Chai IH, Kim HS, Chun HG, Kim HC. Mitral annulus velocity in the evaluation of left ventricular diastolic function in atrial fibrillation. *J Am Soc Echocardiogr* 1999;**12**:927-931.
234. Wada Y, Murata K, Tanaka T, Nose Y, Kihara C, Uchida K, Okuda S, Susa T, Kishida Y, Matsuzaki M. Simultaneous Doppler tracing of transmitral inflow and mitral annular velocity as an estimate of elevated left ventricular filling pressure in patients with atrial fibrillation. *Circ J* 2012;**76**:675-681.
235. Kelly JP, Mentz RJ, Mebazaa A, Voors AA, Butler J, Roessig L, Fiuzat M, Zannad F, Pitt B, O'Connor CM, Lam CS. Patient selection in heart failure with preserved ejection fraction clinical trials. *J Am Coll Cardiol* 2015;**65**:1668-1682.
236. Schneider MP, Hua TA, Bohm M, Wachtell K, Kjeldsen SE, Schmieder RE. Prevention of atrial fibrillation by Renin-Angiotensin system inhibition a meta-analysis. *J Am Coll Cardiol* 2010;**55**:2299-2307.
237. Healey JS, Baranchuk A, Crystal E, Morillo CA, Garfinkle M, Yusuf S, Connolly SJ. Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a meta-analysis. *J Am Coll Cardiol* 2005;**45**:1832-1839.
238. Jibrini MB, Molnar J, Arora RR. Prevention of atrial fibrillation by way of abrogation of the renin-angiotensin system: a systematic review and meta-analysis. *Am J Ther* 2008;**15**:36-43.
239. Ducharme A, Swedberg K, Pfeffer MA, Cohen-Solal A, Granger CB, Maggioni AP, Michelson EL, McMurray JJ, Olsson L, Rouleau JL, Young JB, Olofsson B, Puu M, Yusuf S, CHARM Investigators. Prevention of atrial fibrillation in patients with symptomatic chronic heart failure by candesartan in the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program. *Am Heart J* 2006;**152**:86-92.
240. GISSI-AF Investigators, Disertori M, Latini R, Barlera S, Franzosi MG, Staszewsky L, Maggioni AP, Lucci D, Di Pasquale G, Tognoni G. Valsartan for prevention of recurrent atrial fibrillation. *N Engl J Med* 2009;**360**:1606-1617.
241. Goette A, Schon N, Kirchhof P, Breithardt G, Fetsch T, Hausler KG, Klein HU, Steinbeck G, Wegscheider K, Meinertz T. Angiotensin II-antagonist in paroxysmal atrial fibrillation (ANTIPAF) trial. *Circ Arrhythm Electrophysiol* 2012;**5**:43-51.
242. Active I Investigators, Yusuf S, Healey JS, Pogue J, Chrolavicius S, Flather M, Hart RG, Hohnloser SH, Joyner CD, Pfeffer MA, Connolly SJ. Irbesartan in patients with atrial fibrillation. *N Engl J Med* 2011;**364**:928-938.
243. Swedberg K, Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Shi H, Vincent J, Pitt B. Eplerenone and atrial fibrillation in mild systolic heart failure: results from the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure) study. *J Am Coll Cardiol* 2012;**59**:1598-1603.
244. Goette A, Staack T, Rocken C, Arndt M, Geller JC, Huth C, Ansorge S, Klein HU, Lendeckel U. Increased expression of extracellular signal-regulated kinase and angiotensin-converting enzyme in human atria during atrial fibrillation. *J Am Coll Cardiol* 2000;**35**:1669-1677.
245. Marott SC, Nielsen SF, Benn M, Nordestgaard BG. Antihypertensive treatment and risk of atrial fibrillation: a nationwide study. *Eur Heart J* 2014;**35**:1205-1214.
246. Wachtell K, Lehto M, Gerdts E, Olsen MH, Hornestam B, Dahlof B, Ibsen H, Julius S, Kjeldsen SE, Lindholm LH, Nieminen MS, Devereux RB. Angiotensin II receptor blockade reduces new-onset atrial fibrillation and subsequent stroke compared to atenolol: the Losartan Intervention For End Point Reduction in Hypertension (LIFE) study. *J Am Coll Cardiol* 2005;**45**:712-719.
247. Manolis AJ, Rosei EA, Coca A, Cifkova R, Erdine SE, Kjeldsen S, Lip GY, Narkiewicz K, Parati G, Redon J, Schmieder R, Tsioufis C, Mancia G. Hypertension and atrial fibrillation: diagnostic approach, prevention and treatment. Position paper of the Working Group 'Hypertension Arrhythmias and Thrombosis' of the European Society of Hypertension. *J Hypertens* 2012;**30**:239-252.
248. Madrid AH, Bueno MG, Rebollo JM, Marin I, Pena G, Bernal E, Rodriguez A, Cano L, Cano JM, Cabeza P, Moro C. Use of irbesartan to maintain sinus rhythm in patients with long-lasting persistent atrial fibrillation: a prospective and randomized study. *Circulation* 2002;**106**:331-336.
249. Ueng K-C, Tsai T-P, Yu W-C, Tsai C-F, Lin M-C, Chan K-C, Chen C-Y, Wu D-J, Lin C-S, Chen S-A. Use of enalapril to facilitate sinus rhythm maintenance after external cardioversion of long-standing persistent atrial fibrillation. Results of a prospective and controlled study. *Eur Heart J* 2003;**24**:2090-2098.

250. Anand K, Mooss AN, Hee TT, Mohiuddin SM. Meta-analysis: inhibition of renin-angiotensin system prevents new-onset atrial fibrillation. *Am Heart J* 2006;**152**:217-222.
251. Tveit A, Seljeflot I, Grundvold I, Abdelnoor M, Smith P, Arnesen H. Effect of candesartan and various inflammatory markers on maintenance of sinus rhythm after electrical cardioversion for atrial fibrillation. *Am J Cardiol* 2007;**99**:1544-1548.
252. Furberg CD, Psaty BM, Manolio TA, Gardin JM, Smith VE, Rautaharju PM. Prevalence of atrial fibrillation in elderly subjects (the Cardiovascular Health Study). *Am J Cardiol* 1994;**74**:236-241.
253. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Iung B, Lancellotti P, Pierard L, Price S, Schafers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M, Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC), European Association for Cardio-Thoracic Surgery (EACTS). Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J* 2012;**33**:2451-2496.
254. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM, 3rd, Thomas JD. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;**63**:2438-2488.
255. Nieuwlaat R, Capucci A, Camm AJ, Olsson SB, Andresen D, Davies DW, Cobbe S, Breithardt G, Le Heuzey JY, Prins MH, Levy S, Crijns HJ. Atrial fibrillation management: a prospective survey in ESC member countries: the Euro Heart Survey on Atrial Fibrillation. *Eur Heart J* 2005;**26**:2422-2434.
256. Moretti M, Fabris E, Morosin M, Merlo M, Barbati G, Pinamonti B, Gatti G, Pappalardo A, Sinagra G. Prognostic significance of atrial fibrillation and severity of symptoms of heart failure in patients with low gradient aortic stenosis and preserved left ventricular ejection fraction. *Am J Cardiol* 2014;**114**:1722-1728.
257. Ngaage DL, Schaff HV, Mullany CJ, Barnes S, Dearani JA, Daly RC, Orszulak TA, Sundt TM, 3rd. Influence of preoperative atrial fibrillation on late results of mitral repair: is concomitant ablation justified? *Ann Thorac Surg* 2007;**84**:434-442; discussion 442-433.
258. Ngaage DL, Schaff HV, Barnes SA, Sundt TM, 3rd, Mullany CJ, Dearani JA, Daly RC, Orszulak TA. Prognostic implications of preoperative atrial fibrillation in patients undergoing aortic valve replacement: is there an argument for concomitant arrhythmia surgery? *Ann Thorac Surg* 2006;**82**:1392-1399.
259. Eguchi K, Ohtaki E, Matsumura T, Tanaka K, Tohbaru T, Iguchi N, Misu K, Asano R, Nagayama M, Sumiyoshi T, Kasegawa H, Hosoda S. Pre-operative atrial fibrillation as the key determinant of outcome of mitral valve repair for degenerative mitral regurgitation. *Eur Heart J* 2005;**26**:1866-1872.
260. Lim E, Barlow CW, Hosseinpour AR, Wisbey C, Wilson K, Pidgeon W, Charman S, Barlow JB, Wells FC. Influence of atrial fibrillation on outcome following mitral valve repair. *Circulation* 2001;**104**:I59-63.
261. Maan A, Heist EK, Passeri J, Inglessis I, Baker J, Ptaszek L, Vlahakes G, Ruskin JN, Palacios I, Sundt T, Mansour M. Impact of atrial fibrillation on outcomes in patients who underwent transcatheter aortic valve replacement. *Am J Cardiol* 2015;**115**:220-226.
262. Barbash IM, Minha S, Ben-Dor I, Dvir D, Torguson R, Aly M, Bond E, Satler LF, Pichard AD, Waksman R. Predictors and clinical implications of atrial fibrillation in patients with severe aortic stenosis undergoing transcatheter aortic valve implantation. *Catheter Cardiovasc Interv* 2015;**85**:468-477.
263. Halperin JL, Hart RG. Atrial fibrillation and stroke: new ideas, persisting dilemmas. *Stroke* 1988;**19**:937-941.
264. Messika-Zeitoun D, Bellamy M, Avierinos JF, Breen J, Eusemann C, Rossi A, Behrenbeck T, Scott C, Tajik JA, Enriquez-Sarano M. Left atrial remodelling in mitral regurgitation--methodologic approach, physiological determinants, and outcome implications: a prospective quantitative Doppler-echocardiographic and electron beam-computed tomographic study. *Eur Heart J* 2007;**28**:1773-1781.
265. Calvo N, Bisbal F, Guiu E, Ramos P, Nadal M, Tolosana JM, Arbelo E, Berruezo A, Sitges M, Brugada J, Mont L. Impact of atrial fibrillation-induced tachycardiomyopathy in patients undergoing pulmonary vein isolation. *Int J Cardiol* 2013;**168**:4093-4097.
266. Edner M, Caidahl K, Bergfeldt L, Darpo B, Edvardsson N, Rosenqvist M. Prospective study of left ventricular function after radiofrequency ablation of atrioventricular junction in patients with atrial fibrillation. *Br Heart J* 1995;**74**:261-267.

267. Gertz ZM, Raina A, Saghy L, Zado ES, Callans DJ, Marchlinski FE, Keane MG, Silvestry FE. Evidence of atrial functional mitral regurgitation due to atrial fibrillation: reversal with arrhythmia control. *J Am Coll Cardiol* 2011;**58**:1474-1481.
268. Kihara T, Gillinov AM, Takasaki K, Fukuda S, Song JM, Shiota M, Shiota T. Mitral regurgitation associated with mitral annular dilation in patients with lone atrial fibrillation: an echocardiographic study. *Echocardiography* 2009;**26**:885-889.
269. Zhou X, Otsuji Y, Yoshifuku S, Yuasa T, Zhang H, Takasaki K, Matsukida K, Kisanuki A, Minagoe S, Tei C. Impact of atrial fibrillation on tricuspid and mitral annular dilatation and valvular regurgitation. *Circ J* 2002;**66**:913-916.
270. Ring L, Dutka DP, Wells FC, Fynn SP, Shapiro LM, Rana BS. Mechanisms of atrial mitral regurgitation: insights using 3D transoesophageal echo. *Eur Heart J Cardiovasc Imaging* 2014;**15**:500-508.
271. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Lung B, Lancellotti P, Pierard L, Price S, Schafers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M, ESC Committee for Practice Guidelines (CPG), Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC), European Association for Cardio-Thoracic Surgery (EACTS). Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur J Cardiothorac Surg* 2012;**42**:S1-44.
272. Molteni M, Polo Friz H, Primitz L, Marano G, Boracchi P, Cimminiello C. The definition of valvular and non-valvular atrial fibrillation: results of a physicians' survey. *Europace* 2014;**16**:1720-1725.
273. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. *Ann Thorac Surg* 1996;**61**:755-759.
274. Szekely P. Systemic Embolism and Anticoagulant Prophylaxis in Rheumatic Heart Disease. *Br Med J* 1964;**1**:1209-1212.
275. De Caterina R, Camm AJ. What is 'valvular' atrial fibrillation? A reappraisal. *Eur Heart J* 2014;**35**:3328-3335.
276. Goldstone AB, Patrick WL, Cohen JE, Aribeana CN, Popat R, Woo YJ. Early surgical intervention or watchful waiting for the management of asymptomatic mitral regurgitation: a systematic review and meta-analysis. *Ann Cardiothorac Surg* 2015;**4**:220-229.
277. Schoen T, Pradhan AD, Albert CM, Conen D. Type 2 diabetes mellitus and risk of incident atrial fibrillation in women. *J Am Coll Cardiol* 2012;**60**:1421-1428.
278. Du X, Ninomiya T, de Galan B, Abadir E, Chalmers J, Pillai A, Woodward M, Cooper M, Harrap S, Hamet P, Poulter N, Lip GY, Patel A. Risks of cardiovascular events and effects of routine blood pressure lowering among patients with type 2 diabetes and atrial fibrillation: results of the ADVANCE study. *Eur Heart J* 2009;**30**:1128-1135.
279. Rizzo MR, Sasso FC, Marfella R, Siniscalchi M, Paolisso P, Carbonara O, Capoluongo MC, Lascar N, Pace C, Sardu C, Passavanti B, Barbieri M, Mauro C, Paolisso G. Autonomic dysfunction is associated with brief episodes of atrial fibrillation in type 2 diabetes. *J Diabetes Complications* 2015;**29**:88-92.
280. Olson TM, Terzic A. Human K(ATP) channelopathies: diseases of metabolic homeostasis. *Pflugers Arch* 2010;**460**:295-306.
281. Chung MK, Martin DO, Sprecher D, Wazni O, Kanderian A, Carnes CA, Bauer JA, Tchou PJ, Niebauer MJ, Natale A, Van Wagoner DR. C-reactive protein elevation in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation. *Circulation* 2001;**104**:2886-2891.
282. Donath MY, Shoelson SE. Type 2 diabetes as an inflammatory disease. *Nat Rev Immunol* 2011;**11**:98-107.
283. Ziolo MT, Mohler PJ. Defining the role of oxidative stress in atrial fibrillation and diabetes. *J Cardiovasc Electrophysiol* 2015;**26**:223-225.
284. Fatemi O, Yuriditsky E, Tsioufis C, Tsachris D, Morgan T, Basile J, Bigger T, Cushman W, Goff D, Soliman EZ, Thomas A, Papademetriou V. Impact of intensive glycemic control on the incidence of atrial fibrillation and associated cardiovascular outcomes in patients with type 2 diabetes mellitus (from the Action to Control Cardiovascular Risk in Diabetes Study). *Am J Cardiol* 2014;**114**:1217-1222.

285. Overvad TF, Skjoth F, Lip GY, Lane DA, Albertsen IE, Rasmussen LH, Larsen TB. Duration of Diabetes Mellitus and Risk of Thromboembolism and Bleeding in Atrial Fibrillation: Nationwide Cohort Study. *Stroke* 2015;**46**:2168-2174.
286. Chang S-H, Wu L-S, Chiou M-J, Liu J-R, Yu K-H, Kuo C-F, Wen M-S, Chen W-J, Yeh Y-H, See L-C. Association of metformin with lower atrial fibrillation risk among patients with type 2 diabetes mellitus: a population-based dynamic cohort and in vitro studies. *Cardiovasc Diabetol* 2014;**13**:123.
287. Lip GY, Clementy N, Pierre B, Boyer M, Fauchier L. The impact of associated diabetic retinopathy on stroke and severe bleeding risk in diabetic patients with atrial fibrillation: the Loire valley atrial fibrillation project. *Chest* 2015;**147**:1103-1110.
288. Huxley RR, Misialek JR, Agarwal SK, Loehr LR, Soliman EZ, Chen LY, Alonso A. Physical activity, obesity, weight change, and risk of atrial fibrillation: the Atherosclerosis Risk in Communities study. *Circ Arrhythm Electrophysiol* 2014;**7**:620-625.
289. Murphy NF, MacIntyre K, Stewart S, Hart CL, Hole D, McMurray JJ. Long-term cardiovascular consequences of obesity: 20-year follow-up of more than 15 000 middle-aged men and women (the Renfrew-Paisley study). *Eur Heart J* 2006;**27**:96-106.
290. Wanahita N, Messerli FH, Bangalore S, Gami AS, Somers VK, Steinberg JS. Atrial fibrillation and obesity--results of a meta-analysis. *Am Heart J* 2008;**155**:310-315.
291. Wang TJ, Parise H, Levy D, D'Agostino RB, Sr., Wolf PA, Vasan RS, Benjamin EJ. Obesity and the risk of new-onset atrial fibrillation. *JAMA* 2004;**292**:2471-2477.
292. Overvad TF, Rasmussen LH, Skjoth F, Overvad K, Lip GY, Larsen TB. Body mass index and adverse events in patients with incident atrial fibrillation. *Am J Med* 2013;**126**:640.e649-617.
293. Karason K, Molgaard H, Wikstrand J, Sjostrom L. Heart rate variability in obesity and the effect of weight loss. *Am J Cardiol* 1999;**83**:1242-1247.
294. Russo C, Jin Z, Homma S, Rundek T, Elkind MS, Sacco RL, Di Tullio MR. Effect of obesity and overweight on left ventricular diastolic function: a community-based study in an elderly cohort. *J Am Coll Cardiol* 2011;**57**:1368-1374.
295. Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. Elevated C-reactive protein levels in overweight and obese adults. *Jama* 1999;**282**:2131-2135.
296. Pathak RK, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Wong CX, Twomey D, Elliott AD, Kalman JM, Abhayaratna WP, Lau DH, Sanders P. Long-Term Effect of Goal-Directed Weight Management in an Atrial Fibrillation Cohort: A Long-Term Follow-Up Study (LEGACY). *J Am Coll Cardiol* 2015;**65**:2159-2169.
297. Pathak RK, Elliott A, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Hendriks JM, Twomey D, Kalman JM, Abhayaratna WP, Lau DH, Sanders P. Impact of CARDIOrespiratory FITness on Arrhythmia Recurrence in Obese Individuals With Atrial Fibrillation: The CARDIO-FIT Study. *J Am Coll Cardiol* 2015;**66**:985-996.
298. Cha YM, Friedman PA, Asirvatham SJ, Shen WK, Munger TM, Rea RF, Brady PA, Jahangir A, Monahan KH, Hodge DO, Meverden RA, Gersh BJ, Hammill SC, Packer DL. Catheter ablation for atrial fibrillation in patients with obesity. *Circulation* 2008;**117**:2583-2590.
299. Jongnarangsin K, Chugh A, Good E, Mukerji S, Dey S, Crawford T, Sarrazin JF, Kuhne M, Chalfoun N, Wells D, Boonyapisit W, Pelosi F, Jr., Bogun F, Morady F, Oral H. Body mass index, obstructive sleep apnea, and outcomes of catheter ablation of atrial fibrillation. *J Cardiovasc Electrophysiol* 2008;**19**:668-672.
300. Guijian L, Jinchuan Y, Rongzeng D, Jun Q, Jun W, Wenqing Z. Impact of body mass index on atrial fibrillation recurrence: a meta-analysis of observational studies. *Pacing Clin Electrophysiol* 2013;**36**:748-756.
301. Zhuang J, Lu Y, Tang K, Peng W, Xu Y. Influence of body mass index on recurrence and quality of life in atrial fibrillation patients after catheter ablation: a meta-analysis and systematic review. *Clin Cardiol* 2013;**36**:269-275.
302. Ector J, Dragusin O, Adriaenssens B, Huybrechts W, Willems R, Ector H, Heidbuchel H. Obesity is a major determinant of radiation dose in patients undergoing pulmonary vein isolation for atrial fibrillation. *J Am Coll Cardiol* 2007;**50**:234-242.
303. Shoemaker MB, Muhammad R, Farrell M, Parvez B, White BW, Streur M, Stubblefield T, Rytlewski J, Parvathaneni S, Nagarakanti R, Roden DM, Saavedra P, Ellis C, Whalen SP, Darbar D. Relation of morbid obesity and female gender to risk of procedural complications in patients undergoing atrial fibrillation ablation. *Am J Cardiol* 2013;**111**:368-373.
304. Vizzardi E, Sciatti E, Bonadei I, D'Aloia A, Curnis A, Metra M. Obstructive sleep apnoea-hypopnoea and arrhythmias: new updates. *J Cardiovasc Med (Hagerstown)* 2014.
305. Digby GC, Baranchuk A. Sleep apnea and atrial fibrillation; 2012 update. *Curr Cardiol Rev* 2012;**8**:265-272.

306. Lin YK, Lai MS, Chen YC, Cheng CC, Huang JH, Chen SA, Chen YJ, Lin CI. Hypoxia and reoxygenation modulate the arrhythmogenic activity of the pulmonary vein and atrium. *Clin Sci (Lond)* 2012;**122**:121-132.
307. Linz D. Atrial fibrillation in obstructive sleep apnea: atrial arrhythmogenic substrate of a different sort. *Am J Cardiol* 2012;**110**:1071.
308. Patel D, Mohanty P, Di Biase L, Shaheen M, Lewis WR, Quan K, Cummings JE, Wang P, Al-Ahmad A, Venkatraman P, Nashawati E, Lakkireddy D, Schweikert R, Horton R, Sanchez J, Gallinghouse J, Hao S, Beheiry S, Cardinal DS, Zagrodzky J, Canby R, Bailey S, Burkhardt JD, Natale A. Safety and efficacy of pulmonary vein antral isolation in patients with obstructive sleep apnea: the impact of continuous positive airway pressure. *Circ Arrhythm Electrophysiol* 2010;**3**:445-451.
309. Fein AS, Shvilkin A, Shah D, Haffajee CI, Das S, Kumar K, Kramer DB, Zimetbaum PJ, Buxton AE, Josephson ME, Anter E. Treatment of obstructive sleep apnea reduces the risk of atrial fibrillation recurrence after catheter ablation. *J Am Coll Cardiol* 2013;**62**:300-305.
310. Naruse Y, Tada H, Satoh M, Yanagihara M, Tsuneoka H, Hirata Y, Ito Y, Kuroki K, Machino T, Yamasaki H, Igarashi M, Sekiguchi Y, Sato A, Aonuma K. Concomitant obstructive sleep apnea increases the recurrence of atrial fibrillation following radiofrequency catheter ablation of atrial fibrillation: clinical impact of continuous positive airway pressure therapy. *Heart Rhythm* 2013;**10**:331-337.
311. Neilan TG, Farhad H, Dodson JA, Shah RV, Abbasi SA, Bakker JP, Michaud GF, van der Geest R, Blankstein R, Steigner M, John RM, Jerosch-Herold M, Malhotra A, Kwong RY. Effect of sleep apnea and continuous positive airway pressure on cardiac structure and recurrence of atrial fibrillation. *J Am Heart Assoc* 2013;**2**:e000421.
312. Li L, Wang ZW, Li J, Ge X, Guo LZ, Wang Y, Guo WH, Jiang CX, Ma CS. Efficacy of catheter ablation of atrial fibrillation in patients with obstructive sleep apnoea with and without continuous positive airway pressure treatment: a meta-analysis of observational studies. *Europace* 2014;**16**:1309-1314.
313. Cowie MR, Woehrle H, Wegscheider K, Angermann C, d'Ortho MP, Erdmann E, Levy P, Simonds AK, Somers VK, Zannad F, Teschler H. Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure. *N Engl J Med* 2015;**373**:1095-1105.
314. Bitter T, Nolker G, Vogt J, Prinz C, Horstkotte D, Oldenburg O. Predictors of recurrence in patients undergoing cryoballoon ablation for treatment of atrial fibrillation: the independent role of sleep-disordered breathing. *J Cardiovasc Electrophysiol* 2012;**23**:18-25.
315. Ng CY, Liu T, Shehata M, Stevens S, Chugh SS, Wang X. Meta-analysis of obstructive sleep apnea as predictor of atrial fibrillation recurrence after catheter ablation. *Am J Cardiol* 2011;**108**:47-51.
316. Hart RG, Eikelboom JW, Brimble KS, McMurtry MS, Ingram AJ. Stroke prevention in atrial fibrillation patients with chronic kidney disease. *Can J Cardiol* 2013;**29**:S71-78.
317. Roldan V, Marin F, Fernandez H, Manzano-Fernandez S, Gallego P, Valdes M, Vicente V, Lip GY. Renal impairment in a "real-life" cohort of anticoagulated patients with atrial fibrillation (implications for thromboembolism and bleeding). *Am J Cardiol* 2013;**111**:1159-1164.
318. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L, RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;**361**:1139-1151.
319. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L, ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;**365**:981-992.
320. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM, ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;**365**:883-891.
321. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Spinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Mercuri M, Antman EM, Investigators EA-T. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;**369**:2093-2104.

322. Page K, Marwick TH, Lee R, Grenfell R, Abhayaratna WP, Aggarwal A, Briffa TG, Cameron J, Davidson PM, Driscoll A, Garton-Smith J, Gascard DJ, Hickey A, Korczyk D, Mitchell JA, Sanders R, Spicer D, Stewart S, Wade V. A systematic approach to chronic heart failure care: a consensus statement. *Med J Aust* 2014;**201**:146-150.
323. Stock S, Pitcavage JM, Simic D, Altin S, Graf C, Feng W, Graf TR. Chronic care model strategies in the United States and Germany deliver patient-centered, high-quality diabetes care. *Health Aff (Millwood)* 2014;**33**:1540-1548.
324. Lundstrom H, Siersma V, Nielsen AB, Brodersen J, Reventlow S, Andersen PK, de Fine Olivarius N. The effectiveness of structured personal care of type 2 diabetes on recurrent outcomes: a 19 year follow-up of the study Diabetes Care in General Practice (DCGP). *Diabetologia* 2014;**57**:1119-1123.
325. 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.
326. Wagner EH, Austin BT, Von Korff M. Organizing care for patients with chronic illness. *Milbank Q* 1996;**74**:511-544.
327. Nieuwlaat R, Olsson SB, Lip GY, Camm AJ, Breithardt G, Capucci A, Meeder JG, Prins MH, Levy S, Crijns HJ, Euro Heart Survey Investigators. Guideline-adherent antithrombotic treatment is associated with improved outcomes compared with undertreatment in high-risk patients with atrial fibrillation. The Euro Heart Survey on Atrial Fibrillation. *Am Heart J* 2007;**153**:1006-1012.
328. Nuno R, Coleman K, Bengoa R, Sauto R. Integrated care for chronic conditions: the contribution of the ICCC Framework. *Health Policy* 2012;**105**:55-64.
329. 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.
330. 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.
331. 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.
332. 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.
333. Tran HN, Tafreshi J, Hernandez EA, Pai SM, Torres VI, Pai RG. A multidisciplinary atrial fibrillation clinic. *Curr Cardiol Rev* 2013;**9**:55-62.
334. Conti A, Canuti E, Mariannini Y, Viviani G, Poggioni C, Boni V, Pini R, Vanni S, Padeletti L, Gensini GF. Clinical management of atrial fibrillation: early interventions, observation, and structured follow-up reduce hospitalizations. *Am J Emerg Med* 2012;**30**:1962-1969.
335. Carter L, Gardner M, Magee K, Fearon A, Morgulis I, Doucette S, Sapp JL, Gray C, Abdelwahab A, Parkash R. An Integrated Management Approach to Atrial Fibrillation. *J Am Heart Assoc* 2016;**5**:e002950.
336. Peterson ED, Ho PM, Barton M, Beam C, Burgess LH, Casey DE, Jr., Drozda JP, Jr., Fonarow GC, Goff D, Jr., Grady KL, King DE, King ML, Masoudi FA, Nielsen DR, Stanko S. ACC/AHA/AACVPR/AAFP/ANA Concepts for Clinician-Patient Shared Accountability in Performance Measures: A Report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. *Circulation* 2014.
337. Lane DA, Aguinaga L, Blomstrom-Lundqvist C, Boriani G, Dan GA, Hills MT, Hylek EM, LaHaye SA, Lip GY, Lobban T, Mandrola J, McCabe PJ, Pedersen SS, Pisters R, Stewart S, Wood K, Potpara TS, Gorenek B, Conti JB, Keegan R, Power S, Hendriks J, Ritter P, Calkins H, Violi F, Hurwitz J. Cardiac tachyarrhythmias and patient values and preferences for their management: the European Heart Rhythm Association (EHRA) consensus document endorsed by the Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), and Sociedad Latinoamericana de Estimulacion Cardiaca y Electrofisiologia (SOLEACE). *Europace* 2015;**17**:1747-1769.
338. 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.

339. Donal E, Lip GY, Galderisi M, Goette A, Shah D, Marwan M, Lederlin M, Mondillo S, Edvardsen T, Sitges M, Grapsa J, Garbi M, Senior R, Gimelli A, Potpara TS, Van Gelder IC, Gorenek B, Mabo P, Lancellotti P, Kuck KH, Popescu BA, Hindricks G, Habib G, Cosyns B, Delgado V, Haugaa KH, Muraru D, Nieman K, Cohen A. EACVI/EHRA Expert Consensus Document on the role of multi-modality imaging for the evaluation of patients with atrial fibrillation. *Eur Heart J Cardiovasc Imaging* 2016;**17**:355-383.
340. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the american society of echocardiography and the European association of cardiovascular imaging. *Eur Heart J Cardiovasc Imaging* 2015;**16**:233-271.
341. Filion KB, Agarwal SK, Ballantyne CM, Eberg M, Hoogeveen RC, Huxley RR, Loehr LR, Nambi V, Soliman EZ, Alonso A. High-sensitivity cardiac troponin T and the risk of incident atrial fibrillation: The Atherosclerosis Risk in Communities (ARIC) study. *Am Heart J* 2015;**169**:31-38
342. 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.
343. 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.
344. Bartel T, Erbel R, Acute Trial Investigators. Transoesophageal echocardiography for immediate and safe cardioversion in patients with atrial fibrillation. *Eur Heart J* 2001;**22**:2041-2044.
345. Mahnkopf C, Mitlacher M, Brachmann J. [Relevance of magnetic resonance imaging for catheter ablation of atrial fibrillation]. *Herzschrittmacherther Elektrophysiol* 2014;**25**:252-257.
346. Haemers P, Claus P, Willems R. The use of cardiac magnetic resonance imaging in the diagnostic workup and treatment of atrial fibrillation. *Cardiol Res Pract* 2012;**2012**:658937.
347. Ling LH, Kistler PM, Ellims AH, Iles LM, Lee G, Hughes GL, Kalman JM, Kaye DM, Taylor AJ. Diffuse ventricular fibrosis in atrial fibrillation: noninvasive evaluation and relationships with aging and systolic dysfunction. *J Am Coll Cardiol* 2012;**60**:2402-2408.
348. Lewalter T, Ibrahim R, Albers B, Camm AJ. An update and current expert opinions on percutaneous left atrial appendage occlusion for stroke prevention in atrial fibrillation. *Europace* 2013;**15**:652-656.
349. Kirchhof P, Auricchio A, Bax J, Crijns H, Camm J, Diener HC, Goette A, Hindricks G, Hohnloser S, Kappenberger L, Kuck KH, Lip GY, Olsson B, Meinertz T, Priori S, Ravens U, Steinbeck G, Svernhage E, Tijssen J, Vincent A, Breithardt G. Outcome parameters for trials in atrial fibrillation: executive summary: Recommendations from a consensus conference organized by the German Atrial Fibrillation Competence NETwork (AFNET) and the European Heart Rhythm Association (EHRA). *Eur Heart J* 2007;**28**:2803-2817.
350. Alonso-Coello P, Montori VM, Sola I, Schunemann HJ, Devereaux P, Charles C, Roura M, Diaz MG, Souto JC, Alonso R, Oliver S, Ruiz R, Coll-Vinent B, Diez AI, Gich I, Guyatt G. Values and preferences in oral anticoagulation in patients with atrial fibrillation, physicians' and patients' perspectives: protocol for a two-phase study. *BMC Health Serv Res* 2008;**8**:221.
351. 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**.
352. 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;**13**:495-504.
353. Hart RG, Pearce LA, Aguilar MI. Adjusted-dose warfarin versus aspirin for preventing stroke in patients with atrial fibrillation. *Ann Intern Med* 2007;**147**:590-592.
354. Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, Flaker G, Avezum A, Hohnloser SH, Diaz R, Talajic M, Zhu J, Pais P, Budaj A, Parkhomenko A, Jansky P, Commerford P, Tan RS, Sim KH, Lewis BS, Van Mieghem W, Lip GY, Kim JH, Lanas-Zanetti F, Gonzalez-Hermosillo A, Dans AL, Munawar M, O'Donnell M, Lawrence J, Lewis G, Afzal R, Yusuf S, AVERROES Steering Committee Investigators. Apixaban in patients with atrial fibrillation. *N Engl J Med* 2011;**364**:806-817.
355. Frankel DS, Parker SE, Rosenfeld LE, Gorelick PB. HRS/NSA 2014 Survey of Atrial Fibrillation and Stroke: Gaps in Knowledge and Perspective, Opportunities for Improvement. *Heart Rhythm* 2015.

356. 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.
357. O'Brien EC, Holmes DN, Ansell JE, Allen LA, Hylek E, Kowey PR, Gersh BJ, Fonarow GC, Koller CR, Ezekowitz MD, Mahaffey KW, Chang P, Peterson ED, Piccini JP, Singer DE. Physician practices regarding contraindications to oral anticoagulation in atrial fibrillation: findings from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry. *Am Heart J* 2014;**167**:601-609 e601.
358. Fang MC, Go AS, Chang Y, Borowsky LH, Pomernacki NK, Udaltsova N, Singer DE. Warfarin discontinuation after starting warfarin for atrial fibrillation. *Circ Cardiovasc Qual Outcomes* 2010;**3**:624-631.
359. Zalesak M, Siu K, Francis K, Yu C, Alvrtsyan H, Rao Y, Walker D, Sander S, Miyasato G, Matchar D, Sanchez H. Higher persistence in newly diagnosed nonvalvular atrial fibrillation patients treated with dabigatran versus warfarin. *Circ Cardiovasc Qual Outcomes* 2013;**6**:567-574.
360. 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.
361. 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.
362. Mant J, Hobbs FD, Fletcher K, Roalfe A, Fitzmaurice D, Lip GY, Murray E, BAFTA investigators, Midland Research Practices Network (MidReC). Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet* 2007;**370**:493-503.
363. Diener HC, Eikelboom J, Connolly SJ, Joyner CD, Hart RG, Lip GY, O'Donnell M, Hohnloser SH, Hankey GJ, Shestakovska O, Yusuf S, AVERROES Steering Committee and Investigators. Apixaban versus aspirin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a predefined subgroup analysis from AVERROES, a randomised trial. *Lancet Neurol* 2012;**11**:225-231.
364. The SPAF III Writing Committee for the Stroke Prevention in Atrial Fibrillation Investigators. Patients with nonvalvular atrial fibrillation at low risk of stroke during treatment with aspirin: Stroke Prevention in Atrial Fibrillation III Study. *JAMA* 1998;**279**:1273-1277.
365. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001;**285**:2864-2870.
366. van Walraven C, Hart RG, Wells GA, Petersen P, Koudstaal PJ, Gullov AL, Hellemons BS, Koefed BG, Laupacis A. A clinical prediction rule to identify patients with atrial fibrillation and a low risk for stroke while taking aspirin. *Arch Intern Med* 2003;**163**:936-943.
367. Wang TJ, Massaro JM, Levy D, Vasan RS, Wolf PA, D'Agostino RB, Larson MG, Kannel WB, Benjamin EJ. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. *JAMA* 2003;**290**:1049-1056.
368. 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.
369. 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, ESC Committee for Practice Guidelines, European Heart Rhythm Association, European Association for Cardio-Thoracic Surgery. 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.
370. Kirchhof P, Curtis AB, Skanes AC, Gillis AM, Samuel Wann L, Camm AJ. Atrial fibrillation guidelines across the Atlantic: a comparison of the current recommendations of the European Society of Cardiology/European Heart Rhythm Association/European Association of Cardiothoracic Surgeons, the American College of Cardiology Foundation/American Heart Association/Heart Rhythm Society, and the Canadian Cardiovascular Society. *Eur Heart J* 2013;**34**:1471-1474.
371. Olesen JB, Lip GY, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, Selmer C, Ahlehoff O, Olsen AM, Gislason GH, Torp-Pedersen C. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. *BMJ* 2011;**342**:d124.

372. Chao TF, Liu CJ, Wang KL, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Chen TJ, Lip GY, Chen SA. Should atrial fibrillation patients with 1 additional risk factor of the CHA2DS2-VASc score (beyond sex) receive oral anticoagulation? *J Am Coll Cardiol* 2015;**65**:635-642.
373. Lip GY, Skjoth F, Rasmussen LH, Larsen TB. Oral anticoagulation, aspirin, or no therapy in patients with nonvalvular AF with 0 or 1 stroke risk factor based on the CHA2DS2-VASc score. *J Am Coll Cardiol* 2015;**65**:1385-1394.
374. Fauchier L, Lecoq C, Clementy N, Bernard A, Angoulvant D, Ivanes F, Babuty D, Lip GY. Oral Anticoagulation and the Risk of Stroke or Death in Patients With Atrial Fibrillation and One Additional Stroke Risk Factor: The Loire Valley Atrial Fibrillation Project. *Chest* 2016;**149**:960-968.
375. Joundi RA, Cipriano LE, Sposato LA, Saposnik G, Stroke Outcomes Research Working Group. Ischemic Stroke Risk in Patients With Atrial Fibrillation and CHA2DS2-VASc Score of 1: Systematic Review and Meta-Analysis. *Stroke* 2016;**47**:1364-1367.
376. Friberg L, Skeppholm M, Terent A. Benefit of anticoagulation unlikely in patients with atrial fibrillation and a CHA2DS2-VASc score of 1. *J Am Coll Cardiol* 2015;**65**:225-232.
377. Lip GY, Skjoth F, Nielsen PB, Larsen TB. Non-valvular atrial fibrillation patients with none or one additional risk factor of the CHA2DS2-VASc score. A comprehensive net clinical benefit analysis for warfarin, aspirin, or no therapy. *Thromb Haemost* 2015;**114**:826-834.
378. Mikkelsen AP, Lindhardsen J, Lip GY, Gislason GH, Torp-Pedersen C, Olesen JB. Female sex as a risk factor for stroke in atrial fibrillation: a nationwide cohort study. *J Thromb Haemost* 2012;**10**:1745-1751.
379. Wagstaff AJ, Overvad TF, Lip GY, Lane DA. Is female sex a risk factor for stroke and thromboembolism in patients with atrial fibrillation? A systematic review and meta-analysis. *Qjm* 2014;**107**:955-967.
380. 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.
381. 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.
382. Hijazi Z, Lindback J, Alexander JH, Hanna M, Held C, Hylek EM, Lopes RD, Oldgren J, Siegbahn A, Stewart RA, White HD, Granger CB, Wallentin L, ARISTOTLE and STABILITY Investigators. The ABC (age, biomarkers, clinical history) stroke risk score: a biomarker-based risk score for predicting stroke in atrial fibrillation. *Eur Heart J* 2016:[Epub ahead of print].
383. Gage BF, Yan Y, Milligan PE, Waterman AD, Culverhouse R, Rich MW, Radford MJ. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). *Am Heart J* 2006;**151**:713-719.
384. 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.
385. 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.
386. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. *Eur Heart J* 2012;**33**:1500-1510.
387. Hijazi Z, Oldgren J, Lindback J, Alexander JH, Connolly SJ, Eikelboom JW, Ezekowitz MD, Held C, Hylek EM, Lopes RD, Siegbahn A, Yusuf S, Granger CB, Wallentin L, ARISTOTLE and RE-LY Investigators. The novel biomarker-based ABC (age, biomarkers, clinical history)-bleeding risk score for patients with atrial fibrillation: a derivation and validation study. *Lancet* 2016:[Epub ahead of print].
388. O'Brien EC, Simon DN, Thomas LE, Hylek EM, Gersh BJ, Ansell JE, Kowey PR, Mahaffey KW, Chang P, Fonarow GC, Pencina MJ, Piccini JP, Peterson ED. The ORBIT bleeding score: a simple bedside score to assess bleeding risk in atrial fibrillation. *Eur Heart J* 2015;**36**:3258-3264.
389. Loewen P, Dahri K. Risk of bleeding with oral anticoagulants: an updated systematic review and performance analysis of clinical prediction rules. *Ann Hematol* 2011;**90**:1191-1200.
390. Olesen JB, Lip GY, Hansen PR, Lindhardsen J, Ahlehoff O, Andersson C, Weeke P, Hansen ML, Gislason GH, Torp-Pedersen C. Bleeding risk in 'real world' patients with atrial fibrillation:

4021 comparison of two established bleeding prediction schemes in a nationwide cohort. *J Thromb*
4022 *Haemost* 2011;**9**:1460-1467.
4023 391. Van Staa TP, Setakis E, Di Tanna GL, Lane DA, Lip GY. A comparison of risk stratification
4024 schemes for stroke in 79,884 atrial fibrillation patients in general practice. *J Thromb Haemost*
4025 2011;**9**:39-48.
4026 392. Roldan V, Marin F, Manzano-Fernandez S, Gallego P, Vilchez JA, Valdes M, Vicente V, Lip
4027 GY. The HAS-BLED score has better prediction accuracy for major bleeding than CHADS2 or
4028 CHA2DS2-VASc scores in anticoagulated patients with atrial fibrillation. *J Am Coll Cardiol*
4029 2013;**62**:2199-2204.
4030 393. Wallentin L, Hijazi Z, Andersson U, Alexander JH, De Caterina R, Hanna M, Horowitz JD,
4031 Hylek EM, Lopes RD, Asberg S, Granger CB, Siegbahn A, ARISTOTLE Investigators. Growth
4032 differentiation factor 15, a marker of oxidative stress and inflammation, for risk assessment in patients
4033 with atrial fibrillation: insights from the Apixaban for Reduction in Stroke and Other Thromboembolic
4034 Events in Atrial Fibrillation (ARISTOTLE) trial. *Circulation* 2014;**130**:1847-1858.
4035 394. Raunso J, Selmer C, Olesen JB, Charlot MG, Olsen AM, Bretler DM, Nielsen JD, Dominguez
4036 H, Gadsboll N, Kober L, Gislason GH, Torp-Pedersen C, Hansen ML. Increased short-term risk of
4037 thrombo-embolism or death after interruption of warfarin treatment in patients with atrial fibrillation.
4038 *Eur Heart J* 2012;**33**:1886-1892.
4039 395. Sjogren V, Grzymala-Lubanski B, Renlund H, Friberg L, Lip GY, Svensson PJ, Sjalander A.
4040 Safety and efficacy of well managed warfarin. A report from the Swedish quality register Auricula.
4041 *Thromb Haemost* 2015;**113**:1370-1377.
4042 396. Graham DJ, Reichman ME, Wernecke M, Zhang R, Southworth MR, Levenson M, Sheu TC,
4043 Mott K, Goulding MR, Houstoun M, MaCurdy TE, Worrall C, Kelman JA. Cardiovascular, bleeding,
4044 and mortality risks in elderly medicare patients treated with dabigatran or warfarin for nonvalvular
4045 atrial fibrillation. *Circulation* 2015;**131**:157-164.
4046 397. Apostolakis S, Sullivan RM, Olshansky B, Lip GY. Factors affecting quality of anticoagulation
4047 control among patients with atrial fibrillation on warfarin: the SAMe-TT(2)R(2) score. *Chest*
4048 2013;**144**:1555-1563.
4049 398. Lip GY, Haguenoer K, Saint-Etienne C, Fauchier L. Relationship of the SAMe-TT(2)R(2)
4050 score to poor-quality anticoagulation, stroke, clinically relevant bleeding, and mortality in patients with
4051 atrial fibrillation. *Chest* 2014;**146**:719-726.
4052 399. Gallego P, Roldan V, Marin F, Galvez J, Valdes M, Vicente V, Lip GY. SAMe-TT2R2 score,
4053 time in therapeutic range, and outcomes in anticoagulated patients with atrial fibrillation. *Am J Med*
4054 2014;**127**:1083-1088.
4055 400. Eikelboom JW, Connolly SJ, Brueckmann M, Granger CB, Kappetein AP, Mack MJ,
4056 Blatchford J, Devenny K, Friedman J, Guiver K, Harper R, Khder Y, Lobmeyer MT, Maas H, Voigt JU,
4057 Simoons ML, Van de Werf F, RE-ALIGN Investigators. Dabigatran versus warfarin in patients with
4058 mechanical heart valves. *N Engl J Med* 2013;**369**:1206-1214.
4059 401. Olesen JB, Sorensen R, Hansen ML, Lamberts M, Weeke P, Mikkelsen AP, Kober L,
4060 Gislason GH, Torp-Pedersen C, Fosbol EL. Non-vitamin K antagonist oral anticoagulation agents in
4061 anticoagulant naive atrial fibrillation patients: Danish nationwide descriptive data 2011-2013.
4062 *Europace* 2015;**17**:187-193.
4063 402. Hylek EM, Held C, Alexander JH, Lopes RD, De Caterina R, Wojdyla DM, Huber K, Jansky P,
4064 Steg PG, Hanna M, Thomas L, Wallentin L, Granger CB. Major bleeding in patients with atrial
4065 fibrillation receiving apixaban or warfarin: The ARISTOTLE Trial (Apixaban for Reduction in Stroke
4066 and Other Thromboembolic Events in Atrial Fibrillation): Predictors, Characteristics, and Clinical
4067 Outcomes. *J Am Coll Cardiol* 2014;**63**:2141-2147.
4068 403. Flaker GC, Eikelboom JW, Shestakovska O, Connolly SJ, Kaatz S, Budaj A, Husted S, Yusuf
4069 S, Lip GY, Hart RG. Bleeding during treatment with aspirin versus apixaban in patients with atrial
4070 fibrillation unsuitable for warfarin: the apixaban versus acetylsalicylic acid to prevent stroke in atrial
4071 fibrillation patients who have failed or are unsuitable for vitamin K antagonist treatment (AVERROES)
4072 trial. *Stroke* 2012;**43**:3291-3297.
4073 404. Connolly SJ, Ezekowitz MD, Yusuf S, Reilly PA, Wallentin L, Randomized Evaluation of Long-
4074 Term Anticoagulation Therapy Investigators. Newly identified events in the RE-LY trial. *N Engl J Med*
4075 2010;**363**:1875-1876.
4076 405. Ruff CT, Giugliano RP, Braunwald E, Morrow DA, Murphy SA, Kuder JF, Deenadayalu N,
4077 Jarolim P, Betcher J, Shi M, Brown K, Patel I, Mercuri M, Antman EM. Association between edoxaban
4078 dose, concentration, anti-Factor Xa activity, and outcomes: an analysis of data from the randomised,
4079 double-blind ENGAGE AF-TIMI 48 trial. *Lancet* 2015;**385**:2288-2295.

406. Beyer-Westendorf J, Forster K, Pannach S, Ebertz F, Gelbricht V, Thieme C, Michalski F, Kohler C, Werth S, Sahin K, Tittl L, Hansel U, Weiss N. Rates, management, and outcome of rivaroxaban bleeding in daily care: results from the Dresden NOAC registry. *Blood* 2014;**124**:955-962.
407. Camm AJ, Amarenco P, Haas S, Hess S, Kirchhof P, Kuhls S, van Eickels M, Turpie AG, XANTUS Investigators. XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation. *Eur Heart J* 2016;**37**:1145-1153.
408. 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, RE-LY investigators. 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.
409. Piccini JP, Hellkamp AS, Lokhnygina Y, Patel MR, Harrell FE, Singer DE, Becker RC, Breithardt G, Halperin JL, Hankey GJ, Berkowitz SD, Nessel CC, Mahaffey KW, Fox KA, Califf RM, ROCKET AF Investigators. Relationship between time in therapeutic range and comparative treatment effect of rivaroxaban and warfarin: results from the ROCKET AF trial. *J Am Heart Assoc* 2014;**3**:e000521.
410. Olesen JB, Lip GY, Kamper AL, Hommel K, Kober L, Lane DA, Lindhardsen J, Gislason GH, Torp-Pedersen C. Stroke and bleeding in atrial fibrillation with chronic kidney disease. *N Engl J Med* 2012;**367**:625-635.
411. Albertsen IE, Rasmussen LH, Overvad TF, Graungaard T, Larsen TB, Lip GY. Risk of stroke or systemic embolism in atrial fibrillation patients treated with warfarin: A systematic review and meta-analysis. *Stroke* 2013;**44**:1329-1336.
412. Hart RG, Pearce LA, Asinger RW, Herzog CA. Warfarin in atrial fibrillation patients with moderate chronic kidney disease. *Clin J Am Soc Nephrol* 2011;**6**:2599-2604.
413. Friberg L, Benson L, Lip GY. Balancing stroke and bleeding risks in patients with atrial fibrillation and renal failure: the Swedish Atrial Fibrillation Cohort study. *Eur Heart J* 2014.
414. Jun M, James MT, Manns BJ, Quinn RR, Ravani P, Tonelli M, Perkovic V, Winkelmayer WC, Ma Z, Hemmelgarn BR. The association between kidney function and major bleeding in older adults with atrial fibrillation starting warfarin treatment: population based observational study. *BMJ* 2015;**350**:h246.
415. Del-Carpio Munoz F, Gharacholou SM, Munger TM, Friedman PA, Asirvatham SJ, Packer DL, Noseworthy PA. Meta-Analysis of Renal Function on the Safety and Efficacy of Novel Oral Anticoagulants for Atrial Fibrillation. *Am J Cardiol* 2016;**117**:69-75.
416. Heidbuchel H, Verhamme P, Alings M, Antz M, Diener HC, Hacke W, Oldgren J, Sinnaeve P, Camm AJ, Kirchhof P. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. *Europace* 2015;**17**:1467-1507.
417. Zimmerman D, Sood MM, Rigatto C, Holden RM, Hiremath S, Clase CM. Systematic review and meta-analysis of incidence, prevalence and outcomes of atrial fibrillation in patients on dialysis. *Nephrol Dial Transplant* 2012;**27**:3816-3822.
418. Marinigh R, Lane DA, Lip GY. Severe renal impairment and stroke prevention in atrial fibrillation: implications for thromboprophylaxis and bleeding risk. *J Am Coll Cardiol* 2011;**57**:1339-1348.
419. Wizemann V, Tong L, Satayathum S, Disney A, Akiba T, Fissell RB, Kerr PG, Young EW, Robinson BM. Atrial fibrillation in hemodialysis patients: clinical features and associations with anticoagulant therapy. *Kidney Int* 2010;**77**:1098-1106.
420. Chan KE, Lazarus JM, Thadhani R, Hakim RM. Warfarin use associates with increased risk for stroke in hemodialysis patients with atrial fibrillation. *J Am Soc Nephrol* 2009;**20**:2223-2233.
421. Winkelmayer WC, Liu J, Setoguchi S, Choudhry NK. Effectiveness and safety of warfarin initiation in older hemodialysis patients with incident atrial fibrillation. *Clin J Am Soc Nephrol* 2011;**6**:2662-2668.
422. Shah M, Avgil Tsadok M, Jackevicius CA, Essebag V, Eisenberg MJ, Rahme E, Humphries KH, Tu JV, Behlouli H, Guo H, Pilote L. Warfarin use and the risk for stroke and bleeding in patients with atrial fibrillation undergoing dialysis. *Circulation* 2014;**129**:1196-1203.
423. Bonde AN, Lip GY, Kamper AL, Hansen PR, Lamberts M, Hommel K, Hansen ML, Gislason GH, Torp-Pedersen C, Olesen JB. Net clinical benefit of antithrombotic therapy in patients with atrial fibrillation and chronic kidney disease: a nationwide observational cohort study. *J Am Coll Cardiol* 2014;**64**:2471-2482.
424. Chan KE, Edelman ER, Wenger JB, Thadhani RI, Maddux FW. Dabigatran and rivaroxaban use in atrial fibrillation patients on hemodialysis. *Circulation* 2015;**131**:972-979.

425. 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.
426. Fox KA, Piccini JP, Wojdyla D, Becker RC, Halperin JL, Nessel CC, Paolini JF, Hankey GJ, Mahaffey KW, Patel MR, Singer DE, Califf RM. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. *Eur Heart J* 2011;**32**:2387-2394.
427. 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.
428. Stroke Prevention in Atrial Fibrillation Investigators. Stroke Prevention in Atrial Fibrillation Study. Final results. *Circulation* 1991;**84**:527-539.
429. Olesen JB, Lip GY, Lindhardsen J, Lane DA, Ahlehoff O, Hansen ML, Raunso J, Tolstrup JS, Hansen PR, Gislason GH, Torp-Pedersen C. Risks of thromboembolism and bleeding with thromboprophylaxis in patients with atrial fibrillation: A net clinical benefit analysis using a 'real world' nationwide cohort study. *Thromb Haemost* 2011;**106**:739-749.
430. Sjalander S, Sjalander A, Svensson PJ, Friberg L. Atrial fibrillation patients do not benefit from acetylsalicylic acid. *Europace* 2014;**16**:631-638.
431. ACTIVE Writing Group of the ACTIVE Investigators, Connolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, Chrolavicius S, Pfeffer M, Hohnloser S, Yusuf S. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet* 2006;**367**:1903-1912.
432. Connolly SJ, Pogue J, Eikelboom J, Flaker G, Commerford P, Franzosi MG, Healey JS, Yusuf S, ACTIVE W Investigators. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. *Circulation* 2008;**118**:2029-2037.
433. Connolly SJ, Pogue J, Hart RG, Hohnloser SH, Pfeffer M, Chrolavicius S, Yusuf S, ACTIVE Investigators. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med* 2009;**360**:2066-2078.
434. van Walraven C, Hart RG, Connolly S, Austin PC, Mant J, Hobbs FD, Koudstaal PJ, Petersen P, Perez-Gomez F, Knottnerus JA, Boode B, Ezekowitz MD, Singer DE. Effect of age on stroke prevention therapy in patients with atrial fibrillation: the atrial fibrillation investigators. *Stroke* 2009;**40**:1410-1416.
435. Olesen KH. The natural history of 271 patients with mitral stenosis under medical treatment. *Br Heart J* 1962;**24**:349-357.
436. Perez-Gomez F, Alegria E, Berjon J, Iriarte JA, Zumalde J, Salvador A, Mataix L, NASPEAF Investigators. Comparative effects of antiplatelet, anticoagulant, or combined therapy in patients with valvular and nonvalvular atrial fibrillation: a randomized multicenter study. *J Am Coll Cardiol* 2004;**44**:1557-1566.
437. Rowe JC, Bland EF, Sprague HB, White PD. The course of mitral stenosis without surgery: ten- and twenty-year perspectives. *Ann Intern Med* 1960;**52**:741-749.
438. Wilson JK, Greenwood WF. The natural history of mitral stenosis. *Can Med Assoc J* 1954;**71**:323-331.
439. Cannegieter SC, van der Meer FJ, Briet E, Rosendaal FR. Warfarin and aspirin after heart-valve replacement. *N Engl J Med* 1994;**330**:507-508; author reply 508-509.
440. Chiang CW, Lo SK, Ko YS, Cheng NJ, Lin PJ, Chang CH. Predictors of systemic embolism in patients with mitral stenosis. A prospective study. *Ann Intern Med* 1998;**128**:885-889.
441. Wan Y, Heneghan C, Perera R, Roberts N, Hollowell J, Glasziou P, Bankhead C, Xu Y. Anticoagulation control and prediction of adverse events in patients with atrial fibrillation: a systematic review. *Circ Cardiovasc Qual Outcomes* 2008;**1**:84-91.
442. Morgan CL, McEwan P, Tukiendorf A, Robinson PA, Clemens A, Plumb JM. Warfarin treatment in patients with atrial fibrillation: observing outcomes associated with varying levels of INR control. *Thromb Res* 2009;**124**:37-41.
443. Gallagher AM, Setakis E, Plumb JM, Clemens A, van Staa TP. Risks of stroke and mortality associated with suboptimal anticoagulation in atrial fibrillation patients. *Thromb Haemost* 2011;**106**:968-977.

444. 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.
445. Dans AL, Connolly SJ, Wallentin L, Yang S, Nakamya J, Brueckmann M, Ezekowitz M, Oldgren J, Eikelboom JW, Reilly PA, Yusuf S. Concomitant use of antiplatelet therapy with dabigatran or warfarin in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial. *Circulation* 2013;**127**:634-640.
446. Bajaj NS, Parashar A, Agarwal S, Sodhi N, Poddar KL, Garg A, Tuzcu EM, Kapadia SR. Percutaneous left atrial appendage occlusion for stroke prophylaxis in nonvalvular atrial fibrillation: a systematic review and analysis of observational studies. *JACC Cardiovasc Interv* 2014;**7**:296-304.
447. 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.
448. Meier B, Blaauw Y, Khattab AA, Lewalter T, Sievert H, Tondo C, Glikson M. EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion. *Europace* 2014;**16**:1397-1416.
449. Holmes DR, Jr., Kar S, Price MJ, Whisenant B, Sievert H, Doshi SK, Huber K, Reddy VY. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. *J Am Coll Cardiol* 2014;**64**:1-12.
450. Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, Mullin CM, Sick P. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet* 2009;**374**:534-542.
451. Reddy VY, Doshi SK, Sievert H, Buchbinder M, Neuzil P, Huber K, Halperin JL, Holmes D. Percutaneous left atrial appendage closure for stroke prophylaxis in patients with atrial fibrillation: 2.3-Year Follow-up of the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) Trial. *Circulation* 2013;**127**:720-729.
452. Reddy VY, Sievert H, Halperin J, Doshi SK, Buchbinder M, Neuzil P, Huber K, Whisenant B, Kar S, Swarup V, Gordon N, Holmes D, PROTECT AF Steering Committee and Investigators. Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial. *JAMA* 2014;**312**:1988-1998.
453. Holmes DR, Jr., Doshi SK, Kar S, Price MJ, Sanchez JM, Sievert H, Valderrabano M, Reddy VY. Left Atrial Appendage Closure as an Alternative to Warfarin for Stroke Prevention in Atrial Fibrillation: A Patient-Level Meta-Analysis. *J Am Coll Cardiol* 2015;**65**:2614-2623.
454. Reddy VY, Mobius-Winkler S, Miller MA, Neuzil P, Schuler G, Wiebe J, Sick P, Sievert H. Left atrial appendage closure with the Watchman device in patients with a contraindication for oral anticoagulation: the ASAP study (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology). *J Am Coll Cardiol* 2013;**61**:2551-2556.
455. Santoro G, Meucci F, Stolcova M, Rezzaghi M, Mori F, Palmieri C, Paradossi U, Pastormerlo LE, Rosso G, Berti S. Percutaneous left atrial appendage occlusion in patients with non-valvular atrial fibrillation: implantation and up to four years follow-up of the AMPLATZER Cardiac Plug. *EuroIntervention* 2014.
456. Badheka AO, Chothani A, Mehta K, Patel NJ, Deshmukh A, Hoosien M, Shah N, Singh V, Grover P, Savani GT, Panaich SS, Rathod A, Patel N, Arora S, Bhalara V, Coffey JO, O'Neill W, Makkar R, Grines CL, Schreiber T, Di Biase L, Natale A, Viles-Gonzalez JF. Utilization and adverse outcomes of percutaneous left atrial appendage closure for stroke prevention in atrial fibrillation in the United States: influence of hospital volume. *Circ Arrhythm Electrophysiol* 2015;**8**:42-48.
457. Pison L, Potpara TS, Chen J, Larsen TB, Bongiorni MG, Blomstrom-Lundqvist C. Left atrial appendage closure-indications, techniques, and outcomes: results of the European Heart Rhythm Association Survey. *Europace* 2015;**17**:642-646.
458. Price MJ, Gibson DN, Yakubov SJ, Schultz JC, Di Biase L, Natale A, Burkhardt JD, Pershad A, Byrne TJ, Gidney B, Aragon JR, Goldstein J, Moulton K, Patel T, Knight B, Lin AC, Valderrabano M. Early safety and efficacy of percutaneous left atrial appendage suture ligation: results from the U.S. transcatheter LAA ligation consortium. *J Am Coll Cardiol* 2014;**64**:565-572.
459. Boersma LV, Schmidt B, Betts TR, Sievert H, Tamburino C, Teiger E, Pokushalov E, Kische S, Schmitz T, Stein KM, Bergmann MW, EWOLUTION investigators. Implant success and safety of

left atrial appendage closure with the WATCHMAN device: peri-procedural outcomes from the EWOLUTION registry. *Eur Heart J* 2016:[Epub ahead of print].
460. 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.
461. Budera P, Straka Z, Osmancik P, Vanek T, Jelinek S, Hlavicka J, Fojt R, Cervinka P, Hulman M, Smid M, Maly M, Widimsky P. Comparison of cardiac surgery with left atrial surgical ablation vs. cardiac surgery without atrial ablation in patients with coronary and/or valvular heart disease plus atrial fibrillation: final results of the PRAGUE-12 randomized multicentre study. *Eur Heart J* 2012;**33**:2644-2652.
462. Healey JS, Crystal E, Lamy A, Teoh K, Semelhago L, Hohnloser SH, Cybulsky I, Abouzahr L, Sawchuck C, Carroll S, Morillo C, Kleine P, Chu V, Lonn E, Connolly SJ. Left Atrial Appendage Occlusion Study (LAAOS): results of a randomized controlled pilot study of left atrial appendage occlusion during coronary bypass surgery in patients at risk for stroke. *Am Heart J* 2005;**150**:288-293.
463. Tsai YC, Phan K, Munkholm-Larsen S, Tian DH, La Meir M, Yan TD. Surgical left atrial appendage occlusion during cardiac surgery for patients with atrial fibrillation: a meta-analysis. *Eur J Cardiothorac Surg* 2015;**47**:847-854.
464. Whitlock RP, Vincent J, Blackall MH, Hirsh J, Fremes S, Novick R, Devereaux PJ, Teoh K, Lamy A, Connolly SJ, Yusuf S, Carrier M, Healey JS. Left Atrial Appendage Occlusion Study II (LAAOS II). *Can J Cardiol* 2013;**29**:1443-1447.
465. Aryana A, Singh SK, Singh SM, Gearoid O'Neill P, Bowers MR, Allen SL, Lewandowski SL, Vierra EC, d'Avila A. Association between incomplete surgical ligation of left atrial appendage and stroke and systemic embolization. *Heart Rhythm* 2015;**12**:1431-1437.
466. Gillinov AM, Gelijns AC, Parides MK, DeRose JJ, Jr., Moskowitz AJ, Voisine P, Ailawadi G, Bouchard D, Smith PK, Mack MJ, Acker MA, Mullen JC, Rose EA, Chang HL, Puskas JD, Couderc JP, Gardner TJ, Varghese R, Horvath KA, Bolling SF, Michler RE, Geller NL, Ascheim DD, Miller MA, Bagiella E, Moquete EG, Williams P, Taddei-Peters WC, O'Gara PT, Blackstone EH, Argenziano M, CTSN Investigators. Surgical ablation of atrial fibrillation during mitral-valve surgery. *N Engl J Med* 2015;**372**:1399-1409.
467. Whitlock R, Healey J, Vincent J, Brady K, Teoh K, Royse A, Shah P, Guo Y, Alings M, Folkeringa RJ, Paparella D, Colli A, Meyer SR, Legare JF, Lamontagne F, Reents W, Boning A, Connolly S. Rationale and design of the Left Atrial Appendage Occlusion Study (LAAOS) III. *Ann Cardiothorac Surg* 2014;**3**:45-54.
468. Boersma LV, Castella M, van Boven W, Berruezo A, Yilmaz A, Nadal M, Sandoval E, Calvo N, Brugada J, Kelder J, Wijffels M, Mont L. Atrial fibrillation catheter ablation versus surgical ablation treatment (FAST): a 2-center randomized clinical trial. *Circulation* 2012;**125**:23-30.
469. Grau AJ, Weimar C, Buggle F, Heinrich A, Goertler M, Neumaier S, Glahn J, Brandt T, Hacke W, Diener H. Risk factors, outcome, and treatment in subtypes of ischemic stroke: the German stroke data bank. *Stroke* 2001;**32**:2559-2566.
470. Giles MF, Rothwell PM. Risk of stroke early after transient ischaemic attack: a systematic review and meta-analysis. *Lancet Neurol* 2007;**6**:1063-1072.
471. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, Brott T, Cohen G, Davis S, Donnan G, Grotta J, Howard G, Kaste M, Koga M, von Kummer R, Lansberg M, Lindley RI, Murray G, Olivot JM, Parsons M, Tilley B, Toni D, Toyoda K, Wahlgren N, Wardlaw J, Whiteley W, Del Zoppo GJ, Baigent C, Sandercock P, Hacke W, Stroke Thrombolysis Trialists' Collaborative Group. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet* 2014.
472. Diener HC, Stanford S, Abdul-Rahim A, Christensen L, Hougaard KD, Bakhai A, Veltkamp R, Worthmann H. Anti-thrombotic therapy in patients with atrial fibrillation and intracranial hemorrhage. *Expert Rev Neurother* 2014;**14**:1019-1028.
473. Hankey GJ, Norrving B, Hacke W, Steiner T. Management of acute stroke in patients taking novel oral anticoagulants. *Int J Stroke* 2014;**9**:627-632.
474. Xian Y, Liang L, Smith EE, Schwamm LH, Reeves MJ, Olson DM, Hernandez AF, Fonarow GC, Peterson ED. Risks of intracranial hemorrhage among patients with acute ischemic stroke

4317 receiving warfarin and treated with intravenous tissue plasminogen activator. *JAMA* 2012;**307**:2600-
4318 2608.
4319 475. Pollack CV, Jr., Reilly PA, Eikelboom J, Glund S, Verhamme P, Bernstein RA, Dubiel R,
4320 Huisman MV, Hylek EM, Kamphuisen PW, Kreuzer J, Levy JH, Sellke FW, Stangier J, Steiner T,
4321 Wang B, Kam CW, Weitz JI. Idarucizumab for Dabigatran Reversal. *N Engl J Med* 2015;**373**:511-520.
4322 476. Badhiwala JH, Nassiri F, Alhazzani W, Selim MH, Farrokhyar F, Spears J, Kulkarni AV, Singh
4323 S, Alqahtani A, Rochwerg B, Alshahrani M, Murty NK, Alhazzani A, Yarascavitch B, Reddy K, Zaidat
4324 OO, Almenawer SA. Endovascular Thrombectomy for Acute Ischemic Stroke: A Meta-analysis. *Jama*
4325 2015;**314**:1832-1843.
4326 477. Paciaroni M, Agnelli G, Micheli S, Caso V. Efficacy and safety of anticoagulant treatment in
4327 acute cardioembolic stroke: a meta-analysis of randomized controlled trials. *Stroke* 2007;**38**:423-430.
4328 478. Heidbuchel H, Verhamme P, Alings M, Antz M, Hacke W, Oldgren J, Sinnaeve P, Camm AJ,
4329 Kirchhof P. European Heart Rhythm Association Practical Guide on the use of new oral
4330 anticoagulants in patients with non-valvular atrial fibrillation. *Europace* 2013;**15**:625-651.
4331 479. Diener HC, Connolly SJ, Ezekowitz MD, Wallentin L, Reilly PA, Yang S, Xavier D, Di
4332 Pasquale G, Yusuf S. Dabigatran compared with warfarin in patients with atrial fibrillation and
4333 previous transient ischaemic attack or stroke: a subgroup analysis of the RE-LY trial. *Lancet Neurol*
4334 2010;**9**:1157-1163.
4335 480. Hankey GJ, Patel MR, Stevens SR, Becker RC, Breithardt G, Carolei A, Diener HC, Donnan
4336 GA, Halperin JL, Mahaffey KW, Mas JL, Massaro A, Norrving B, Nessel CC, Paolini JF, Roine RO,
4337 Singer DE, Wong L, Califf RM, Fox KA, Hacke W, ROCKET AF Steering Committee Investigators.
4338 Rivaroxaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient
4339 ischaemic attack: a subgroup analysis of ROCKET AF. *Lancet Neurol* 2012;**11**:315-322.
4340 481. Easton JD, Lopes RD, Bahit MC, Wojdyla DM, Granger CB, Wallentin L, Alings M, Goto S,
4341 Lewis BS, Rosenqvist M, Hanna M, Mohan P, Alexander JH, Diener HC, ARISTOTLE Committees
4342 and Investigators. Apixaban compared with warfarin in patients with atrial fibrillation and previous
4343 stroke or transient ischaemic attack: a subgroup analysis of the ARISTOTLE trial. *Lancet Neurol*
4344 2012;**11**:503-511.
4345 482. Ntaios G, Papavasileiou V, Diener HC, Makaritsis K, Michel P. Nonvitamin-K-antagonist oral
4346 anticoagulants in patients with atrial fibrillation and previous stroke or transient ischemic attack: a
4347 systematic review and meta-analysis of randomized controlled trials. *Stroke* 2012;**43**:3298-3304.
4348 483. Paciaroni M, Agnelli G. Should oral anticoagulants be restarted after warfarin-associated
4349 cerebral haemorrhage in patients with atrial fibrillation? *Thromb Haemost* 2014;**111**:14-18.
4350 484. Nielsen PB, Larsen TB, Skjoth F, Gorst-Rasmussen A, Rasmussen LH, Lip GY. Restarting
4351 Anticoagulant Treatment After Intracranial Hemorrhage in Patients With Atrial Fibrillation and the
4352 Impact on Recurrent Stroke, Mortality, and Bleeding: A Nationwide Cohort Study. *Circulation*
4353 2015;**132**:517-525.
4354 485. Weber R, Brenck J, Diener HC. Antiplatelet therapy in cerebrovascular disorders. *Handb Exp*
4355 *Pharmacol* 2012:519-546.
4356 486. Flaker GC, Gruber M, Connolly SJ, Goldman S, Chaparro S, Vahanian A, Halinen MO,
4357 Horrow J, Halperin JL. Risks and benefits of combining aspirin with anticoagulant therapy in patients
4358 with atrial fibrillation: an exploratory analysis of stroke prevention using an oral thrombin inhibitor in
4359 atrial fibrillation (SPORTIF) trials. *Am Heart J* 2006;**152**:967-973.
4360 487. Yung D, Kapral MK, Asllani E, Fang J, Lee DS, Investigators of the Registry of the Canadian
4361 Stroke Network. Reinitiation of anticoagulation after warfarin-associated intracranial hemorrhage and
4362 mortality risk: the Best Practice for Reinitiating Anticoagulation Therapy After Intracranial Bleeding
4363 (BRAIN) study. *Can J Cardiol* 2012;**28**:33-39.
4364 488. Roskell NS, Samuel M, Noack H, Monz BU. Major bleeding in patients with atrial fibrillation
4365 receiving vitamin K antagonists: a systematic review of randomized and observational studies.
4366 *Europace* 2013;**15**:787-797.
4367 489. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, Christiaens T, Cifkova R,
4368 De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent
4369 S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B,
4370 Zannad F, Redon J, Dominiczak A, Narkiewicz K, Nilsson PM, Burnier M, Viigimaa M, Ambrosioni E,
4371 Caufield M, Coca A, Olsen MH, Schmieder RE, Tsioufis C, van de Borne P, Zamorano JL, Achenbach
4372 S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes
4373 AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski
4374 P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Clement DL, Coca A,
4375 Gillebert TC, Tendera M, Rosei EA, Ambrosioni E, Anker SD, Bauersachs J, Hitij JB, Caulfield M, De
4376 Buyzere M, De Geest S, Derumeaux GA, Erdine S, Farsang C, Funck-Brentano C, Gerc V, Germano

G, Gielen S, Haller H, Hoes AW, Jordan J, Kahan T, Komajda M, Lovic D, Mahrholdt H, Olsen MH, Ostergren J, Parati G, Perk J, Polonia J, Popescu BA, Reiner Z, Ryden L, Sirenko Y, Stanton A, Struijker-Boudier H, Tsioufis C, van de Borne P, Vlachopoulos C, Volpe M, Wood DA. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013;**34**:2159-2219.

490. Eikelboom JW, Wallentin L, Connolly SJ, Ezekowitz M, Healey JS, Oldgren J, Yang S, Alings M, Kaatz S, Hohnloser SH, Diener HC, Franzosi MG, Huber K, Reilly P, Varrone J, Yusuf S. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. *Circulation* 2011;**123**:2363-2372.

491. Goodman SG, Wojdyla DM, Piccini JP, White HD, Paolini JF, Nessel CC, Berkowitz SD, Mahaffey KW, Patel MR, Sherwood MW, Becker RC, Halperin JL, Hacke W, Singer DE, Hankey GJ, Breithardt G, Fox KA, Califf RM, ROCKET AF Investigators. Factors associated with major bleeding events: insights from the ROCKET AF trial (rivaroxaban once-daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation). *J Am Coll Cardiol* 2014;**63**:891-900.

492. Chang HY, Zhou M, Tang W, Alexander GC, Singh S. Risk of gastrointestinal bleeding associated with oral anticoagulants: population based retrospective cohort study. *BMJ* 2015;**350**:h1585.

493. Abraham NS, Singh S, Alexander GC, Heien H, Haas LR, Crown W, Shah ND. Comparative risk of gastrointestinal bleeding with dabigatran, rivaroxaban, and warfarin: population based cohort study. *Bmj* 2015;**350**:h1857.

494. Björck F, Renlund H, Lip GYH, Wester P, Svensson PJ, Själander A. Outcomes in a Warfarin-Treated Population With Atrial Fibrillation. *JAMA Cardiology* 2016.

495. Jacobs LG, Billett HH, Freeman K, Dinglas C, Jumaquio L. Anticoagulation for stroke prevention in elderly patients with atrial fibrillation, including those with falls and/or early-stage dementia: a single-center, retrospective, observational study. *Am J Geriatr Pharmacother* 2009;**7**:159-166.

496. Banerjee A, Clementy N, Haguenoer K, Fauchier L, Lip GY. Prior history of falls and risk of outcomes in atrial fibrillation: the Loire Valley Atrial Fibrillation Project. *Am J Med* 2014;**127**:972-978.

497. Palareti G, Cosmi B. Bleeding with anticoagulation therapy - who is at risk, and how best to identify such patients. *Thromb Haemost* 2009;**102**:268-278.

498. van Schie RM, Wadelius MI, Kamali F, Daly AK, Manolopoulos VG, de Boer A, Barallon R, Verhoef TI, Kirchheiner J, Haschke-Becher E, Briz M, Rosendaal FR, Redekop WK, Pirmohamed M, Maitland van der Zee AH. Genotype-guided dosing of coumarin derivatives: the European pharmacogenetics of anticoagulant therapy (EU-PACT) trial design. *Pharmacogenomics* 2009;**10**:1687-1695.

499. International Warfarin Pharmacogenetics Consortium, Klein TE, Altman RB, Eriksson N, Gage BF, Kimmel SE, Lee MT, Limdi NA, Page D, Roden DM, Wagner MJ, Caldwell MD, Johnson JA. Estimation of the warfarin dose with clinical and pharmacogenetic data. *N Engl J Med* 2009;**360**:753-764.

500. Schwarz UI, Ritchie MD, Bradford Y, Li C, Dudek SM, Frye-Anderson A, Kim RB, Roden DM, Stein CM. Genetic determinants of response to warfarin during initial anticoagulation. *N Engl J Med* 2008;**358**:999-1008.

501. Tang T, Liu J, Zuo K, Cheng J, Chen L, Lu C, Han S, Xu J, Jia Z, Ye M, Pei E, Zhang X, Li M. Genotype-Guided Dosing of Coumarin Anticoagulants: A Meta-analysis of Randomized Controlled Trials. *J Cardiovasc Pharmacol Ther* 2015;**20**:387-394.

502. Douketis JD, Spyropoulos AC, Kaatz S, Becker RC, Caprini JA, Dunn AS, Garcia DA, Jacobson A, Jaffer AK, Kong DF, Schulman S, Turpie AG, Hasselblad V, Ortel TL, BRIDGE Investigators. Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation. *N Engl J Med* 2015;**373**:823-833.

503. Cuker A, Siegal DM, Crowther MA, Garcia DA. Laboratory measurement of the anticoagulant activity of the non-vitamin K oral anticoagulants. *J Am Coll Cardiol* 2014;**64**:1128-1139.

504. Niessner A, Tamargo J, Morais J, Koller L, Wassmann S, Husted SE, Torp-Pedersen C, Kjeldsen K, Lewis BS, Drexel H, Kaski JC, Atar D, Storey RF, Lip GY, Verheugt FW, Agewall S. Reversal strategies for non-vitamin K antagonist oral anticoagulants: a critical appraisal of available evidence and recommendations for clinical management-a joint position paper of the European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy and European Society of Cardiology Working Group on Thrombosis. *Eur Heart J* 2015:[Epub ahead of print].

505. Hanley JP. Warfarin reversal. *J Clin Pathol* 2004;**57**:1132-1139.
506. Parry-Jones AR, Di Napoli M, Goldstein JN, Schreuder FH, Tetri S, Tatlisumak T, Yan B, van Nieuwenhuizen KM, Dequatre-Ponchelle N, Lee-Archer M, Horstmann S, Wilson D, Pomero F, Masotti L, Lerpiniere C, Godoy DA, Cohen AS, Houben R, Salman RA, Pennati P, Fenoglio L, Werring D, Veltkamp R, Wood E, Dewey HM, Cordonnier C, Klijn CJ, Meligeni F, Davis SM, Huhtakangas J, Staals J, Rosand J, Meretoja A. Reversal strategies for vitamin K antagonists in acute intracerebral hemorrhage. *Ann Neurol* 2015;**78**:54-62.
507. Goldstein JN, Refaai MA, Milling TJ, Jr., Lewis B, Goldberg-Alberts R, Hug BA, Sarode R. Four-factor prothrombin complex concentrate versus plasma for rapid vitamin K antagonist reversal in patients needing urgent surgical or invasive interventions: a phase 3b, open-label, non-inferiority, randomised trial. *Lancet* 2015;**385**:2077-2087.
508. Siegal DM, Curnutte JT, Connolly SJ, Lu G, Conley PB, Wiens BL, Mathur VS, Castillo J, Bronson MD, Leeds JM, Mar FA, Gold A, Crowther MA. Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity. *N Engl J Med* 2015;**373**:2413-2424.
509. Crowther M, Crowther MA. Antidotes for novel oral anticoagulants: current status and future potential. *Arterioscler Thromb Vasc Biol* 2015;**35**:1736-1745.
510. Staerk L, Lip GY, Olesen JB, Fosbol EL, Pallisgaard JL, Bonde AN, Gundlund A, Lindhardt TB, Hansen ML, Torp-Pedersen C, Gislason GH. Stroke and recurrent haemorrhage associated with antithrombotic treatment after gastrointestinal bleeding in patients with atrial fibrillation: nationwide cohort study. *BMJ* 2015;**351**:h5876.
511. Felmeden DC, Lip GY. Antithrombotic therapy in hypertension: a Cochrane Systematic review. *J Hum Hypertens* 2005;**19**:185-196.
512. Sharma M, Cornelius VR, Patel JP, Davies JG, Molokhia M. Efficacy and Harms of Direct Oral Anticoagulants in the Elderly for Stroke Prevention in Atrial Fibrillation and Secondary Prevention of Venous Thromboembolism: Systematic Review and Meta-Analysis. *Circulation* 2015;**132**:194-204.
513. Ruiz-Nodar JM, Marin F, Hurtado JA, Valencia J, Pinar E, Pineda J, Gimeno JR, Sogorb F, Valdes M, Lip GYH. Anticoagulant and antiplatelet therapy use in 426 patients with atrial fibrillation undergoing percutaneous coronary intervention and stent implantation implications for bleeding risk and prognosis. *J Am Coll Cardiol* 2008;**51**:818-825.
514. Hansen ML, Sorensen R, Clausen MT, Fog-Petersen ML, Raunso J, Gadsboll N, Gislason GH, Folke F, Andersen SS, Schramm TK, Abildstrom SZ, Poulsen HE, Kober L, Torp-Pedersen C. Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. *Arch Intern Med* 2010;**170**:1433-1441.
515. Lamberts M, Olesen JB, Ruwald MH, Hansen CM, Karasoy D, Kristensen SL, Kober L, Torp-Pedersen C, Gislason GH, Hansen ML. Bleeding after initiation of multiple antithrombotic drugs, including triple therapy, in atrial fibrillation patients following myocardial infarction and coronary intervention: a nationwide cohort study. *Circulation* 2012;**126**:1185-1193.
516. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Juni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2014;**35**:2541-2619.
517. Vandvik PO, Lincoff AM, Gore JM, Gutterman DD, Sonnenberg FA, Alonso-Coello P, Akl EA, Lansberg MG, Guyatt GH, Spencer FA, American College of Chest Physicians. Primary and secondary prevention of cardiovascular disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;**141**:e637S-668S.
518. Rubboli A, Faxon DP, Juhani Airaksinen KE, Schlitt A, Marin F, Bhatt DL, Lip GYH. The optimal management of patients on oral anticoagulation undergoing coronary artery stenting. The 10th Anniversary Overview. *Thromb Haemost* 2014;**112**:1080-1087.
519. Oldgren J, Wallentin L, Alexander JH, James S, Jonelid B, Steg G, Sundstrom J. New oral anticoagulants in addition to single or dual antiplatelet therapy after an acute coronary syndrome: a systematic review and meta-analysis. *Eur Heart J* 2013;**34**:1670-1680.
520. Lip GY, Windecker S, Huber K, Kirchhof P, Marin F, Ten Berg JM, Haeusler KG, Boriani G, Capodanno D, Gilard M, Zeymer U, Lane D, Storey RF, Bueno H, Collet JP, Fauchier L, Halvorsen S, Lettino M, Morais J, Mueller C, Potpara TS, Rasmussen LH, Rubboli A, Tamargo J, Valgimigli M, Zamorano JL. Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary or valve interventions: a joint

consensus document of the European Society of Cardiology Working Group on Thrombosis, European Heart Rhythm Association (EHRA), European Association of Percutaneous Cardiovascular Interventions (EAPCI) and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS) and Asia-Pacific Heart Rhythm Society (APHRS). *Eur Heart J* 2014;**35**:3155-3179.
521. Mega JL, Braunwald E, Mohanavelu S, Burton P, Poulter R, Misselwitz F, Hricak V, Barnathan ES, Bordes P, Witkowski A, Markov V, Oppenheimer L, Gibson CM, ATLAS ACS-TIMI 46 study group. Rivaroxaban versus placebo in patients with acute coronary syndromes (ATLAS ACS-TIMI 46): a randomised, double-blind, phase II trial. *Lancet* 2009;**374**:29-38.
522. Sarafoff N, Martischnig A, Wealer J, Mayer K, Mehilli J, Sibbing D, Kastrati A. Triple therapy with aspirin, prasugrel, and vitamin K antagonists in patients with drug-eluting stent implantation and an indication for oral anticoagulation. *J Am Coll Cardiol* 2013;**61**:2060-2066.
523. Jackson LR, 2nd, Ju C, Zettler M, Messenger JC, Cohen DJ, Stone GW, Baker BA, Effron M, Peterson ED, Wang TY. Outcomes of Patients With Acute Myocardial Infarction Undergoing Percutaneous Coronary Intervention Receiving an Oral Anticoagulant and Dual Antiplatelet Therapy: A Comparison of Clopidogrel Versus Prasugrel From the TRANSLATE-ACS Study. *JACC Cardiovasc Interv* 2015;**8**:1880-1889.
524. Dewilde WJM, Oirbans T, Verheugt FWA, Kelder JC, De Smet BJGL, Herrman J-P, Adriaenssens T, Vrolix M, Heestermans AACM, Vis MM, Tijsen JGP, van 't Hof AW, ten Berg JM. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet* 2013;**381**:1107-1115.
525. Braun OÖ, Bico B, Chaudhry U, Wagner H, Koul S, Tyden P, Schersten F, Jovinge S, Svensson PJ, Gustav Smith J, van der Pals J. Concomitant use of warfarin and ticagrelor as an alternative to triple antithrombotic therapy after an acute coronary syndrome. *Thromb Res* 2015;**135**:26-30.
526. Nikolaidou T, Channer KS. Chronic atrial fibrillation: a systematic review of medical heart rate control management. *Postgrad Med J* 2009;**85**:303-312.
527. Tamariz LJ, Bass EB. Pharmacological rate control of atrial fibrillation. *Cardiol Clin* 2004;**22**:35-45.
528. Segal JB, McNamara RL, Miller MR, Kim N, Goodman SN, Powe NR, Robinson K, Yu D, Bass EB. The evidence regarding the drugs used for ventricular rate control. In. *J Fam Practice*; 2000, 47-59.
529. Schreck DM, Rivera AR, Tricarico VJ. Emergency management of atrial fibrillation and flutter: intravenous diltiazem versus intravenous digoxin. *Ann Emerg Med* 1997;**29**:135-140.
530. Siu CW, Lau CP, Lee WL, Lam KF, Tse HF. Intravenous diltiazem is superior to intravenous amiodarone or digoxin for achieving ventricular rate control in patients with acute uncomplicated atrial fibrillation. *Crit Care Med* 2009;**37**:2174-2179; quiz 2180.
531. Tisdale JE, Padhi ID, Goldberg AD, Silverman NA, Webb CR, Higgins RS, Paone G, Frank DM, Borzak S. A randomized, double-blind comparison of intravenous diltiazem and digoxin for atrial fibrillation after coronary artery bypass surgery. *Am Heart J* 1998;**135**:739-747.
532. Scheuermeyer FX, Grafstein E, Stenstrom R, Christenson J, Heslop C, Heilbron B, McGrath L, Innes G. Safety and efficiency of calcium channel blockers versus beta-blockers for rate control in patients with atrial fibrillation and no acute underlying medical illness. *Acad Emerg Med* 2013;**20**:222-230.
533. Darby AE, Dimarco JP. Management of atrial fibrillation in patients with structural heart disease. *Circulation* 2012;**125**:945-957.
534. Elkayam U. Calcium channel blockers in heart failure. *Cardiology* 1998;**89 Suppl 1**:38-46.
535. Goldstein RE, Boccuzzi SJ, Cruess D, Nattel S. Diltiazem increases late-onset congestive heart failure in postinfarction patients with early reduction in ejection fraction. The Adverse Experience Committee; and the Multicenter Diltiazem Postinfarction Research Group. *Circulation* 1991;**83**:52-60.
536. Clemo HF, Wood MA, Gilligan DM, Ellenbogen KA. Intravenous amiodarone for acute heart rate control in the critically ill patient with atrial tachyarrhythmias. *Am J Cardiol* 1998;**81**:594-598.
537. Delle Karth G, Geppert A, Neunteufl T, Priglinger U, Haumer M, Gschwandtner M, Siostrzonek P, Heinz G. Amiodarone versus diltiazem for rate control in critically ill patients with atrial tachyarrhythmias. *Crit Care Med* 2001;**29**:1149-1153.
538. Hou ZY, Chang MS, Chen CY, Tu MS, Lin SL, Chiang HT, Woosley RL. Acute treatment of recent-onset atrial fibrillation and flutter with a tailored dosing regimen of intravenous amiodarone. A randomized, digoxin-controlled study. *Eur Heart J* 1995;**16**:521-528.

539. National Institute for Health and Care Excellence (NICE). *Atrial fibrillation: management. NICE guidelines [CG180]*. http://www.nice.org.uk/guidance/cg180/. Date last accessed 5 May 2016 Accessed 15/09/2014; http://www.nice.org.uk/guidance/cg180/
540. Kotecha D, Manzano L, Krum H, Rosano G, Holmes J, Altman DG, Collins P, Packer M, Wikstrand J, Coats AJS, Cleland JGF, Kirchhof P, von Lueder TG, Rigby A, Andersson B, Lip GYH, van Veldhuisen DJ, Shibata MC, Wedel H, Böhm M, Flather MD, Beta-Blockers in Heart Failure Collaborative Group. Effect of age and sex on efficacy and tolerability of β blockers in patients with heart failure with reduced ejection fraction: individual patient data meta-analysis. *BMJ* 2016;**353**:i1855.
541. Ulimoen SR, Enger S, Carlson J, Platonov PG, Pripp AH, Abdelnoor M, Arnesen H, Gjesdal K, Tveit A. Comparison of four single-drug regimens on ventricular rate and arrhythmia-related symptoms in patients with permanent atrial fibrillation. *Am J Cardiol* 2013;**111**:225-230.
542. Ulimoen SR, Enger S, Pripp AH, Abdelnoor M, Arnesen H, Gjesdal K, Tveit A. Calcium channel blockers improve exercise capacity and reduce N-terminal Pro-B-type natriuretic peptide levels compared with beta-blockers in patients with permanent atrial fibrillation. *Eur Heart J* 2014;**35**:517-524.
543. Goldberger ZD, Alexander GC. Digitalis use in contemporary clinical practice: refitting the foxglove. *JAMA Intern Med* 2014;**174**:151-154.
544. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997;**336**:525-533.
545. Ahmed A, Rich MW, Fleg JL, Zile MR, Young JB, Kitzman DW, Love TE, Aronow WS, Adams KF, Jr., Gheorghiade M. Effects of digoxin on morbidity and mortality in diastolic heart failure: the ancillary digitalis investigation group trial. *Circulation* 2006;**114**:397-403.
546. Ziff OJ, Kotecha D. Digoxin: The good and the bad. *Trends in Cardiovascular Medicine* 2016:[Epub ahead of print].
547. Turakhia MP, Santangeli P, Winkelmayer WC, Xu X, Ullal AJ, Than CT, Schmitt S, Holmes TH, Frayne SM, Phibbs CS, Yang F, Hoang DD, Ho PM, Heidenreich PA. Increased mortality associated with digoxin in contemporary patients with atrial fibrillation: findings from the TREAT-AF study. *J Am Coll Cardiol* 2014;**64**:660-668.
548. Hallberg P, Lindback J, Lindahl B, Stenestrand U, Melhus H. Digoxin and mortality in atrial fibrillation: a prospective cohort study. *Eur J Clin Pharmacol* 2007;**63**:959-971.
549. Whitbeck MG, Charnigo RJ, Khairy P, Ziada K, Bailey AL, Zegarra MM, Shah J, Morales G, Macaulay T, Sorrell VL, Campbell CL, Gurley J, Anaya P, Nasr H, Bai R, Di Biase L, Booth DC, Jondeau G, Natale A, Roy D, Smyth S, Moliterno DJ, Elayi CS. Increased mortality among patients taking digoxin--analysis from the AFFIRM study. *Eur Heart J* 2013;**34**:1481-1488.
550. Gheorghiade M, Fonarow GC, van Veldhuisen DJ, Cleland JG, Butler J, Epstein AE, Patel K, Aban IB, Aronow WS, Anker SD, Ahmed A. Lack of evidence of increased mortality among patients with atrial fibrillation taking digoxin: findings from post hoc propensity-matched analysis of the AFFIRM trial. *Eur Heart J* 2013;**34**:1489-1497.
551. Flory JH, Ky B, Haynes K, S MB, Munson J, Rowan C, Strom BL, Hennessy S. Observational cohort study of the safety of digoxin use in women with heart failure. *BMJ Open* 2012;**2**:e000888.
552. Andrey JL, Romero S, Garcia-Egido A, Escobar MA, Corzo R, Garcia-Dominguez G, Lechuga V, Gomez F. Mortality and morbidity of heart failure treated with digoxin. A propensity-matched study. *Int J Clin Pract* 2011;**65**:1250-1258.
553. Allen LA, Fonarow GC, Simon DN, Thomas LE, Marzec LN, Pokorney SD, Gersh BJ, Go AS, Hylek EM, Kowey PR, Mahaffey KW, Chang P, Peterson ED, Piccini JP, ORBIT-AF Investigators. Digoxin Use and Subsequent Outcomes Among Patients in a Contemporary Atrial Fibrillation Cohort. *J Am Coll Cardiol* 2015;**65**:2691-2698.
554. Khand AU, Rankin AC, Martin W, Taylor J, Gemmell I, Cleland JG. Carvedilol alone or in combination with digoxin for the management of atrial fibrillation in patients with heart failure? *J Am Coll Cardiol* 2003;**42**:1944-1951.
555. Farshi R, Kistner D, Sarma JS, Longmate JA, Singh BN. Ventricular rate control in chronic atrial fibrillation during daily activity and programmed exercise: a crossover open-label study of five drug regimens. *J Am Coll Cardiol* 1999;**33**:304-310.
556. Koh KK, Kwon KS, Park HB, Baik SH, Park SJ, Lee KH, Kim EJ, Kim SH, Cho SK, Kim SS. Efficacy and safety of digoxin alone and in combination with low-dose diltiazem or betaxolol to control ventricular rate in chronic atrial fibrillation. *Am J Cardiol* 1995;**75**:88-90.
557. Lewis RV, McMurray J, McDevitt DG. Effects of atenolol, verapamil, and xamoterol on heart rate and exercise tolerance in digitalised patients with chronic atrial fibrillation. *J Cardiovasc Pharmacol* 1989;**13**:1-6.

558. Tsuneda T, Yamashita T, Fukunami M, Kumagai K, Niwano S, Okumura K, Inoue H. Rate control and quality of life in patients with permanent atrial fibrillation: the Quality of Life and Atrial Fibrillation (QOLAF) Study. *Circ J* 2006;**70**:965-970.
559. ClinicalTrials.gov. *Rate Control Therapy Evaluation in Permanent Atrial Fibrillation (RATE-AF)*. https://clinicaltrials.gov/ct2/show/NCT02391337. Date last accessed 5 May 2016
560. 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, RACE II Investigators. Lenient versus strict rate control in patients with atrial fibrillation. *N Engl J Med* 2010;**362**:1363-1373.
561. Groenveld HF, Crijns HJ, Van den Berg MP, Van Sonderen E, Alings AM, Tijssen JG, Hillege HL, Tuininga YS, Van Veldhuisen DJ, Ranchor AV, Van Gelder IC, RACE II Investigators. The effect of rate control on quality of life in patients with permanent atrial fibrillation: data from the RACE II (Rate Control Efficacy in Permanent Atrial Fibrillation II) study. *J Am Coll Cardiol* 2011;**58**:1795-1803.
562. Van Gelder IC, Wyse DG, Chandler ML, Cooper HA, Olshansky B, Hagens VE, Crijns HJ, RACE and AFFIRM Investigators. Does intensity of rate-control influence outcome in atrial fibrillation? An analysis of pooled data from the RACE and AFFIRM studies. *Europace* 2006;**8**:935-942.
563. Queiroga A, Marshall HJ, Clune M, Gammage MD. Ablate and pace revisited: long term survival and predictors of permanent atrial fibrillation. *Heart* 2003;**89**:1035-1038.
564. Lim KT, Davis MJ, Powell A, Arnolda L, Moulden K, Bulsara M, Weerasooriya R. Ablate and pace strategy for atrial fibrillation: long-term outcome of AIRCRAFT trial. *Europace* 2007;**9**:498-505.
565. Geelen P, Brugada J, Andries E, Brugada P. Ventricular fibrillation and sudden death after radiofrequency catheter ablation of the atrioventricular junction. *Pacing Clin Electrophysiol* 1997;**20**:343-348.
566. Wang RX, Lee HC, Hodge DO, Cha YM, Friedman PA, Rea RF, Munger TM, Jahangir A, Srivathsan K, Shen WK. Effect of pacing method on risk of sudden death after atrioventricular node ablation and pacemaker implantation in patients with atrial fibrillation. *Heart Rhythm* 2013;**10**:696-701.
567. Chatterjee NA, Upadhyay GA, Ellenbogen KA, McAlister FA, Choudhry NK, Singh JP. Atrioventricular nodal ablation in atrial fibrillation: a meta-analysis and systematic review. *Circ Arrhythm Electrophysiol* 2012;**5**:68-76.
568. Bradley DJ, Shen WK. Overview of management of atrial fibrillation in symptomatic elderly patients: pharmacologic therapy versus AV node ablation. *Clin Pharmacol Ther* 2007;**81**:284-287.
569. Wood MA, Brown-Mahoney C, Kay GN, Ellenbogen KA. Clinical outcomes after ablation and pacing therapy for atrial fibrillation : a meta-analysis. *Circulation* 2000;**101**:1138-1144.
570. Ozcan C, Jahangir A, Friedman PA, Patel PJ, Munger TM, Rea RF, Lloyd MA, Packer DL, Hodge DO, Gersh BJ, Hammill SC, Shen WK. Long-term survival after ablation of the atrioventricular node and implantation of a permanent pacemaker in patients with atrial fibrillation. *N Engl J Med* 2001;**344**:1043-1051.
571. Hess PL, Jackson KP, Hasselblad V, Al-Khatib SM. Is cardiac resynchronization therapy an antiarrhythmic therapy for atrial fibrillation? A systematic review and meta-analysis. *Curr Cardiol Rep* 2013;**15**:330.
572. Hoppe UC, Casares JM, Eiskjaer H, Hagemann A, Cleland JG, Freemantle N, Erdmann E. Effect of cardiac resynchronization on the incidence of atrial fibrillation in patients with severe heart failure. *Circulation* 2006;**114**:18-25.
573. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, Cleland J, Deharo JC, Delgado V, Elliott PM, Gorenek B, Israel CW, Leclercq C, Linde C, Mont L, Padeletti L, Sutton R, Vardas PE, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Kirchhof P, Blomstrom-Lundqvist C, Badano LP, Aliyev F, Bansch D, Baumgartner H, Bsata W, Buser P, Charron P, Daubert JC, Dobreanu D, Faerestrand S, Hasdai D, Hoes AW, Le Heuzey JY, Mavrakis H, McDonagh T, Merino JL, Nawar MM, Nielsen JC, Pieske B, Poposka L, Ruschitzka F, Tendera M, Van Gelder IC, Wilson CM. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Eur Heart J* 2013;**34**:2281-2329.
574. Chatterjee NA, Upadhyay GA, Ellenbogen KA, Hayes DL, Singh JP. Atrioventricular nodal ablation in atrial fibrillation: a meta-analysis of biventricular vs. right ventricular pacing mode. *Eur J Heart Fail* 2012;**14**:661-667.

575. Lewis RV, Irvine N, McDevitt DG. Relationships between heart rate, exercise tolerance and cardiac output in atrial fibrillation: the effects of treatment with digoxin, verapamil and diltiazem. *Eur Heart J* 1988;**9**:777-781.
576. Mulder BA, Van Veldhuisen DJ, Crijns HJ, Tijssen JG, Hillege HL, Alings M, Rienstra M, Van den Berg MP, Van Gelder IC, RACE II Investigators. Digoxin in patients with permanent atrial fibrillation: data from the RACE II study. *Heart Rhythm* 2014;**11**:1543-1550.
577. Koh KK, Song JH, Kwon KS, Park HB, Baik SH, Park YS, In HH, Moon TH, Park GS, Cho SK, Kim SS. Comparative study of efficacy and safety of low-dose diltiazem or betaxolol in combination with digoxin to control ventricular rate in chronic atrial fibrillation: randomized crossover study. *Int J Cardiol* 1995;**52**:167-174.
578. Chatterjee S, Sardar P, Lichstein E, Mukherjee D, Aikat S. Pharmacologic rate versus rhythm-control strategies in atrial fibrillation: an updated comprehensive review and meta-analysis. *PACE* 2013;**36**:122-133.
579. de Denus S, Sanoski CA, Carlsson J, Opolski G, Spinler SA. Rate vs rhythm control in patients with atrial fibrillation: a meta-analysis. *Arch Intern Med* 2005;**165**:258-262.
580. Lafuente-Lafuente C, Longas-Tejero MA, Bergmann JF, Belmin J. Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation. *Cochrane Database Syst Rev* 2012;**5**:CD005049.
581. Roy D, Talajic M, Dorian P, Connolly S, Eisenberg MJ, Green M, Kus T, Lambert J, Dubuc M, Gagne P, Nattel S, Thibault B. Amiodarone to prevent recurrence of atrial fibrillation. Canadian Trial of Atrial Fibrillation Investigators. *N Engl J Med* 2000;**342**:913-920.
582. Roy D, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, Bourassa MG, Arnold JM, Buxton AE, Camm AJ, Connolly SJ, Dubuc M, Ducharme A, Guerra PG, Hohnloser SH, Lambert J, Le Heuzey JY, O'Hara G, Pedersen OD, Rouleau JL, Singh BN, Stevenson LW, Stevenson WG, Thibault B, Waldo AL. Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med* 2008;**358**:2667-2677.
583. Singh BN, Connolly SJ, Crijns HJ, Roy D, Kowey PR, Capucci A, Radzik D, Aliot EM, Hohnloser SH. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. *N Engl J Med* 2007;**357**:987-999.
584. 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.
585. 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.
586. 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 AF Trial Investigators. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. *JAMA* 2010;**303**:333-340.
587. 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 Investigators. 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.
588. Hohnloser SH, Crijns HJ, van Eickels M, Gaudin C, Page RL, Torp-Pedersen C, Connolly SJ. Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med* 2009;**360**:668-678.
589. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, Kellen JC, Greene HL, Mickel MC, Dalquist JE, Corley SD. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002;**347**:1825-1833.
590. Van Gelder IC, Hagens VE, Bosker HA, Kingma JH, Kamp O, Kingma T, Said SA, Darmanata JI, Timmermans AJ, Tijssen JG, Crijns HJ, Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation Study Group. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med* 2002;**347**:1834-1840.
591. Opolski G, Torbicki A, Kosior DA, Szulc M, Wozakowska-Kaplon B, Kolodziej P, Achremczyk P, Investigators of the Polish How to Treat Chronic Atrial Fibrillation Study. Rate control vs rhythm control in patients with nonvalvular persistent atrial fibrillation: the results of the Polish How to Treat Chronic Atrial Fibrillation (HOT CAFE) Study. *Chest* 2004;**126**:476-486.

592. Kong MH, Shaw LK, O'Connor C, Califf RM, Blazing MA, Al-Khatib SM. Is rhythm-control superior to rate-control in patients with atrial fibrillation and diastolic heart failure? *Ann Noninvasive Electrocardiol* 2010;**15**:209-217.
593. 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.
594. ClinicalTrials.gov. *Catheter Ablation vs Anti-arrhythmic Drug Therapy for Atrial Fibrillation Trial (CABANA)*. https://clinicaltrials.gov/ct2/show/NCT00911508. Date last accessed 5 May 2016 NLM Identifier: NCT00911508 [Accessed 20-May-2015]
595. Khan IA. Oral loading single dose flecainide for pharmacological cardioversion of recent-onset atrial fibrillation. *Int J Cardiol* 2003;**87**:121-128.
596. Chevalier P, Durand-Dubief A, Burri H, Cucherat M, Kirkorian G, Touboul P. Amiodarone versus placebo and class Ic drugs for cardioversion of recent-onset atrial fibrillation: a meta-analysis. *J Am Coll Cardiol* 2003;**41**:255-262.
597. Letelier LM, Udol K, Ena J, Weaver B, Guyatt GH. Effectiveness of amiodarone for conversion of atrial fibrillation to sinus rhythm: a meta-analysis. *Arch Intern Med* 2003;**163**:777-785.
598. Khan IA, Mehta NJ, Gowda RM. Amiodarone for pharmacological cardioversion of recent-onset atrial fibrillation. *Int J Cardiol* 2003;**89**:239-248.
599. Thomas SP, Guy D, Wallace E, Crampton R, Kijvanit P, Eipper V, Ross DL, Cooper MJ. Rapid loading of sotalol or amiodarone for management of recent onset symptomatic atrial fibrillation: a randomized, digoxin-controlled trial. *Am Heart J* 2004;**147**:E3.
600. Vijayalakshmi K, Whittaker VJ, Sutton A, Campbell P, Wright RA, Hall JA, Harcombe AA, Linker NJ, Stewart MJ, Davies A, de Belder MA. A randomized trial of prophylactic antiarrhythmic agents (amiodarone and sotalol) in patients with atrial fibrillation for whom direct current cardioversion is planned. *Am Heart J* 2006;**151**:863 e861-866.
601. Singh BN, Singh SN, Reda DJ, Tang XC, Lopez B, Harris CL, Fletcher RD, Sharma SC, Atwood JE, Jacobson AK, Lewis HD, Jr., Raisch DW, Ezekowitz MD. Amiodarone versus sotalol for atrial fibrillation. *N Engl J Med* 2005;**352**:1861-1872.
602. Roy D, Pratt CM, Torp-Pedersen C, Wyse DG, Toft E, Juul-Moller S, Nielsen T, Rasmussen SL, Stiell IG, Coutu B, Ip JH, Pritchett EL, Camm AJ. Vernakalant hydrochloride for rapid conversion of atrial fibrillation: a phase 3, randomized, placebo-controlled trial. *Circulation* 2008;**117**:1518-1525.
603. Kowey PR, Dorian P, Mitchell LB, Pratt CM, Roy D, Schwartz PJ, Sadowski J, Sobczyk D, Bochenek A, Toft E. Vernakalant hydrochloride for the rapid conversion of atrial fibrillation after cardiac surgery: a randomized, double-blind, placebo-controlled trial. *Circ Arrhythm Electrophysiol* 2009;**2**:652-659.
604. Camm AJ, Capucci A, Hohnloser SH, Torp-Pedersen C, Van Gelder IC, Mangal B, Beatch G. A randomized active-controlled study comparing the efficacy and safety of vernakalant to amiodarone in recent-onset atrial fibrillation. *J Am Coll Cardiol* 2011;**57**:313-321.
605. Bash LD, Buono JL, Davies GM, Martin A, Fahrbach K, Phatak H, Avetisyan R, Mwamburi M. Systematic review and meta-analysis of the efficacy of cardioversion by vernakalant and comparators in patients with atrial fibrillation. *Cardiovasc Drugs Ther* 2012;**26**:167-179.
606. Falk RH, Pollak A, Singh SN, Friedrich T. Intravenous dofetilide, a class III antiarrhythmic agent, for the termination of sustained atrial fibrillation or flutter. Intravenous Dofetilide Investigators [see comments]. *J Am Coll Cardiol* 1997;**29**:385-390.
607. Dankner R, Shahar A, Novikov I, Agmon U, Ziv A, Hod H. Treatment of stable atrial fibrillation in the emergency department: a population-based comparison of electrical direct-current versus pharmacological cardioversion or conservative management. *Cardiology* 2009;**112**:270-278.
608. Chen WS, Gao BR, Chen WQ, Li ZZ, Xu ZY, Zhang YH, Yang K, Guan XQ. Comparison of pharmacological and electrical cardioversion in permanent atrial fibrillation after prosthetic cardiac valve replacement: a prospective randomized trial. *J Int Med Res* 2013;**41**:1067-1073.
609. Gitt AK, Smolka W, Michailov G, Bernhardt A, Pittrow D, Lewalter T. Types and outcomes of cardioversion in patients admitted to hospital for atrial fibrillation: results of the German RHYTHM-AF Study. *Clin Res Cardiol* 2013;**102**:713-723.
610. Cristoni L, Tampieri A, Mucci F, Iannone P, Venturi A, Cavazza M, Lenzi T. Cardioversion of acute atrial fibrillation in the short observation unit: comparison of a protocol focused on electrical cardioversion with simple antiarrhythmic treatment. *Emerg Med J* 2011;**28**:932-937.
611. Bellone A, Etteri M, Vettorello M, Bonetti C, Clerici D, Gini G, Maino C, Mariani M, Natalizi A, Nessi I, Rampoldi A, Colombo L. Cardioversion of acute atrial fibrillation in the emergency department: a prospective randomised trial. *Emerg Med J* 2012;**29**:188-191.
612. Crijns HJ, Weijs B, Fairley AM, Lewalter T, Maggioni AP, Martin A, Ponikowski P, Rosenqvist M, Sanders P, Scanavacca M, Bash LD, Chazelle F, Bernhardt A, Gitt AK, Lip GY, Le Heuzey JY.

Contemporary real life cardioversion of atrial fibrillation: Results from the multinational RHYTHM-AF study. *Int J Cardiol* 2014;**172**:588-594.
613. Lip GY, Gitt AK, Le Heuzey JY, Bash LD, Morabito CJ, Bernhardt AA, Sisk CM, Chazelle F, Crijns HJ. Overtreatment and undertreatment with anticoagulation in relation to cardioversion of atrial fibrillation (the RHYTHM-AF study). *Am J Cardiol* 2014;**113**:480-484.
614. Reisinger J, Gatterer E, Lang W, Vanicek T, Eisserer G, Bachleitner T, Niemeth C, Aicher F, Grander W, Heinze G, Kuhn P, Siostrzonek P. Flecainide versus ibutilide for immediate cardioversion of atrial fibrillation of recent onset. *Eur Heart J* 2004;**25**:1318-1324.
615. Stambler BS, Wood MA, Ellenbogen KA, Perry KT, Wakefield LK, VanderLugt JT. Efficacy and safety of repeated intravenous doses of ibutilide for rapid conversion of atrial flutter or fibrillation. Ibutilide Repeat Dose Study Investigators. *Circulation* 1996;**94**:1613-1621.
616. Torp-Pedersen C, Camm AJ, Butterfield NN, Dickinson G, Beatch GN. Vernakalant: conversion of atrial fibrillation in patients with ischemic heart disease. *Int J Cardiol* 2013;**166**:147-151.
617. Savelieva I, Graydon R, Camm AJ. Pharmacological cardioversion of atrial fibrillation with vernakalant: evidence in support of the ESC Guidelines. *Europace* 2014;**16**:162-173.
618. Simon A, Niederdoeckl J, Skyllouriotis E, Schuetz N, Herkner H, Weiser C, Laggner AN, Domanovits H, Spiel AO. Vernakalant is superior to ibutilide for achieving sinus rhythm in patients with recent-onset atrial fibrillation: a randomized controlled trial at the emergency department. *Europace* 2016;**10.1093/europace/euw052**:[Epub ahead of print].
619. Reisinger J, Gatterer E, Heinze G, Wiesinger K, Zeindlhofer E, Gattermeier M, Poelzl G, Kratzer H, Ebner A, Hohenwallner W, Lenz K, Slany J, Kuhn P. Prospective comparison of flecainide versus sotalol for immediate cardioversion of atrial fibrillation. *Am J Cardiol* 1998;**81**:1450-1454.
620. Alboni P, Botto GL, Baldi N, Luzi M, Russo V, Gianfranchi L, Marchi P, Calzolari M, Solano A, Baroffio R, Gaggioli G. Outpatient treatment of recent-onset atrial fibrillation with the "pill-in-the-pocket" approach. *N Engl J Med* 2004;**351**:2384-2391.
621. Saborido CM, Hockenhull J, Bagust A, Boland A, Dickson R, Todd D. Systematic review and cost-effectiveness evaluation of 'pill-in-the-pocket' strategy for paroxysmal atrial fibrillation compared to episodic in-hospital treatment or continuous antiarrhythmic drug therapy. *Health Technol Assess* 2010;**14**:iii-iv, 1-75.
622. Khan IA. Single oral loading dose of propafenone for pharmacological cardioversion of recent-onset atrial fibrillation. *J Am Coll Cardiol* 2001;**37**:542-547.
623. Stroobandt R, Stiels B, Hoebrechts R. Propafenone for conversion and prophylaxis of atrial fibrillation. Propafenone Atrial Fibrillation Trial Investigators. *Am J Cardiol* 1997;**79**:418-423.
624. Hughes C, Sunderji R, Gin K. Oral propafenone for rapid conversion of recent onset atrial fibrillation - A review. *CAN J CARDIOL. Canadian Journal of Cardiology* 1997;**13**:839-842.
625. Zhang N, Guo JH, Zhang H, Li XB, Zhang P, Xn Y. Comparison of intravenous ibutilide vs. propafenone for rapid termination of recent onset atrial fibrillation. *Int J Clin Pract* 2005;**59**:1395-1400.
626. Mittal S, Ayati S, Stein KM, Schwartzman D, Cavlovich D, Tchou PJ, Markowitz SM, Slotwiner DJ, Scheiner MA, Lerman BB. Transthoracic cardioversion of atrial fibrillation: comparison of rectilinear biphasic versus damped sine wave monophasic shocks. *Circulation* 2000;**101**:1282-1287.
627. Kirchhof P, Eckardt L, Loh P, Weber K, Fischer RJ, Seidl KH, Böcker D, Breithardt G, Haverkamp W, Borggrefe M. Anterior-posterior versus anterior-lateral electrode positions for external cardioversion of atrial fibrillation: a randomised trial. *Lancet* 2002;**360**:1275-1279.
628. Kirchhof P, Monnig G, Wasmer K, Heinecke A, Breithardt G, Eckardt L, Bocker D. A trial of self-adhesive patch electrodes and hand-held paddle electrodes for external cardioversion of atrial fibrillation (MOBIPAPA). *Eur Heart J* 2005;**26**:1292-1297.
629. Furniss SS, Sneyd JR. Safe sedation in modern cardiological practice. *Heart* 2015;**101**:1526-1530.
630. Alp N, Rahman S, Bell J, Shahi M. Randomised comparison of antero-lateral versus antero-posterior paddle positions for DC cardioversion of persistent atrial fibrillation. *Int J Cardiol* 2000;**75**:211-216.
631. Singh SN, Tang XC, Reda D, Singh BN. Systematic electrocardioversion for atrial fibrillation and role of antiarrhythmic drugs: a substudy of the SAFE-T trial. *Heart Rhythm* 2009;**6**:152-155.
632. Channer KS, Birchall A, Steeds RP, Walters SJ, Yeo WW, West JN, Muthusamy R, Rhoden WE, Saeed BT, Batin P, Brooksby WP, Wilson I, Grant S. A randomized placebo-controlled trial of pre-treatment and short- or long-term maintenance therapy with amiodarone supporting DC cardioversion for persistent atrial fibrillation. *Eur Heart J* 2004;**25**:144-150.
633. Oral H, Souza JJ, Michaud GF, Knight BP, Goyal R, Strickberger SA, Morady F. Facilitating transthoracic cardioversion of atrial fibrillation with ibutilide pretreatment. *N Engl J Med* 1999;**340**:1849-1854.

634. Mussigbrodt A, John S, Kosiuk J, Richter S, Hindricks G, Bollmann A. Vernakalant-facilitated electrical cardioversion: comparison of intravenous vernakalant and amiodarone for drug-enhanced electrical cardioversion of atrial fibrillation after failed electrical cardioversion. *Europace* 2016;**18**:51-56.
635. Bianconi L, Mennuni M, Lukic V, Castro A, Chieffi M, Santini M. Effects of oral propafenone administration before electrical cardioversion of chronic atrial fibrillation: a placebo-controlled study. *J Am Coll Cardiol* 1996;**28**:700-706.
636. Nergardh AK, Rosenqvist M, Nordlander R, Frick M. Maintenance of sinus rhythm with metoprolol CR initiated before cardioversion and repeated cardioversion of atrial fibrillation: a randomized double-blind placebo-controlled study. *Eur Heart J* 2007;**28**:1351-1357.
637. Hemels ME, Van Noord T, Crijns HJ, Van Veldhuisen DJ, Veeger NJ, Bosker HA, Wiesfeld AC, Van den Berg MP, Ranchor AV, Van Gelder IC. Verapamil versus digoxin and acute versus routine serial cardioversion for the improvement of rhythm control for persistent atrial fibrillation. *J Am Coll Cardiol* 2006;**48**:1001-1009.
638. Villani GQ, Piepoli MF, Terracciano C, Capucci A. Effects of diltiazem pretreatment on direct-current cardioversion in patients with persistent atrial fibrillation: a single-blind, randomized, controlled study. *Am Heart J* 2000;**140**:e12.
639. De Simone A, Stabile G, Vitale DF, Turco P, Di Stasio M, Petrazzuoli F, Gasparini M, De Matteis C, Rotunno R, Di Napoli T. Pretreatment with verapamil in patients with persistent or chronic atrial fibrillation who underwent electrical cardioversion. *J Am Coll Cardiol* 1999;**34**:810-814.
640. The Digitalis in Acute Atrial Fibrillation (DAAF) Trial Group. Intravenous digoxin in acute atrial fibrillation. Results of a randomized, placebo-controlled multicentre trial in 239 patients. *Eur Heart J* 1997;**18**:649-654.
641. Atarashi H, Inoue H, Fukunami M, Sugi K, Hamada C, Origasa H. Double-blind placebo-controlled trial of aprindine and digoxin for the prevention of symptomatic atrial fibrillation. *Circ J* 2002;**66**:553-556.
642. Airaksinen KE, Gronberg T, Nuotio I, Nikkinen M, Ylitalo A, Biancari F, Hartikainen JE. Thromboembolic complications after cardioversion of acute atrial fibrillation: the FinCV (Finnish CardioVersion) study. *J Am Coll Cardiol* 2013;**62**:1187-1192.
643. Hansen ML, Jepsen RM, Olesen JB, Ruwald MH, Karasoy D, Gislason GH, Hansen J, Kober L, Husted S, Torp-Pedersen C. Thromboembolic risk in 16 274 atrial fibrillation patients undergoing direct current cardioversion with and without oral anticoagulant therapy. *Europace* 2015;**17**:18-23.
644. Schadlich PK, Schmidt-Lucke C, Huppertz E, Lehmacher W, Nixdorff U, Stellbrink C, Brecht JG. Economic evaluation of enoxaparin for anticoagulation in early cardioversion of persisting nonvalvular atrial fibrillation: a statutory health insurance perspective from Germany. *Am J Cardiovasc Drugs* 2007;**7**:199-217.
645. Schmidt-Lucke C, Paar WD, Stellbrink C, Nixdorff U, Hofmann T, Meurer J, Grewe R, Daniel WG, Hanrath P, Mugge A, Klein HU, Schmidt-Lucke JA. Quality of anticoagulation with unfractionated heparin plus phenprocoumon for the prevention of thromboembolic complications in cardioversion for non-valvular atrial fibrillation. Sub-analysis from the Anticoagulation in Cardioversion using Enoxaparin (ACE) trial. *Thromb Res* 2007;**119**:27-34.
646. Stellbrink C, Nixdorff U, Hofmann T, Lehmacher W, Daniel WG, Hanrath P, Geller C, Mugge A, Sehnert W, Schmidt-Lucke C, Schmidt-Lucke JA. Safety and efficacy of enoxaparin compared with unfractionated heparin and oral anticoagulants for prevention of thromboembolic complications in cardioversion of nonvalvular atrial fibrillation: the Anticoagulation in Cardioversion using Enoxaparin (ACE) trial. *Circulation* 2004;**109**:997-1003.
647. Nuotio I, Hartikainen JE, Gronberg T, Biancari F, Airaksinen KE. Time to cardioversion for acute atrial fibrillation and thromboembolic complications. *JAMA* 2014;**312**:647-649.
648. Klein AL, Grimm RA, Murray RD, Apperson-Hansen C, Asinger RW, Black IW, Davidoff R, Erbel R, Halperin JL, Orsinelli DA, Porter TR, Stoddard MF. Use of transesophageal echocardiography to guide cardioversion in patients with atrial fibrillation. *N Engl J Med* 2001;**344**:1411-1420.
649. Cappato R, Ezekowitz MD, Klein AL, Camm AJ, Ma CS, Le Heuzey JY, Talajic M, Scanavacca M, Vardas PE, Kirchhof P, Hemmrich M, Lanius V, Meng IL, Wildgoose P, van Eickels M, Hohnloser SH, Investigators XV. Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial fibrillation. *Eur Heart J* 2014;**35**:3346-3355.
650. 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.

651. Singh SN, Fletcher RD, Fisher SG, Singh BN, Lewis HD, Deedwania PC, Massie BM, Colling C, Lazzeri D. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure. *N Engl J Med* 1995;**333**:77-82.
652. Kirchhof P, Franz MR, Bardai A, Wilde AM. Giant T-U waves precede torsades de pointes in long QT syndrome: a systematic electrocardiographic analysis in patients with acquired and congenital QT prolongation. *J Am Coll Cardiol* 2009;**54**:143-149.
653. Goldschlager N, Epstein AE, Naccarelli GV, Olshansky B, Singh B, Collard HR, Murphy E. A practical guide for clinicians who treat patients with amiodarone: 2007. *Heart Rhythm* 2007;**4**:1250-1259.
654. Wolkove N, Baltzan M. Amiodarone pulmonary toxicity. *Can Respir J* 2009;**16**:43-48.
655. Ahmed S, Rienstra M, Crijns HJ, Links TP, Wiesfeld AC, Hillege HL, Bosker HA, Lok DJ, Van Veldhuisen DJ, Van Gelder IC. Continuous vs episodic prophylactic treatment with amiodarone for the prevention of atrial fibrillation: a randomized trial. *JAMA* 2008;**300**:1784-1792.
656. Davy JM, Herold M, Hoglund C, Timmermans A, Alings A, Radzik D, Van Kempen L. Dronedarone for the control of ventricular rate in permanent atrial fibrillation: the Efficacy and safety of dRonedArone for the cOntrol of ventricular rate during atrial fibrillation (ERATO) study. *Am Heart J* 2008;**156**:527 e521-529.
657. Kober L, Torp-Pedersen C, McMurray JJ, Gotzsche O, Levy S, Crijns H, Amlie J, Carlsen J, Dronedarone Study Group. Increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med* 2008;**358**:2678-2687.
658. Connolly SJ, Camm AJ, Halperin JL, Joyner C, Alings M, Amerena J, Atar D, Avezum A, Blomstrom P, Borggrefe M, Budaj A, Chen SA, Ching CK, Commerford P, Dans A, Davy JM, Delacretaz E, Di Pasquale G, Diaz R, Dorian P, Flaker G, Golitsyn S, Gonzalez-Hermosillo A, Granger CB, Heidbuchel H, Kautzner J, Kim JS, Lanas F, Lewis BS, Merino JL, Morillo C, Murin J, Narasimhan C, Paolasso E, Parkhomenko A, Peters NS, Sim KH, Stiles MK, Tanomsup S, Toivonen L, Tomcsanyi J, Torp-Pedersen C, Tse HF, Vardas P, Vinereanu D, Xavier D, Zhu J, Zhu JR, Baret-Cormel L, Weinling E, Staiger C, Yusuf S, Chrolavicius S, Afzal R, Hohnloser SH. Dronedarone in high-risk permanent atrial fibrillation. *N Engl J Med* 2011;**365**:2268-2276.
659. Tschuppert Y, Buclin T, Rothuizen LE, Decosterd LA, Galleyrand J, Gaud C, Biollaz J. Effect of dronedarone on renal function in healthy subjects. *Br J Clin Pharmacol* 2007;**64**:785-791.
660. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med* 1989;**321**:406-412.
661. Freemantle N, Lafuente-Lafuente C, Mitchell S, Eckert L, Reynolds M. Mixed treatment comparison of dronedarone, amiodarone, sotalol, flecainide, and propafenone, for the management of atrial fibrillation. *Europace* 2011;**13**:329-345.
662. Sherrid MV, Barac I, McKenna WJ, Elliott PM, Dickie S, Chojnowska L, Casey S, Maron BJ. Multicenter study of the efficacy and safety of disopyramide in obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2005;**45**:1251-1258.
663. Sirak TE, Sherrid MV. Oral disopyramide for the acute treatment of severe outflow obstruction in hypertrophic cardiomyopathy in the ICU setting. *Chest* 2008;**133**:1243-1246.
664. Sherrid MV, Shetty A, Winson G, Kim B, Musat D, Alviar CL, Homel P, Balaram SK, Swistel DG. Treatment of obstructive hypertrophic cardiomyopathy symptoms and gradient resistant to first-line therapy with beta-blockade or verapamil. *Circ Heart Fail* 2013;**6**:694-702.
665. Waldo AL, Camm AJ, deRuyter H, Friedman PL, MacNeil DJ, Pauls JF, Pitt B, Pratt CM, Schwartz PJ, Veltri EP. Effect of d-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. The SWORD Investigators. Survival With Oral d-Sotalol. *Lancet* 1996;**348**:7-12.
666. Pedersen OD, Bagger H, Keller N, Marchant B, Kober L, Torp-Pedersen C. Efficacy of dofetilide in the treatment of atrial fibrillation-flutter in patients with reduced left ventricular function: a Danish investigations of arrhythmia and mortality on dofetilide (diamond) substudy. *Circulation* 2001;**104**:292-296.
667. Shamiss Y, Khaykin Y, Oosthuizen R, Tunney D, Sarak B, Beardsall M, Seabrook C, Frost L, Wulffhart Z, Tsang B, Verma A. Dofetilide is safe and effective in preventing atrial fibrillation recurrences in patients accepted for catheter ablation. *Europace* 2009;**11**:1448-1455.
668. Haverkamp W, Breithardt G, Camm AJ, Janse MJ, Rosen MR, Antzelevitch C, Escande D, Franz M, Malik M, Moss A, Shah R. The potential for QT prolongation and pro-arrhythmia by non-anti-arrhythmic drugs: clinical and regulatory implications. Report on a Policy Conference of the European Society of Cardiology. *Cardiovasc Res* 2000;**47**:219-233.

669. Kääb S, Hinterseer M, Näbauer M, Steinbeck G. Sotalol testing unmasks altered repolarization in patients with suspected acquired long-QT-syndrome-a case-control pilot study using i.v. sotalol. *Eur Heart J* 2003;**24**:649-657.
670. Fabritz L, Kirchhof P. Predictable and less predictable unwanted cardiac drugs effects: individual pre-disposition and transient precipitating factors. *Basic Clin Pharmacol Toxicol* 2010;**106**:263-268.
671. Choy AM, Darbar D, Dell'Orto S, Roden DM. Exaggerated QT prolongation after cardioversion of atrial fibrillation. *J Am Coll Cardiol* 1999;**34**:396-401.
672. Patten M, Maas R, Bauer P, Luderitz B, Sonntag F, Dluzniewski M, Hatala R, Opolski G, Muller HW, Meinertz T. Suppression of paroxysmal atrial tachyarrhythmias--results of the SOPAT trial. *Eur Heart J* 2004;**25**:1395-1404.
673. Burashnikov A, Barajas-Martinez H, Hu D, Nof E, Blazek J, Antzelevitch C. Atrial-selective prolongation of refractory period with AVE0118 is due principally to inhibition of sodium channel activity. *J Cardiovasc Pharmacol* 2012;**59**:539-546.
674. Ford J, Milnes J, Wettwer E, Christ T, Rogers M, Sutton K, Madge D, Virag L, Jost N, Horvath Z, Matschke K, Varro A, Ravens U. Human electrophysiological and pharmacological properties of XEN-D0101: a novel atrial-selective Kv1.5/IKur inhibitor. *J Cardiovasc Pharmacol* 2013;**61**:408-415.
675. Loose S, Mueller J, Wettwer E, Knaut M, Ford J, Milnes J, Ravens U. Effects of IKur blocker MK-0448 on human right atrial action potentials from patients in sinus rhythm and in permanent atrial fibrillation. *Front Pharmacol* 2014;**5**:26.
676. Schram G, Zhang L, Derakhchan K, Ehrlich JR, Belardinelli L, Nattel S. Ranolazine: ion-channel-blocking actions and in vivo electrophysiological effects. *Br J Pharmacol* 2004;**142**:1300-1308.
677. McCormack JG, Barr RL, Wolff AA, Lopaschuk GD. Ranolazine stimulates glucose oxidation in normoxic, ischemic, and reperfused ischemic rat hearts. *Circulation* 1996;**93**:135-142.
678. Scirica BM, Morrow DA, Hod H, Murphy SA, Belardinelli L, Hedgepeth CM, Molhoek P, Verheugt FW, Gersh BJ, McCabe CH, Braunwald E. Effect of ranolazine, an antianginal agent with novel electrophysiological properties, on the incidence of arrhythmias in patients with non ST-segment elevation acute coronary syndrome: results from the Metabolic Efficiency With Ranolazine for Less Ischemia in Non ST-Elevation Acute Coronary Syndrome Thrombolysis in Myocardial Infarction 36 (MERLIN-TIMI 36) randomized controlled trial. *Circulation* 2007;**116**:1647-1652.
679. Scirica BM, Belardinelli L, Chaitman BR, Waks JW, Volo S, Karwatowska-Prokopczuk E, Murphy SA, Cheng ML, Braunwald E, Morrow DA. Effect of ranolazine on atrial fibrillation in patients with non-ST elevation acute coronary syndromes: observations from the MERLIN-TIMI 36 trial. *Europace* 2015;**17**:32-37.
680. Reiffel JA, Camm AJ, Belardinelli L, Zeng D, Karwatowska-Prokopczuk E, Olmsted A, Zareba W, Rosero S, Kowey P, HARMONY Investigators. The HARMONY Trial: Combined Ranolazine and Dronedarone in the Management of Paroxysmal Atrial Fibrillation: Mechanistic and Therapeutic Synergism. *Circ Arrhythm Electrophysiol* 2015;**8**:1048-1056.
681. Fragakis N, Koskinas KC, Katritsis DG, Pagourelias ED, Zografos T, Geleris P. Comparison of effectiveness of ranolazine plus amiodarone versus amiodarone alone for conversion of recent-onset atrial fibrillation. *Am J Cardiol* 2012;**110**:673-677.
682. Simopoulos V, Tagarakis GI, Daskalopoulou SS, Daskalopoulos ME, Lenos A, Chryssagis K, Skoularingis I, Molyvdas PA, Tsilimingas NB, Aidonidis I. Ranolazine enhances the antiarrhythmic activity of amiodarone by accelerating conversion of new-onset atrial fibrillation after cardiac surgery. *Angiology* 2014;**65**:294-297.
683. Koskinas KC, Fragakis N, Katritsis D, Skeberis V, Vassilikos V. Ranolazine enhances the efficacy of amiodarone for conversion of recent-onset atrial fibrillation. *Europace* 2014;**16**:973-979.
684. De Ferrari GM, Maier LS, Mont L, Schwartz PJ, Simonis G, Leschke M, Gronda E, Boriani G, Darius H, Guillamon Toran L, Savelieva I, Dusi V, Marchionni N, Quintana Rendon M, Schumacher K, Tonini G, Melani L, Giannelli S, Alberto Maggi C, Camm AJ, RAFFAELLO Investigators. Ranolazine in the treatment of atrial fibrillation: Results of the dose-ranging RAFFAELLO (Ranolazine in Atrial Fibrillation Following An ELectricaL CardiOversion) study. *Heart Rhythm* 2015;**12**:872-878.
685. Martin RI, Pogoryelova O, Koref MS, Bourke JP, Teare MD, Keavney BD. Atrial fibrillation associated with ivabradine treatment: meta-analysis of randomised controlled trials. *Heart* 2014;**100**:1506-1510.
686. Okin PM, Wachtell K, Devereux RB, Harris KE, Jern S, Kjeldsen SE, Julius S, Lindholm LH, Nieminen MS, Edelman JM, Hille DA, Dahlof B. Regression of electrocardiographic left ventricular hypertrophy and decreased incidence of new-onset atrial fibrillation in patients with hypertension. *JAMA* 2006;**296**:1242-1248.

687. Savelieva I, Kakouros N, Kourliouros A, Camm AJ. Upstream therapies for management of atrial fibrillation: review of clinical evidence and implications for European Society of Cardiology guidelines. Part II: secondary prevention. *Europace* 2011;**13**:610-625.
688. Kuhlkamp V, Schirdewan A, Stangl K, Homberg M, Ploch M, Beck OA. Use of metoprolol CR/XL to maintain sinus rhythm after conversion from persistent atrial fibrillation: a randomized, double-blind, placebo-controlled study. *J Am Coll Cardiol* 2000;**36**:139-146.
689. Liakopoulos OJ, Kuhn EW, Slottosch I, Wassmer G, Wahlers T. Preoperative statin therapy for patients undergoing cardiac surgery. *Cochrane Database Syst Rev* 2012;**4**:Cd008493.
690. Kuhn EW, Liakopoulos OJ, Stange S, Deppe AC, Slottosch I, Choi YH, Wahlers T. Preoperative statin therapy in cardiac surgery: a meta-analysis of 90,000 patients. *Eur J Cardiothorac Surg* 2014;**45**:17-26; discussion 26.
691. Zheng Z, Jayaram R, Jiang L, Emberson J, Zhao Y, Li Q, Du J, Guarguagli S, Hill M, Chen Z, Collins R, Casadei B. Perioperative Rosuvastatin in Cardiac Surgery. *N Engl J Med* 2016;**374**:1744-1753.
692. Rahimi K, Emberson J, McGale P, Majoni W, Merhi A, Asselbergs FW, Krane V, Macfarlane PW, PROSPER Executive. Effect of statins on atrial fibrillation: collaborative meta-analysis of published and unpublished evidence from randomised controlled trials. *BMJ* 2011;**342**:d1250.
693. Pinho-Gomes AC, Reilly S, Brandes RP, Casadei B. Targeting inflammation and oxidative stress in atrial fibrillation: role of 3-hydroxy-3-methylglutaryl-coenzyme a reductase inhibition with statins. *Antioxid Redox Signal* 2014;**20**:1268-1285.
694. Bianconi L, Calo L, Mennuni M, Santini L, Morosetti P, Azzolini P, Barbato G, Biscione F, Romano P, Santini M. n-3 polyunsaturated fatty acids for the prevention of arrhythmia recurrence after electrical cardioversion of chronic persistent atrial fibrillation: a randomized, double-blind, multicentre study. *Europace* 2011;**13**:174-181.
695. Kowey PR, Reiffel JA, Ellenbogen KA, Naccarelli GV, Pratt CM. Efficacy and safety of prescription omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation: a randomized controlled trial. *JAMA* 2010;**304**:2363-2372.
696. Mozaffarian D, Marchioli R, Macchia A, Silletta MG, Ferrazzi P, Gardner TJ, Latini R, Libby P, Lombardi F, O'Gara PT, Page RL, Tavazzi L, Tognoni G, OPERA Investigators. Fish oil and postoperative atrial fibrillation: the Omega-3 Fatty Acids for Prevention of Post-operative Atrial Fibrillation (OPERA) randomized trial. *JAMA* 2012;**308**:2001-2011.
697. Yamashita T, Inoue H, Okumura K, Kodama I, Aizawa Y, Atarashi H, Ohe T, Ohtsu H, Kato T, Kamakura S, Kumagai K, Kurachi Y, Koretsune Y, Saikawa T, Sakurai M, Sato T, Sugi K, Nakaya H, Hirai M, Hirayama A, Fukatani M, Mitamura H, Yamazaki T, Watanabe E, Ogawa S, J-RHYTHM II Investigators. Randomized trial of angiotensin II-receptor blocker vs. dihydropiridine calcium channel blocker in the treatment of paroxysmal atrial fibrillation with hypertension (J-RHYTHM II study). *Europace* 2011;**13**:473-479.
698. Macchia A, Grancelli H, Varini S, Nul D, Laffaye N, Mariani J, Ferrante D, Badra R, Figal J, Ramos S, Tognoni G, Doval HC, GESICA Investigators. Omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation: results of the FORWARD (Randomized Trial to Assess Efficacy of PUFA for the Maintenance of Sinus Rhythm in Persistent Atrial Fibrillation) trial. *J Am Coll Cardiol* 2013;**61**:463-468.
699. Dabrowski R, Borowiec A, Smolis-Bak E, Kowalik I, Sosnowski C, Kraska A, Kazimierska B, Wozniak J, Zareba W, Szwed H. Effect of combined spironolactone-β-blocker ± enalapril treatment on occurrence of symptomatic atrial fibrillation episodes in patients with a history of paroxysmal atrial fibrillation (SPIR-AF study). *Am J Cardiol* 2010;**106**:1609-1614.
700. Ito Y, Yamasaki H, Naruse Y, Yoshida K, Kaneshiro T, Murakoshi N, Igarashi M, Kuroki K, Machino T, Xu D, Kunugita F, Sekiguchi Y, Sato A, Tada H, Aonuma K. Effect of eplerenone on maintenance of sinus rhythm after catheter ablation in patients with long-standing persistent atrial fibrillation. *Am J Cardiol* 2013;**111**:1012-1018.
701. Swedberg K, Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Shi H, Vincent J, Pitt B, EMPHASIS-Hf Study Investigators. Eplerenone and atrial fibrillation in mild systolic heart failure: results from the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure) study. *J Am Coll Cardiol* 2012;**59**:1598-1603.
702. Coll-Vinent B, Sala X, Fernandez C, Bragulat E, Espinosa G, Miro O, Milla J, Sanchez M. Sedation for cardioversion in the emergency department: analysis of effectiveness in four protocols. *Ann Emerg Med* 2003;**42**:767-772.
703. del Arco C, Martin A, Laguna P, Gargantilla P. Analysis of current management of atrial fibrillation in the acute setting: GEFAUR-1 study. *Ann Emerg Med* 2005;**46**:424-430.

704. Scheuermeyer FX, Grafstein E, Heilbron B, Innes G. Emergency department management and 1-year outcomes of patients with atrial flutter. *Ann Emerg Med* 2011;**57**:564-571 e562.
705. Goldner BG, Baker J, Accordino A, Sabatino L, DiGiulio M, Kalenderian D, Lin D, Zambrotta V, Stechel J, Maccaro P, Jadonath R. Electrical cardioversion of atrial fibrillation or flutter with conscious sedation in the age of cost containment. *Am Heart J* 1998;**136**:961-964.
706. Martinez-Marcos FJ, Garcia-Garmendia JL, Ortega-Carpio A, Fernandez-Gomez JM, Santos JM, Camacho C. Comparison of intravenous flecainide, propafenone, and amiodarone for conversion of acute atrial fibrillation to sinus rhythm. *Am J Cardiol* 2000;**86**:950-953.
707. Buccelletti F, Iacomini P, Botta G, Marsiliani D, Carroccia A, Gentiloni Silveri N, Franceschi F. Efficacy and safety of vernakalant in recent-onset atrial fibrillation after the European medicines agency approval: systematic review and meta-analysis. *J Clin Pharmacol* 2012;**52**:1872-1878.
708. Cappato R, Ezekowitz MD, Klein AL, Camm AJ, Ma CS, Le Heuzey JY, Talajic M, Scanavacca M, Vardas PE, Kirchhof P, Hemmrich M, Lanius V, Meng IL, Wildgoose P, van Eickels M, Hohnloser SH, X-VeRT Investigators. Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial fibrillation. *Eur Heart J* 2014.
709. Nagarakanti R, Ezekowitz MD, Oldgren J, Yang S, Chernick M, Aikens TH, Flaker G, Brugada J, Kamensky G, Parekh A, Reilly PA, Yusuf S, Connolly SJ. Dabigatran versus warfarin in patients with atrial fibrillation: an analysis of patients undergoing cardioversion. *Circulation* 2011;**123**:131-136.
710. Steinberg JS, Sadaniantz A, Kron J, Krahn A, Denny DM, Daubert J, Campbell WB, Havranek E, Murray K, Olshansky B, O'Neill G, Sami M, Schmidt S, Storm R, Zabalgoitia M, Miller J, Chandler M, Nasco EM, Greene HL. Analysis of cause-specific mortality in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. *Circulation* 2004;**109**:1973-1980.
711. Andersen HR, Nielsen JC, Thomsen PE, Thuesen L, Mortensen PT, Vesterlund T, Pedersen AK. Long-term follow-up of patients from a randomised trial of atrial versus ventricular pacing for sick-sinus syndrome. *Lancet* 1997;**350**:1210-1216.
712. Connolly SJ, Kerr CR, Gent M, Roberts RS, Yusuf S, Gillis AM, Sami MH, Talajic M, Tang AS, Klein GJ, Lau C, Newman DM. Effects of physiologic pacing versus ventricular pacing on the risk of stroke and death due to cardiovascular causes. Canadian Trial of Physiologic Pacing Investigators. *N Engl J Med* 2000;**342**:1385-1391.
713. Calkins H, Reynolds MR, Spector P, Sondhi M, Xu Y, Martin A, Williams CJ, Sledge I. Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation: two systematic literature reviews and meta-analyses. *Circ Arrhythm Electrophysiol* 2009;**2**:349-361.
714. Schmieder RE, Kjeldsen SE, Julius S, McInnes GT, Zanchetti A, Hua TA. Reduced incidence of new-onset atrial fibrillation with angiotensin II receptor blockade: the VALUE trial. *J Hypertens* 2008;**26**:403-411.
715. 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.
716. Kuck KH, Hoffmann BA, Ernst S, Wegscheider K, Treszl A, Metzner A, Eckardt L, Lewalter T, Breithardt G, Willems S, Gap-AF–AFNET 1 Investigators. Impact of Complete Versus Incomplete Circumferential Lines Around the Pulmonary Veins During Catheter Ablation of Paroxysmal Atrial Fibrillation: Results From the Gap-Atrial Fibrillation-German Atrial Fibrillation Competence Network 1 Trial. *Circ Arrhythm Electrophysiol* 2016;**9**:e003337.
717. Mont L, Bisbal F, Hernandez-Madrid A, Perez-Castellano N, Vinolas X, Arenal A, Arribas F, Fernandez-Lozano I, Bodegas A, Cobos A, Matia R, Perez-Villacastin J, Guerra JM, Avila P, Lopez-Gil M, Castro V, Arana JI, Brugada J, SARA investigators. Catheter ablation vs. antiarrhythmic drug treatment of persistent atrial fibrillation: a multicentre, randomized, controlled trial (SARA study). *Eur Heart J* 2014;**35**:501-507.
718. Schreiber D, Rostock T, Frohlich M, Sultan A, Servatius H, Hoffmann BA, Luker J, Berner I, Schaffer B, Wegscheider K, Lezius S, Willems S, Steven D. Five-year follow-up after catheter ablation of persistent atrial fibrillation using the stepwise approach and prognostic factors for success. *Circ Arrhythm Electrophysiol* 2015;**8**:308-317.
719. Scherr D, Khairy P, Miyazaki S, Aurillac-Lavignolle V, Pascale P, Wilton SB, Ramoul K, Komatsu Y, Roten L, Jadidi A, Linton N, Pedersen M, Daly M, O'Neill M, Knecht S, Weerasooriya R,

5153 Rostock T, Manninger M, Cochet H, Shah AJ, Yeim S, Denis A, Derval N, Hocini M, Sacher F,
5154 Haissaguerre M, Jais P. Five-year outcome of catheter ablation of persistent atrial fibrillation using
5155 termination of atrial fibrillation as a procedural endpoint. *Circ Arrhythm Electrophysiol* 2015;**8**:18-24.
5156 720. Al Halabi S, Qintar M, Hussein A, Alraies MC, Jones DG, Wong T, MacDonald MR, Petrie
5157 MC, Cantillon D, Tarakji KG, Kanj M, Bhargava M, Varma N, Baranowski B, Wilkoff BL, Wazni O,
5158 Callahan T, Saliba W, Chung MK. Catheter Ablation for Atrial Fibrillation in Heart Failure Patients: A
5159 Meta-Analysis of Randomized Controlled Trials. *JACC Clin Electrophysiol* 2015;**1**:200-209.
5160 721. Hakalahti A, Biancari F, Nielsen JC, Raatikainen MJ. Radiofrequency ablation vs.
5161 antiarrhythmic drug therapy as first line treatment of symptomatic atrial fibrillation: systematic review
5162 and meta-analysis. *Europace* 2015;**17**:370-378.
5163 722. Morillo CA, Verma A, Connolly SJ, Kuck KH, Nair GM, Champagne J, Sterns LD, Beresh H,
5164 Healey JS, Natale A, RAAFT-2 Investigators. Radiofrequency ablation vs antiarrhythmic drugs as first-
5165 line treatment of paroxysmal atrial fibrillation (RAAFT-2): a randomized trial. *JAMA* 2014;**311**:692-700.
5166 723. Wazni OM, Marrouche NF, Martin DO, Verma A, Bhargava M, Saliba W, Bash D, Schweikert
5167 R, Brachmann J, Gunther J, Gutleben K, Pisano E, Potenza D, Fanelli R, Raviele A, Themistoclakis
5168 S, Rossillo A, Bonso A, Natale A. Radiofrequency ablation vs antiarrhythmic drugs as first-line
5169 treatment of symptomatic atrial fibrillation: a randomized trial. *JAMA* 2005;**293**:2634-2640.
5170 724. Oral H, Pappone C, Chugh A, Good E, Bogun F, Pelosi F, Jr., Bates ER, Lehmann MH,
5171 Vicedomini G, Augello G, Agricola E, Sala S, Santinelli V, Morady F. Circumferential pulmonary-vein
5172 ablation for chronic atrial fibrillation. *N Engl J Med* 2006;**354**:934-941.
5173 725. Stabile G, Bertaglia E, Senatore G, De Simone A, Zoppo F, Donnici G, Turco P, Pascotto P,
5174 Fazzari M, Vitale DF. Catheter ablation treatment in patients with drug-refractory atrial fibrillation: a
5175 prospective, multi-centre, randomized, controlled study (Catheter Ablation For The Cure Of Atrial
5176 Fibrillation Study). *Eur Heart J* 2006;**27**:216-221.
5177 726. Forleo GB, Mantica M, De Luca L, Leo R, Santini L, Panigada S, De Sanctis V, Pappalardo A,
5178 Laurenzi F, Avella A, Casella M, Dello Russo A, Romeo F, Pelargonio G, Tondo C. Catheter ablation
5179 of atrial fibrillation in patients with diabetes mellitus type 2: results from a randomized study
5180 comparing pulmonary vein isolation versus antiarrhythmic drug therapy. *J Cardiovasc Electrophysiol*
5181 2009;**20**:22-28.
5182 727. Cappato R, Calkins H, Chen SA, Davies W, Iesaka Y, Kalman J, Kim YH, Klein G, Natale A,
5183 Packer D, Skanes A, Ambrogi F, Biganzoli E. Updated worldwide survey on the methods, efficacy,
5184 and safety of catheter ablation for human atrial fibrillation. *Circ Arrhythm Electrophysiol* 2010;**3**:32-38.
5185 728. Ganesan AN, Shipp NJ, Brooks AG, Kuklik P, Lau DH, Lim HS, Sullivan T, Roberts-Thomson
5186 KC, Sanders P. Long-term outcomes of catheter ablation of atrial fibrillation: a systematic review and
5187 meta-analysis. *J Am Heart Assoc* 2013;**2**:e004549.
5188 729. McLellan AJ, Ling LH, Azzopardi S, Lee GA, Lee G, Kumar S, Wong MC, Walters TE, Lee
5189 JM, Looi KL, Halloran K, Stiles MK, Lever NA, Fynn SP, Heck PM, Sanders P, Morton JB, Kalman
5190 JM, Kistler PM. A minimal or maximal ablation strategy to achieve pulmonary vein isolation for
5191 paroxysmal atrial fibrillation: a prospective multi-centre randomized controlled trial (the Minimax
5192 study). *Eur Heart J* 2015;**36**:1812-1821.
5193 730. Verma A, Sanders P, Macle L, Deisenhofer I, Morillo CA, Chen J, Jiang CY, Ernst S,
5194 Mantovan R. Substrate and Trigger Ablation for Reduction of Atrial Fibrillation Trial-Part II (STAR AF
5195 II): design and rationale. *Am Heart J* 2012;**164**:1-6 e6.
5196 731. Nery PB, Belliveau D, Nair GM, Bernick J, Redpath CJ, Szczotka A, Sadek MM, Green MS,
5197 Wells G, Birnie DH. Relationship Between Pulmonary Vein Reconnection and
5198 Atrial Fibrillation Recurrence. *JACC Clin Electrophysiol* 2016:[Epub ahead of print].
5199 732. Luik A, Radzewitz A, Kieser M, Walter M, Bramlage P, Hormann P, Schmidt K, Horn N,
5200 Brinkmeier-Theofanopoulou M, Kunzmann K, Riexinger T, Schymik G, Merkel M, Schmitt C.
5201 Cryoballoon Versus Open Irrigated Radiofrequency Ablation in Patients With Paroxysmal Atrial
5202 Fibrillation: The Prospective, Randomized, Controlled, Noninferiority FreezeAF Study. *Circulation*
5203 2015;**132**:1311-1319.
5204 733. Schmidt M, Dorwarth U, Andresen D, Brachmann J, Kuck KH, Kuniss M, Lewalter T, Spitzer
5205 S, Willems S, Senges J, Junger C, Hoffmann E. Cryoballoon versus RF ablation in paroxysmal atrial
5206 fibrillation: results from the German Ablation Registry. *J Cardiovasc Electrophysiol* 2014;**25**:1-7.
5207 734. Kuck KH, Brugada J, Furnkranz A, Metzner A, Ouyang F, Chun KR, Elvan A, Arentz T,
5208 Bestehorn K, Pocock SJ, Albenque JP, Tondo C, FIRE AND ICE Investigators. Cryoballoon or
5209 Radiofrequency Ablation for Paroxysmal Atrial Fibrillation. *N Engl J Med* 2016:[Epub ahead of print].
5210 735. Verma A, Jiang CY, Betts TR, Chen J, Deisenhofer I, Mantovan R, Macle L, Morillo CA,
5211 Haverkamp W, Weerasooriya R, Albenque JP, Nardi S, Menardi E, Novak P, Sanders P, STAR AF II

Investigators. Approaches to catheter ablation for persistent atrial fibrillation. *N Engl J Med* 2015;**372**:1812-1822.
736. Dong JZ, Sang CH, Yu RH, Long DY, Tang RB, Jiang CX, Ning M, Liu N, Liu XP, Du X, Tse HF, Ma CS. Prospective randomized comparison between a fixed '2C3L' approach vs. stepwise approach for catheter ablation of persistent atrial fibrillation. *Europace* 2015;**17**:1798-1806.
737. Hunter RJ, McCready J, Diab I, Page SP, Finlay M, Richmond L, French A, Earley MJ, Sporton S, Jones M, Joseph JP, Bashir Y, Betts TR, Thomas G, Staniforth A, Lee G, Kistler P, Rajappan K, Chow A, Schilling RJ. Maintenance of sinus rhythm with an ablation strategy in patients with atrial fibrillation is associated with a lower risk of stroke and death. *Heart* 2012;**98**:48-53.
738. Providencia R, Lambiase PD, Srinivasan N, Ganesh Babu G, Bronis K, Ahsan S, Khan FZ, Chow AW, Rowland E, Lowe M, Segal OR. Is There Still a Role for Complex Fractionated Atrial Electrogram Ablation in Addition to Pulmonary Vein Isolation in Patients With Paroxysmal and Persistent Atrial Fibrillation? Meta-Analysis of 1415 Patients. *Circ Arrhythm Electrophysiol* 2015;**8**:1017-1029.
739. Mohanty S, Gianni C, Mohanty P, Halbfass P, Metz T, Trivedi C, Deneke T, Tomassoni G, Bai R, Al-Ahmad A, Bailey S, Burkhardt JD, Gallinghouse GJ, Horton R, Hranitzky PM, Sanchez JE, Di Biase L, Natale A. Impact of Rotor Ablation in Non-Paroxysmal AF Patients: Results from a Randomized Trial (OASIS). *J Am Coll Cardiol* 2016.
740. Rolf S, Kircher S, Arya A, Eitel C, Sommer P, Richter S, Gaspar T, Bollmann A, Altmann D, Piedra C, Hindricks G, Piorkowski C. Tailored atrial substrate modification based on low-voltage areas in catheter ablation of atrial fibrillation. *Circ Arrhythm Electrophysiol* 2014;**7**:825-833.
741. Shah AJ, Pascale P, Miyazaki S, Liu X, Roten L, Derval N, Jadidi AS, Scherr D, Wilton SB, Pedersen M, Knecht S, Sacher F, Jais P, Haissaguerre M, Hocini M. Prevalence and types of pitfall in the assessment of mitral isthmus linear conduction block. *Circ Arrhythm Electrophysiol* 2012;**5**:957-967.
742. Macle L, Khairy P, Weerasooriya R, Novak P, Verma A, Willems S, Arentz T, Deisenhofer I, Veenhuyzen G, Scavee C, Jais P, Puererfellner H, Levesque S, Andrade JG, Rivard L, Guerra PG, Dubuc M, Thibault B, Talajic M, Roy D, Nattel S, ADVICE trial investigators. Adenosine-guided pulmonary vein isolation for the treatment of paroxysmal atrial fibrillation: an international, multicentre, randomised superiority trial. *Lancet* 2015;**386**:672-679.
743. Kobori A, Shizuta S, Inoue K, Kaitani K, Morimoto T, Nakazawa Y, Ozawa T, Kurotobi T, Morishima I, Miura F, Watanabe T, Masuda M, Naito M, Fujimoto H, Nishida T, Furukawa Y, Shirayama T, Tanaka M, Okajima K, Yao T, Egami Y, Satomi K, Noda T, Miyamoto K, Haruna T, Kawaji T, Yoshizawa T, Toyota T, Yahata M, Nakai K, Sugiyama H, Higashi Y, Ito M, Horie M, Kusano KF, Shimizu W, Kamakura S, Kimura T, UNDER-ATP Trial Investigators. Adenosine triphosphate-guided pulmonary vein isolation for atrial fibrillation: the UNmasking Dormant Electrical Reconduction by Adenosine TriPhosphate (UNDER-ATP) trial. *Eur Heart J* 2015;**36**:3276-3287.
744. Berntsen RF, Haland TF, Skardal R, Holm T. Focal impulse and rotor modulation as a stand-alone procedure for treatment of paroxysmal atrial fibrillation. A within-patient controlled study with implanted cardiac monitoring. *Heart Rhythm* 2016.
745. Lee G, Sparks PB, Morton JB, Kistler PM, Vohra JK, Medi C, Rosso R, Teh A, Halloran K, Kalman JM. Low risk of major complications associated with pulmonary vein antral isolation for atrial fibrillation: results of 500 consecutive ablation procedures in patients with low prevalence of structural heart disease from a single center. *J Cardiovasc Electrophysiol* 2011;**22**:163-168.
746. Wynn GJ, Das M, Bonnett LJ, Panikker S, Wong T, Gupta D. Efficacy of catheter ablation for persistent atrial fibrillation: a systematic review and meta-analysis of evidence from randomized and nonrandomized controlled trials. *Circ Arrhythm Electrophysiol* 2014;**7**:841-852.
747. 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.
748. Dagres N, Hindricks G, Kottkamp H, Sommer P, Gaspar T, Bode K, Arya A, Husser D, Rallidis LS, Kremastinos DT, Piorkowski C. Complications of atrial fibrillation ablation in a high-volume center in 1,000 procedures: still cause for concern? *J Cardiovasc Electrophysiol* 2009;**20**:1014-1019.
749. Deneke T, Jais P, Scaglione M, Schmitt R, L DIB, Christopoulos G, Schade A, Mugge A, Bansmann M, Nentwich K, Muller P, Krug J, Roos M, Halbfass P, Natale A, Gaita F, Haines D. Silent cerebral events/lesions related to atrial fibrillation ablation: a clinical review. *J Cardiovasc Electrophysiol* 2015;**26**:455-463.
750. Gupta A, Perera T, Ganesan A, Sullivan T, Lau DH, Roberts-Thomson KC, Brooks AG, Sanders P. Complications of catheter ablation of atrial fibrillation: a systematic review. *Circ Arrhythm Electrophysiol* 2013;**6**:1082-1088.

751. Cappato R, Calkins H, Chen SA, Davies W, Iesaka Y, Kalman J, Kim YH, Klein G, Natale A, Packer D, Ricci C, Skanes A, Ranucci M. Delayed cardiac tamponade after radiofrequency catheter ablation of atrial fibrillation: a worldwide report. *J Am Coll Cardiol* 2011;**58**:2696-2697.
752. Haeusler KG, Kirchhof P, Endres M. Left atrial catheter ablation and ischemic stroke. *Stroke* 2012;**43**:265-270.
753. Kosiuk J, Kornej J, Bollmann A, Piorkowski C, Myrda K, Arya A, Sommer P, Richter S, Rolf S, Husser D, Gaspar T, Lip GY, Hindricks G. Early cerebral thromboembolic complications after radiofrequency catheter ablation of atrial fibrillation: incidence, characteristics, and risk factors. *Heart Rhythm* 2014;**11**:1934-1940.
754. Gaita F, Leclercq JF, Schumacher B, Scaglione M, Toso E, Halimi F, Schade A, Froehner S, Ziegler V, Sergi D, Cesarani F, Blandino A. Incidence of silent cerebral thromboembolic lesions after atrial fibrillation ablation may change according to technology used: comparison of irrigated radiofrequency, multipolar nonirrigated catheter and cryoballoon. *J Cardiovasc Electrophysiol* 2011;**22**:961-968.
755. Hsu LF, Jais P, Hocini M, Sanders P, Scavee C, Sacher F, Takahashi Y, Rotter M, Pasquie JL, Clementy J, Haissaguerre M. Incidence and prevention of cardiac tamponade complicating ablation for atrial fibrillation. *Pacing Clin Electrophysiol* 2005;**28 Suppl 1**:S106-109.
756. Michowitz Y, Rahkovich M, Oral H, Zado ES, Tilz R, John S, Denis A, Di Biase L, Winkle RA, Mikhaylov EN, Ruskin JN, Yao Y, Josephson ME, Tanner H, Miller JM, Champagne J, Della Bella P, Kumagai K, Defaye P, Luria D, Lebedev DS, Natale A, Jais P, Hindricks G, Kuck KH, Marchlinski FE, Morady F, Belhassen B. Effects of sex on the incidence of cardiac tamponade after catheter ablation of atrial fibrillation: results from a worldwide survey in 34 943 atrial fibrillation ablation procedures. *Circ Arrhythm Electrophysiol* 2014;**7**:274-280.
757. Nair KK, Shurrab M, Skanes A, Danon A, Birnie D, Morillo C, Chauhan V, Mangat I, Ayala-Paredes F, Champagne J, Nault I, Tang A, Verma A, Lashevsky I, Singh SM, Crystal E. The prevalence and risk factors for atrioesophageal fistula after percutaneous radiofrequency catheter ablation for atrial fibrillation: the Canadian experience. *J Interv Card Electrophysiol* 2014;**39**:139-144.
758. Shah RU, Freeman JV, Shilane D, Wang PJ, Go AS, Hlatky MA. Procedural complications, rehospitalizations, and repeat procedures after catheter ablation for atrial fibrillation. *J Am Coll Cardiol* 2012;**59**:143-149.
759. Straube F, Dorwarth U, Schmidt M, Wankerl M, Ebersberger U, Hoffmann E. Comparison of the first and second cryoballoon: high-volume single-center safety and efficacy analysis. *Circ Arrhythm Electrophysiol* 2014;**7**:293-299.
760. Di Biase L, Burkhardt JD, Santangeli P, Mohanty P, Sanchez JE, Horton R, Gallinghouse GJ, Themistoclakis S, Rossillo A, Lakkireddy D, Reddy M, Hao S, Hongo R, Beheiry S, Zagrodzky J, Rong B, Mohanty S, Elayi CS, Forleo G, Pelargonio G, Narducci ML, Dello Russo A, Casella M, Fassini G, Tondo C, Schweikert RA, Natale A. Periprocedural Stroke and Bleeding Complications in Patients Undergoing Catheter Ablation of Atrial Fibrillation With Different Anticoagulation Management: Results From the Role of Coumadin in Preventing Thromboembolism in Atrial Fibrillation (AF) Patients Undergoing Catheter Ablation (COMPARE) Randomized Trial. *Circulation* 2014;**129**:2638-2644.
761. Di Biase L, Lakkireddy D, Trivedi C, Deneke T, Martinek M, Mohanty S, Mohanty P, Prakash S, Bai R, Reddy M, Gianni C, Horton R, Bailey S, Sigmund E, Derndorfer M, Schade A, Mueller P, Szoelloes A, Sanchez J, Al-Ahmad A, Hranitzky P, Gallinghouse GJ, Hongo RH, Beheiry S, Purerfellner H, Burkhardt JD, Natale A. Feasibility and safety of uninterrupted periprocedural apixaban administration in patients undergoing radiofrequency catheter ablation for atrial fibrillation: Results from a multicenter study. *Heart Rhythm* 2015;**12**:1162-1168.
762. Hohnloser SH, Camm AJ. Safety and efficacy of dabigatran etexilate during catheter ablation of atrial fibrillation: a meta-analysis of the literature. *Europace* 2013;**15**:1407-1411.
763. Lakkireddy D, Reddy YM, Di Biase L, Vallakati A, Mansour MC, Santangeli P, Gangireddy S, Swarup V, Chalhoub F, Atkins D, Bommana S, Verma A, Sanchez JE, Burkhardt JD, Barrett CD, Baheiry S, Ruskin J, Reddy V, Natale A. Feasibility and safety of uninterrupted rivaroxaban for periprocedural anticoagulation in patients undergoing radiofrequency ablation for atrial fibrillation: results from a multicenter prospective registry. *J Am Coll Cardiol* 2014;**63**:982-988.
764. Providencia R, Marijon E, Albenque JP, Combes S, Combes N, Jourda F, Hireche H, Morais J, Boveda S. Rivaroxaban and dabigatran in patients undergoing catheter ablation of atrial fibrillation. *Europace* 2014;**16**:1137-1144.
765. Stepanyan G, Badhwar N, Lee RJ, Marcus GM, Lee BK, Tseng ZH, Vedantham V, Olgin J, Scheinman M, Gerstenfeld EP. Safety of new oral anticoagulants for patients undergoing atrial fibrillation ablation. *J Interv Card Electrophysiol* 2014;**40**:33-38.

766. Aryal MR, Ukaigwe A, Pandit A, Karmacharya P, Pradhan R, Mainali NR, Pathak R, Jalota L, Bhandari Y, Donato A. Meta-analysis of efficacy and safety of rivaroxaban compared with warfarin or dabigatran in patients undergoing catheter ablation for atrial fibrillation. *Am J Cardiol* 2014;**114**:577-582.
767. Kaess BM, Ammar S, Reents T, Dillier R, Lennerz C, Semmler V, Grebmer C, Bourier F, Buiatti A, Kolb C, Deisenhofer I, Hessling G. Comparison of safety of left atrial catheter ablation procedures for atrial arrhythmias under continuous anticoagulation with apixaban versus phenprocoumon. *Am J Cardiol* 2015;**115**:47-51.
768. Cappato R, Marchlinski FE, Hohnloser SH, Naccarelli GV, Xiang J, Wilber DJ, Ma CS, Hess S, Wells DS, Juang G, Vijgen J, Hugl BJ, Balasubramaniam R, De Chillou C, Davies DW, Fields LE, Natale A, VENTURE-AF Investigators. Uninterrupted rivaroxaban vs. uninterrupted vitamin K antagonists for catheter ablation in non-valvular atrial fibrillation. *Eur Heart J* 2015;**36**:1805-1811.
769. Wu S, Yang YM, Zhu J, Wan HB, Wang J, Zhang H, Shao XH. Meta-Analysis of Efficacy and Safety of New Oral Anticoagulants Compared With Uninterrupted Vitamin K Antagonists in Patients Undergoing Catheter Ablation for Atrial Fibrillation. *Am J Cardiol* 2016;**117**:926-934.
770. Santarpia G, De Rosa S, Polimeni A, Giampa S, Micieli M, Curcio A, Indolfi C. Efficacy and Safety of Non-Vitamin K Antagonist Oral Anticoagulants versus Vitamin K Antagonist Oral Anticoagulants in Patients Undergoing Radiofrequency Catheter Ablation of Atrial Fibrillation: A Meta-Analysis. *PLoS One* 2015;**10**:e0126512.
771. Karasoy D, Gislason GH, Hansen J, Johannessen A, Kober L, Hvidtfeldt M, Ozcan C, Torp-Pedersen C, Hansen ML. Oral anticoagulation therapy after radiofrequency ablation of atrial fibrillation and the risk of thromboembolism and serious bleeding: long-term follow-up in nationwide cohort of Denmark. *Eur Heart J* 2015;**36**:307-314a.
772. Themistoclakis S, Corrado A, Marchlinski FE, Jais P, Zado E, Rossillo A, Di Biase L, Schweikert RA, Saliba WI, Horton R, Mohanty P, Patel D, Burkhardt DJ, Wazni OM, Bonso A, Callans DJ, Haissaguerre M, Raviele A, Natale A. The risk of thromboembolism and need for oral anticoagulation after successful atrial fibrillation ablation. *J Am Coll Cardiol* 2010;**55**:735-743.
773. Bunch TJ, May HT, Bair TL, Weiss JP, Crandall BG, Osborn JS, Mallender C, Anderson JL, Muhlestein BJ, Lappe DL, Day JD. Atrial fibrillation ablation patients have long-term stroke rates similar to patients without atrial fibrillation regardless of CHADS2 score. *Heart Rhythm* 2013;**10**:1272-1277.
774. Nedios S, Kornej J, Koutalas E, Bertagnolli L, Kosiuk J, Rolf S, Arya A, Sommer P, Husser D, Hindricks G, Bollmann A. Left atrial appendage morphology and thromboembolic risk after catheter ablation for atrial fibrillation. *Heart Rhythm* 2014;**11**:2239-2246.
775. Reynolds MR, Gunnarsson CL, Hunter TD, Ladapo JA, March JL, Zhang M, Hao SC. Health outcomes with catheter ablation or antiarrhythmic drug therapy in atrial fibrillation: results of a propensity-matched analysis. *Circ Cardiovasc Qual Outcomes* 2012;**5**:171-181.
776. Gallo C, Battaglia A, Anselmino M, Bianchi F, Grossi S, Nangeroni G, Toso E, Gaido L, Scaglione M, Ferraris F, Gaita F. Long-term events following atrial fibrillation rate control or transcatheter ablation: a multicenter observational study. *J Cardiovasc Med (Hagerstown)* 2016;**17**:187-193.
777. Di Biase L, Mohanty P, Mohanty S, Santangeli P, Trivedi C, Lakkireddy D, Reddy M, Jais P, Themistoclakis S, Dello Russo A, Casella M, Pelargonio G, Narducci ML, Schweikert R, Neuzil P, Sanchez J, Horton R, Beheiry S, Hongo R, Hao S, Rossillo A, Forleo G, Tondo C, Burkhardt JD, Haissaguerre M, Natale A. Ablation vs. Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted Device: Results From the AATAC Multicenter Randomized Trial. *Circulation* 2016.
778. Hunter RJ, Berriman TJ, Diab I, Kamdar R, Richmond L, Baker V, Goromonzi F, Sawhney V, Duncan E, Page SP, Ullah W, Unsworth B, Mayet J, Dhinoja M, Earley MJ, Sporton S, Schilling RJ. A randomized controlled trial of catheter ablation versus medical treatment of atrial fibrillation in heart failure (the CAMTAF trial). *Circ Arrhythm Electrophysiol* 2014;**7**:31-38.
779. MacDonald MR, Connelly DT, Hawkins NM, Steedman T, Payne J, Shaw M, Denvir M, Bhagra S, Small S, Martin W, McMurray JJ, Petrie MC. Radiofrequency ablation for persistent atrial fibrillation in patients with advanced heart failure and severe left ventricular systolic dysfunction: a randomised controlled trial. *Heart* 2011;**97**:740-747.
780. Dagres N, Varounis C, Gaspar T, Piorkowski C, Eitel C, Iliodromitis EK, Lekakis JP, Flevari P, Simeonidou E, Rallidis LS, Tsougos E, Hindricks G, Sommer P, Anastasiou-Nana M. Catheter ablation for atrial fibrillation in patients with left ventricular systolic dysfunction. A systematic review and meta-analysis. *J Card Fail* 2011;**17**:964-970.

781. Piorkowski C, Kottkamp H, Tanner H, Kobza R, Nielsen JC, Arya A, Hindricks G. Value of different follow-up strategies to assess the efficacy of circumferential pulmonary vein ablation for the curative treatment of atrial fibrillation. *J Cardiovasc Electrophysiol* 2005;**16**:1286-1292.
782. Verma A, Champagne J, Sapp J, Essebag V, Novak P, Skanes A, Morillo CA, Khaykin Y, Birnie D. Discerning the incidence of symptomatic and asymptomatic episodes of atrial fibrillation before and after catheter ablation (DISCERN AF): a prospective, multicenter study. *JAMA Intern Med* 2013;**173**:149-156.
783. Cox JL, Boineau JP, Schuessler RB, Ferguson TB, Jr., Cain ME, Lindsay BD, Corr PB, Kater KM, Lappas DG. Successful surgical treatment of atrial fibrillation. Review and clinical update. *JAMA* 1991;**266**:1976-1980.
784. Cox JL, Schuessler RB, D'Agostino HJ, Jr., Stone CM, Chang BC, Cain ME, Corr PB, Boineau JP. The surgical treatment of atrial fibrillation. III. Development of a definitive surgical procedure. *J Thorac Cardiovasc Surg* 1991;**101**:569-583.
785. Stulak JM, Suri RM, Burkhart HM, Daly RC, Dearani JA, Greason KL, Joyce LD, Park SJ, Schaff HV. Surgical ablation for atrial fibrillation for two decades: are the results of new techniques equivalent to the Cox maze III procedure? *J Thorac Cardiovasc Surg* 2014;**147**:1478-1486.
786. Basu S, Nagendran M, Maruthappu M. How effective is bipolar radiofrequency ablation for atrial fibrillation during concomitant cardiac surgery? *Interact Cardiovasc Thorac Surg* 2012;**15**:741-748.
787. Lin Z, Shan ZG, Liao CX, Chen LW. The effect of microwave and bipolar radio-frequency ablation in the surgical treatment of permanent atrial fibrillation during valve surgery. *Thorac Cardiovasc Surg* 2011;**59**:460-464.
788. McCarthy PM, Kruse J, Shalli S, Ilkhanoff L, Goldberger JJ, Kadish AH, Arora R, Lee R. Where does atrial fibrillation surgery fail? Implications for increasing effectiveness of ablation. *J Thorac Cardiovasc Surg* 2010;**139**:860-867.
789. Abreu Filho CA, Lisboa LA, Dallan LA, Spina GS, Grinberg M, Scanavacca M, Sosa EA, Ramires JA, Oliveira SA. Effectiveness of the maze procedure using cooled-tip radiofrequency ablation in patients with permanent atrial fibrillation and rheumatic mitral valve disease. *Circulation* 2005;**112**:I20-25.
790. Blomstrom-Lundqvist C, Johansson B, Berglin E, Nilsson L, Jensen SM, Thelin S, Holmgren A, Edvardsson N, Kallner G, Blomstrom P. A randomized double-blind study of epicardial left atrial cryoablation for permanent atrial fibrillation in patients undergoing mitral valve surgery: the SWEDish Multicentre Atrial Fibrillation study (SWEDMAF). *Eur Heart J* 2007;**28**:2902-2908.
791. Chevalier P, Leizorovicz A, Maureira P, Carteaux JP, Corbineau H, Caus T, DeBreyne B, Mabot P, Dechillou C, Deharo JC, Barry S, Touboul P, Villemot JP, Obadia JF. Left atrial radiofrequency ablation during mitral valve surgery: a prospective randomized multicentre study (SAFIR). *Arch Cardiovasc Dis* 2009;**102**:769-775.
792. Deneke T, Khargi K, Grewe PH, Laczkovics A, von Dryander S, Lawo T, Muller KM, Lemke B. Efficacy of an additional MAZE procedure using cooled-tip radiofrequency ablation in patients with chronic atrial fibrillation and mitral valve disease. A randomized, prospective trial. *Eur Heart J* 2002;**23**:558-566.
793. Doukas G, Samani NJ, Alexiou C, Oc M, Chin DT, Stafford PG, Ng LL, Spyt TJ. Left atrial radiofrequency ablation during mitral valve surgery for continuous atrial fibrillation: a randomized controlled trial. *JAMA* 2005;**294**:2323-2329.
794. Schuetz A, Schulze CJ, Sarvanakis KK, Mair H, Plazer H, Kilger E, Reichart B, Wildhirt SM. Surgical treatment of permanent atrial fibrillation using microwave energy ablation: a prospective randomized clinical trial. *Eur J Cardiothorac Surg* 2003;**24**:475-480; discussion 480.
795. Liu X, Tan HW, Wang XH, Shi HF, Li YZ, Li F, Zhou L, Gu JN. Efficacy of catheter ablation and surgical CryoMaze procedure in patients with long-lasting persistent atrial fibrillation and rheumatic heart disease: a randomized trial. *Eur Heart J* 2010;**31**:2633-2641.
796. Cheng DC, Ad N, Martin J, Berglin EE, Chang BC, Doukas G, Gammie JS, Nitta T, Wolf RK, Puskas JD. Surgical ablation for atrial fibrillation in cardiac surgery: a meta-analysis and systematic review. *Innovations (Phila)* 2010;**5**:84-96.
797. Barnett SD, Ad N. Surgical ablation as treatment for the elimination of atrial fibrillation: a meta-analysis. *J Thorac Cardiovasc Surg* 2006;**131**:1029-1035.
798. Ad N, Henry L, Massimiano P, Pritchard G, Holmes SD. The state of surgical ablation for atrial fibrillation in patients with mitral valve disease. *Curr Opin Cardiol* 2013;**28**:170-180.
799. Gammie JS, Haddad M, Milford-Beland S, Welke KF, Ferguson TB, Jr., O'Brien SM, Griffith BP, Peterson ED. Atrial fibrillation correction surgery: lessons from the Society of Thoracic Surgeons National Cardiac Database. *Ann Thorac Surg* 2008;**85**:909-914.

800. Chen MC, Chang JP, Chang HW. Preoperative atrial size predicts the success of radiofrequency maze procedure for permanent atrial fibrillation in patients undergoing concomitant valvular surgery. *Chest* 2004;**125**:2129-2134.
801. Sunderland N, Maruthappu M, Nagendran M. What size of left atrium significantly impairs the success of maze surgery for atrial fibrillation? *Interact Cardiovasc Thorac Surg* 2011;**13**:332-338.
802. Chaiyaroj S, Ngarmukos T, Lertsithichai P. Predictors of sinus rhythm after radiofrequency maze and mitral valve surgery. *Asian Cardiovasc Thorac Ann* 2008;**16**:292-297.
803. Gillinov AM, Bhavani S, Blackstone EH, Rajeswaran J, Svensson LG, Navia JL, Pettersson BG, Sabik JF, 3rd, Smedira NG, Mihaljevic T, McCarthy PM, Shewchik J, Natale A. Surgery for permanent atrial fibrillation: impact of patient factors and lesion set. *Ann Thorac Surg* 2006;**82**:502-513; discussion 513-504.
804. Beukema WP, Sie HT, Misier AR, Delnoy PP, Wellens HJ, Elvan A. Predictive factors of sustained sinus rhythm and recurrent atrial fibrillation after a radiofrequency modified Maze procedure. *Eur J Cardiothorac Surg* 2008;**34**:771-775.
805. Gillinov AM, Bakaeen F, McCarthy PM, Blackstone EH, Rajeswaran J, Pettersson G, Sabik JF, 3rd, Najam F, Hill KM, Svensson LG, Cosgrove DM, Marrouche N, Natale A. Surgery for paroxysmal atrial fibrillation in the setting of mitral valve disease: a role for pulmonary vein isolation? *Ann Thorac Surg* 2006;**81**:19-26; discussion 27-18.
806. Onorati F, Mariscalco G, Rubino AS, Serraino F, Santini F, Musazzi A, Klersy C, Sala A, Renzulli A. Impact of lesion sets on mid-term results of surgical ablation procedure for atrial fibrillation. *J Am Coll Cardiol* 2011;**57**:931-940.
807. Saint LL, Bailey MS, Prasad S, Guthrie TJ, Bell J, Moon MR, Lawton JS, Munfakh NA, Schuessler RB, Damiano RJ, Jr., Maniar HS. Cox-Maze IV results for patients with lone atrial fibrillation versus concomitant mitral disease. *Ann Thorac Surg* 2012;**93**:789-794; discussion 794-785.
808. Lawrance CP, Henn MC, Miller JR, Sinn LA, Schuessler RB, Maniar HS, Damiano RJ, Jr. A minimally invasive Cox maze IV procedure is as effective as sternotomy while decreasing major morbidity and hospital stay. *J Thorac Cardiovasc Surg* 2014;**148**:955-961; discussion 962-952.
809. Edgerton JR, Brinkman WT, Weaver T, Prince SL, Culica D, Herbert MA, Mack MJ. Pulmonary vein isolation and autonomic denervation for the management of paroxysmal atrial fibrillation by a minimally invasive surgical approach. *J Thorac Cardiovasc Surg* 2010;**140**:823-828.
810. McClelland JH, Duke D, Reddy R. Preliminary results of a limited thoracotomy: new approach to treat atrial fibrillation. *J Cardiovasc Electrophysiol* 2007;**18**:1289-1295.
811. Castella M, Pereda D, Mestres CA, Gomez F, Quintana E, Mulet J. Thoracoscopic pulmonary vein isolation in patients with atrial fibrillation and failed percutaneous ablation. *J Thorac Cardiovasc Surg* 2010;**140**:633-638.
812. Krul SP, Driessen AH, van Boven WJ, Linnenbank AC, Geuzebroek GS, Jackman WM, Wilde AA, de Bakker JM, de Groot JR. Thoracoscopic video-assisted pulmonary vein antrum isolation, ganglionated plexus ablation, and periprocedural confirmation of ablation lesions: first results of a hybrid surgical-electrophysiological approach for atrial fibrillation. *Circ Arrhythm Electrophysiol* 2011;**4**:262-270.
813. La Meir M, Gelsomino S, Lorusso R, Luca F, Pison L, Parise O, Wellens F, Gensini GF, Maessen J. The hybrid approach for the surgical treatment of lone atrial fibrillation: one-year results employing a monopolar radiofrequency source. *J Cardiothorac Surg* 2012;**7**:71.
814. Wang S, Liu L, Zou C. Comparative study of video-assisted thoracoscopic surgery ablation and radiofrequency catheter ablation on treating paroxysmal atrial fibrillation: a randomized, controlled short-term trial. *Chin Med J (Engl)* 2014;**127**:2567-2570.
815. Phan K, Phan S, Thiagalingam A, Medi C, Yan TD. Thoracoscopic surgical ablation versus catheter ablation for atrial fibrillation. *Eur J Cardiothorac Surg* 2016;**49**:1044-1051.
816. Hu QM, Li Y, Xu CL, Han J, Zhang HB, Han W, Meng X. Analysis of risk factors for recurrence after video-assisted pulmonary vein isolation of lone atrial fibrillation-results of 5 years of follow-up. *J Thorac Cardiovasc Surg* 2014;**148**:2174-2180.
817. Edgerton JR, Edgerton ZJ, Weaver T, Reed K, Prince S, Herbert MA, Mack MJ. Minimally invasive pulmonary vein isolation and partial autonomic denervation for surgical treatment of atrial fibrillation. *Ann Thorac Surg* 2008;**86**:35-38; discussion 39.
818. Wang J, Li Y, Shi J, Han J, Xu C, Ma C, Meng X. Minimally invasive surgical versus catheter ablation for the long-lasting persistent atrial fibrillation. *PLoS One* 2011;**6**:e22122.
819. Wang JG, Xin M, Han J, Li Y, Luo TG, Wang J, Meng F, Meng X. Ablation in selective patients with long-standing persistent atrial fibrillation: medium-term results of the Dallas lesion set. *Eur J Cardiothorac Surg* 2014;**46**:213-220.

820. Sirak JH, Schwartzman D. Interim results of the 5-box thoracoscopic maze procedure. *Ann Thorac Surg* 2012;**94**:1880-1884.
821. Kasirajan V, Spradlin EA, Mormando TE, Medina AE, Ovadia P, Schwartzman DS, Gaines TE, Mumtaz MA, Downing SW, Ellenbogen KA. Minimally invasive surgery using bipolar radiofrequency energy is effective treatment for refractory atrial fibrillation. *Ann Thorac Surg* 2012;**93**:1456-1461.
822. Weimar T, Vosseler M, Czesla M, Boscheinen M, Hemmer WB, Doll KN. Approaching a paradigm shift: endoscopic ablation of lone atrial fibrillation on the beating heart. *Ann Thorac Surg* 2012;**94**:1886-1892.
823. La Meir M, Gelsomino S, Luca F, Pison L, Parise O, Colella A, Gensini GF, Crijns H, Wellens F, Maessen JG. Minimally invasive surgical treatment of lone atrial fibrillation: early results of hybrid versus standard minimally invasive approach employing radiofrequency sources. *Int J Cardiol* 2013;**167**:1469-1475.
824. Gelsomino S, Van Breugel HN, Pison L, Parise O, Crijns HJ, Wellens F, Maessen JG, La Meir M. Hybrid thoracoscopic and transvenous catheter ablation of atrial fibrillation. *Eur J Cardiothorac Surg* 2014;**45**:401-407.
825. Pison L, La Meir M, van Opstal J, Blaauw Y, Maessen J, Crijns HJ. Hybrid thoracoscopic surgical and transvenous catheter ablation of atrial fibrillation. *J Am Coll Cardiol* 2012;**60**:54-61.
826. De Maat GE, Van Gelder IC, Rienstra M, Quast AF, Tan ES, Wiesfeld AC, Pozzoli A, Mariani MA. Surgical vs. transcatheter pulmonary vein isolation as first invasive treatment in patients with atrial fibrillation: a matched group comparison. *Europace* 2014;**16**:33-39.
827. Vadmann H, Nielsen PB, Hjortshoj SP, Riahi S, Rasmussen LH, Lip GY, Larsen TB. Atrial flutter and thromboembolic risk: a systematic review. *Heart* 2015;**101**:1446-1455.
828. Stulak JM, Dearani JA, Daly RC, Zehr KJ, Sundt TM, 3rd, Schaff HV. Left ventricular dysfunction in atrial fibrillation: restoration of sinus rhythm by the Cox-maze procedure significantly improves systolic function and functional status. *Ann Thorac Surg* 2006;**82**:494-501.
829. Chen YW, Bai R, Lin T, Salim M, Sang CH, Long DY, Yu RH, Tang RB, Guo XY, Yan XL, Nie JG, Du X, Dong JZ, Ma CS. Pacing or ablation: which is better for paroxysmal atrial fibrillation-related tachycardia-bradycardia syndrome? *Pacing Clin Electrophysiol* 2014;**37**:403-411.
830. Khaykin Y, Marrouche NF, Martin DO, Saliba W, Schweikert R, Wexman M, Strunk B, Beheiry S, Saad E, Bhargava M, Burkhardt JD, Joseph G, Tchou P, Natale A. Pulmonary vein isolation for atrial fibrillation in patients with symptomatic sinus bradycardia or pauses. *J Cardiovasc Electrophysiol* 2004;**15**:784-789.
831. Ad N, Henry L, Hunt S. Current role for surgery in treatment of lone atrial fibrillation. *Semin Thorac Cardiovasc Surg* 2012;**24**:42-50.
832. Weimar T, Schena S, Bailey MS, Maniar HS, Schuessler RB, Cox JL, Damiano RJ, Jr. The cox-maze procedure for lone atrial fibrillation: a single-center experience over 2 decades. *Circ Arrhythm Electrophysiol* 2012;**5**:8-14.
833. Ad N, Henry L, Hunt S, Holmes SD. Do we increase the operative risk by adding the Cox Maze III procedure to aortic valve replacement and coronary artery bypass surgery? *J Thorac Cardiovasc Surg* 2012;**143**:936-944.
834. Prakash A, Saksena S, Krol RB, Filipecki A, Philip G. Catheter ablation of inducible atrial flutter, in combination with atrial pacing and antiarrhythmic drugs ("hybrid therapy") improves rhythm control in patients with refractory atrial fibrillation. *J Interv Card Electrophysiol* 2002;**6**:165-172.
835. Tai CT, Chiang CE, Lee SH, Chen YJ, Yu WC, Feng AN, Ding YA, Chang MS, Chen SA. Persistent atrial flutter in patients treated for atrial fibrillation with amiodarone and propafenone: electrophysiologic characteristics, radiofrequency catheter ablation, and risk prediction [see comments]. *J Cardiovasc Electrophysiol* 1999;**10**:1180-1187.
836. Stabile G, De Simone A, Turco P, La Rocca V, Nocerino P, Astarita C, Maresca F, De Matteis C, Di Napoli T, Stabile E, Vitale DF. Response to flecainide infusion predicts long-term success of hybrid pharmacologic and ablation therapy in patients with atrial fibrillation. *J Am Coll Cardiol* 2001;**37**:1639-1644.
837. Anastasio N, Frankel DS, Deyell MW, Zado E, Gerstenfeld EP, Dixit S, Cooper J, Lin D, Marchlinski FE, Callans DJ. Nearly uniform failure of atrial flutter ablation and continuation of antiarrhythmic agents (hybrid therapy) for the long-term control of atrial fibrillation. *J Interv Card Electrophysiol* 2012;**35**:57-61.
838. Garcia Seara J, Raposeiras Roubin S, Gude Sampedro F, Balboa Barreiro V, Martinez Sande JL, Rodriguez Manero M, Gonzalez Juanatey JR. Failure of hybrid therapy for the prevention of long-term recurrence of atrial fibrillation. *Int J Cardiol* 2014;**176**:74-79.

839. Saksena S, Prakash A, Ziegler P, Hummel JD, Friedman P, Plumb VJ, Wyse DG, Johnson E, Fitts S, Mehra R. Improved suppression of recurrent atrial fibrillation with dual-site right atrial pacing and antiarrhythmic drug therapy. *J Am Coll Cardiol* 2002;**40**:1140-1150; discussion 1151-1142.
840. Wharton JM, Sorrentino RA, Campbell P, Gonzalez-Zuelgaray J, Keating E, Curtis A, Grill C, Hafley G, Lee K. Effect of pacing modality on atrial tachyarrhythmia recurrence in the tachycardia-bradycardia syndrome: preliminary results of the Pacemaker Atrial Tachycardia Trial. *Circulation* 1998;**98 (suppl I)**:I-494 (abstract).
841. Marinigh R, Lip GY, Fiotti N, Giansante C, Lane DA. Age as a risk factor for stroke in atrial fibrillation patients: implications for thromboprophylaxis. *J Am Coll Cardiol* 2010;**56**:827-837.
842. Gage BF, Boechler M, Doggette AL, Fortune G, Flaker GC, Rich MW, Radford MJ. Adverse outcomes and predictors of underuse of antithrombotic therapy in medicare beneficiaries with chronic atrial fibrillation. *Stroke* 2000;**31**:822-827.
843. Andreotti F, Rocca B, Husted S, Ajjan RA, Ten Berg J, Cattaneo M, Collet JP, De Caterina R, Fox KA, Halvorsen S, Huber K, Hylek EM, Lip GY, Montalescot G, Morais J, Patrono C, Verheugt FW, Wallentin L, Weiss TW, Storey RF, ESC Thrombosis Working Group. Antithrombotic therapy in the elderly: expert position paper of the European Society of Cardiology Working Group on Thrombosis. *Eur Heart J* 2015;**36**:3238-3249.
844. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen K, Kuck KH, Hernandez-Madrid A, Nikolaou N, Norekval TM, Spaulding C, Van Veldhuisen DJ. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J* 2015;**36**:2793-2867.
845. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C, Watkins H. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J* 2014;**35**:2733-2779.
846. Johnson JN, Tester DJ, Perry J, Salisbury BA, Reed CR, Ackerman MJ. Prevalence of early-onset atrial fibrillation in congenital long QT syndrome. *Heart Rhythm* 2008;**5**:704-709.
847. Kirchhof P, Eckardt L, Franz MR, Monnig G, Loh P, Wedekind H, Schulze-Bahr E, Breithardt G, Haverkamp W. Prolonged atrial action potential durations and polymorphic atrial tachyarrhythmias in patients with long QT syndrome. *J Cardiovasc Electrophysiol* 2003;**14**:1027-1033.
848. Zellerhoff S, Pistulli R, Monnig G, Hinterseer M, Beckmann BM, Kobe J, Steinbeck G, Kaab S, Haverkamp W, Fabritz L, Gradaus R, Breithardt G, Schulze-Bahr E, Bocker D, Kirchhof P. Atrial Arrhythmias in long-QT syndrome under daily life conditions: a nested case control study. *J Cardiovasc Electrophysiol* 2009;**20**:401-407.
849. Moss AJ, Zareba W, Benhorin J, Locati EH, Hall WJ, Robinson JL, Schwartz PJ, Towbin JA, Vincent GM, Lehmann MH. ECG T-wave patterns in genetically distinct forms of the hereditary long QT syndrome. *Circulation* 1995;**92**:2929-2934.
850. Schwartz PJ, Priori SG, Spazzolini C, Moss AJ, Vincent GM, Napolitano C, Denjoy I, Guicheney P, Breithardt G, Keating MT, Towbin JA, Beggs AH, Brink P, Wilde AA, Toivonen L, Zareba W, Robinson JL, Timothy KW, Corfield V, Wattanasirichaigoon D, Corbett C, Haverkamp W, Schulze-Bahr E, Lehmann MH, Schwartz K, Coumel P, Bloise R. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. *Circulation* 2001;**103**:89-95.
851. Eckardt L, Kirchhof P, Loh P, Schulze-Bahr E, Johna R, Wichter T, Breithardt G, Haverkamp W, Borggrefe M. Brugada syndrome and supraventricular tachyarrhythmias: a novel association? *J Cardiovasc Electrophysiol* 2001;**12**:680-685.
852. Kaufman ES. Mechanisms and clinical management of inherited channelopathies: long QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, and short QT syndrome. *Heart Rhythm* 2009;**6**:S51-55.
853. Antzelevitch C, Pollevick GD, Cordeiro JM, Casis O, Sanguinetti MC, Aizawa Y, Guerchicoff A, Pfeiffer R, Oliva A, Wollnik B, Gelber P, Bonaros EP, Jr., Burashnikov E, Wu Y, Sargent JD, Schickel S, Oberheiden R, Bhatia A, Hsu LF, Haissaguerre M, Schimpf R, Borggrefe M, Wolpert C. Loss-of-function mutations in the cardiac calcium channel underlie a new clinical entity characterized by ST-segment elevation, short QT intervals, and sudden cardiac death. *Circulation* 2007;**115**:442-449.

854. London B, Michalec M, Mehdi H, Zhu X, Kerchner L, Sanyal S, Viswanathan PC, Pfahnl AE, Shang LL, Madhusudanan M, Baty CJ, Lagana S, Aleong R, Gutmann R, Ackerman MJ, McNamara DM, Weiss R, Dudley SC, Jr. Mutation in glycerol-3-phosphate dehydrogenase 1 like gene (GPD1-L) decreases cardiac Na+ current and causes inherited arrhythmias. *Circulation* 2007;**116**:2260-2268.
855. Watanabe H, Koopmann TT, Le Scouarnec S, Yang T, Ingram CR, Schott JJ, Demolombe S, Probst V, Anselme F, Escande D, Wiesfeld AC, Pfeufer A, Kaab S, Wichmann HE, Hasdemir C, Aizawa Y, Wilde AA, Roden DM, Bezzina CR. Sodium channel beta1 subunit mutations associated with Brugada syndrome and cardiac conduction disease in humans. *J Clin Invest* 2008;**118**:2260-2268.
856. Brugada R, Hong K, Dumaine R, Cordeiro J, Gaita F, Borggrefe M, Menendez TM, Brugada J, Pollevick GD, Wolpert C, Burashnikov E, Matsuo K, Wu YS, Guerchicoff A, Bianchi F, Giustetto C, Schimpf R, Brugada P, Antzelevitch C. Sudden death associated with short-QT syndrome linked to mutations in HERG. *Circulation* 2004;**109**:30-35.
857. Gaita F, Giustetto C, Bianchi F, Wolpert C, Schimpf R, Riccardi R, Grossi S, Richiardi E, Borggrefe M. Short QT Syndrome: a familial cause of sudden death. *Circulation* 2003;**108**:965-970.
858. Giustetto C, Di Monte F, Wolpert C, Borggrefe M, Schimpf R, Sbragia P, Leone G, Maury P, Anttonen O, Haissaguerre M, Gaita F. Short QT syndrome: clinical findings and diagnostic-therapeutic implications. *Eur Heart J* 2006;**27**:2440-2447.
859. Bhuiyan ZA, van den Berg MP, van Tintelen JP, Bink-Boelkens MT, Wiesfeld AC, Alders M, Postma AV, van Langen I, Mannens MM, Wilde AA. Expanding spectrum of human RYR2-related disease: new electrocardiographic, structural, and genetic features. *Circulation* 2007;**116**:1569-1576.
860. Napolitano C, Priori SG. Diagnosis and treatment of catecholaminergic polymorphic ventricular tachycardia. *Heart Rhythm* 2007;**4**:675-678.
861. Mohamed U, Napolitano C, Priori SG. Molecular and electrophysiological bases of catecholaminergic polymorphic ventricular tachycardia. *J Cardiovasc Electrophysiol* 2007;**18**:791-797.
862. Lee CH, Liu PY, Lin LJ, Chen JH, Tsai LM. Clinical characteristics and outcomes of hypertrophic cardiomyopathy in Taiwan--a tertiary center experience. *Clin Cardiol* 2007;**30**:177-182.
863. Losi MA, Betocchi S, Aversa M, Lombardi R, Miranda M, D'Alessandro G, Cacace A, Tocchetti CG, Barbati G, Chiariello M. Determinants of atrial fibrillation development in patients with hypertrophic cardiomyopathy. *Am J Cardiol* 2004;**94**:895-900.
864. Maron BJ, Olivotto I, Bellone P, Conte MR, Cecchi F, Flygenring BP, Casey SA, Gohman TE, Bongioanni S, Spirito P. Clinical profile of stroke in 900 patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2002;**39**:301-307.
865. Gollob MH, Seger JJ, Gollob TN, Tapscott T, Gonzales O, Bachinski L, Roberts R. Novel PRKAG2 mutation responsible for the genetic syndrome of ventricular preexcitation and conduction system disease with childhood onset and absence of cardiac hypertrophy. *Circulation* 2001;**104**:3030-3033.
866. Postma AV, van de Meerakker JB, Mathijssen IB, Barnett P, Christoffels VM, Ilgun A, Lam J, Wilde AA, Lekanne Deprez RH, Moorman AF. A gain-of-function TBX5 mutation is associated with atypical Holt-Oram syndrome and paroxysmal atrial fibrillation. *Circ Res* 2008;**102**:1433-1442.
867. Marcus FI, Edson S, Towbin JA. Genetics of arrhythmogenic right ventricular cardiomyopathy: a practical guide for physicians. *J Am Coll Cardiol* 2013;**61**:1945-1948.
868. Chu AF, Zado E, Marchlinski FE. Atrial arrhythmias in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia and ventricular tachycardia. *Am J Cardiol* 2010;**106**:720-722.
869. Blomstrom-Lundqvist C, Scheinman MM, Aliot EM, Alpert JS, Calkins H, Camm AJ, Campbell WB, Haines DE, Kuck KH, Lerman BB, Miller DD, Shaeffer CW, Stevenson WG, Tomaselli GF, Antman EM, Smith SC, Jr., Alpert JS, Faxon DP, Fuster V, Gibbons RJ, Gregoratos G, Hiratzka LF, Hunt SA, Jacobs AK, Russell RO, Jr., Priori SG, Blanc JJ, Budaj A, Burgos EF, Cowie M, Deckers JW, Garcia MA, Klein WW, Lekakis J, Lindahl B, Mazzotta G, Morais JC, Oto A, Smiseth O, Trappe HJ, European Society of Cardiology Committee, NASPE-Heart Rhythm Society. ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias--executive summary. a report of the American college of cardiology/American heart association task force on practice guidelines and the European society of cardiology committee for practice guidelines (writing committee to develop guidelines for the management of patients with supraventricular arrhythmias) developed in collaboration with NASPE-Heart Rhythm Society. *J Am Coll Cardiol* 2003;**42**:1493-1531.
870. Tischenko A, Fox DJ, Yee R, Krahn AD, Skanes AC, Gula LJ, Klein GJ. When should we recommend catheter ablation for patients with the Wolff-Parkinson-White syndrome? *Curr Opin Cardiol* 2008;**23**:32-37.
871. Kibos A, Deharo JC, Adoubi A, Assouan X, Djianeb P. [Clinical and electrophysiological study of asymptomatic Wolff-Parkinson-White syndrome]. *Ann Cardiol Angeiol (Paris)* 2007;**56**:237-240.

872. Pappone C, Santinelli V, Manguso F, Augello G, Santinelli O, Vicedomini G, Gulletta S, Mazzone P, Tortoriello V, Pappone A, Dicandia C, Rosanio S. A randomized study of prophylactic catheter ablation in asymptomatic patients with the Wolff-Parkinson-White syndrome. *N Engl J Med* 2003;**349**:1803-1811.
873. Boahene KA, Klein GJ, Yee R, Sharma AD, Fujimura O. Termination of acute atrial fibrillation in the Wolff-Parkinson-White syndrome by procainamide and propafenone: importance of atrial fibrillatory cycle length. *J Am Coll Cardiol* 1990;**16**:1408-1414.
874. O'Nunain S, Garratt CJ, Linker NJ, Gill J, Ward DE, Camm AJ. A comparison of intravenous propafenone and flecainide in the treatment of tachycardias associated with the Wolff-Parkinson-White syndrome. *Pacing Clin Electrophysiol* 1991;**14**:2028-2034.
875. Manolis AS, Estes NA, 3rd. Supraventricular tachycardia. Mechanisms and therapy. *Arch Intern Med* 1987;**147**:1706-1716.
876. Simonian SM, Lotfipour S, Wall C, Langdorf MI. Challenging the superiority of amiodarone for rate control in Wolff-Parkinson-White and atrial fibrillation. *Intern Emerg Med* 2010;**5**:421-426.
877. Guttmann OP, Rahman MS, O'Mahony C, Anastasakis A, Elliott PM. Atrial fibrillation and thromboembolism in patients with hypertrophic cardiomyopathy: systematic review. *Heart* 2014;**100**:465-472.
878. Olivotto I, Cecchi F, Casey SA, Dolara A, Traverse JH, Maron BJ. Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy. *Circulation* 2001;**104**:2517-2524.
879. Cecchi F, Olivotto I, Montereggi A, Squillatini G, Dolara A, Maron BJ. Prognostic value of non-sustained ventricular tachycardia and the potential role of amiodarone treatment in hypertrophic cardiomyopathy: assessment in an unselected non-referral based patient population. *Heart* 1998;**79**:331-336.
880. Bunch TJ, Munger TM, Friedman PA, Asirvatham SJ, Brady PA, Cha YM, Rea RF, Shen WK, Powell BD, Ommen SR, Monahan KH, Haroldson JM, Packer DL. Substrate and procedural predictors of outcomes after catheter ablation for atrial fibrillation in patients with hypertrophic cardiomyopathy. *J Cardiovasc Electrophysiol* 2008;**19**:1009-1014.
881. Di Donna P, Olivotto I, Delcre SD, Caponi D, Scaglione M, Nault I, Montefusco A, Girolami F, Cecchi F, Haissaguerre M, Gaita F. Efficacy of catheter ablation for atrial fibrillation in hypertrophic cardiomyopathy: impact of age, atrial remodelling, and disease progression. *Europace* 2010;**12**:347-355.
882. Gaita F, Di Donna P, Olivotto I, Scaglione M, Ferrero I, Montefusco A, Caponi D, Conte MR, Nistri S, Cecchi F. Usefulness and safety of transcatheter ablation of atrial fibrillation in patients with hypertrophic cardiomyopathy. *Am J Cardiol* 2007;**99**:1575-1581.
883. Kilicaslan F, Verma A, Saad E, Themistoclakis S, Bonso A, Raviele A, Bozbas H, Andrews MW, Beheiry S, Hao S, Cummings JE, Marrouche NF, Lakkireddy D, Wazni O, Yamaji H, Saenz LC, Saliba W, Schweikert RA, Natale A. Efficacy of catheter ablation of atrial fibrillation in patients with hypertrophic obstructive cardiomyopathy. *Heart Rhythm* 2006;**3**:275-280.
884. McCready JW, Smedley T, Lambiase PD, Ahsan SY, Segal OR, Rowland E, Lowe MD, Chow AW. Predictors of recurrence following radiofrequency ablation for persistent atrial fibrillation. *Europace* 2011;**13**:355-361.
885. Ritchie MD, Rowan S, Kucera G, Stubblefield T, Blair M, Carter S, Roden DM, Darbar D. Chromosome 4q25 variants are genetic modifiers of rare ion channel mutations associated with familial atrial fibrillation. *J Am Coll Cardiol* 2012;**60**:1173-1181.
886. Mann SA, Otway R, Guo G, Soka M, Karlsdotter L, Trivedi G, Ohanian M, Zodgekar P, Smith RA, Wouters MA, Subbiah R, Walker B, Kuchar D, Sanders P, Griffiths L, Vandenberg JI, Fatkin D. Epistatic effects of potassium channel variation on cardiac repolarization and atrial fibrillation risk. *J Am Coll Cardiol* 2012;**59**:1017-1025.
887. Giustetto C, Cerrato N, Gribaudo E, Scrocco C, Castagno D, Richiardi E, Giachino D, Bianchi F, Barbonaglia L, Ferraro A. Atrial fibrillation in a large population with Brugada electrocardiographic pattern: prevalence, management, and correlation with prognosis. *Heart Rhythm* 2014;**11**:259-265.
888. Darbar D, Kannankeril PJ, Donahue BS, Kucera G, Stubblefield T, Haines JL, George AL, Jr., Roden DM. Cardiac sodium channel (SCN5A) variants associated with atrial fibrillation. *Circulation* 2008;**117**:1927-1935.
889. Olson TM, Michels VV, Ballew JD, Reyna SP, Karst ML, Herron KJ, Horton SC, Rodeheffer RJ, Anderson JL. Sodium channel mutations and susceptibility to heart failure and atrial fibrillation. *JAMA* 2005;**293**:447-454.
890. Ellinor PT, Moore RK, Patton KK, Ruskin JN, Pollak MR, Macrae CA. Mutations in the long QT gene, KCNQ1, are an uncommon cause of atrial fibrillation. *Heart* 2004;**90**:1487-1488.

891. Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, Blom N, Brugada J, Chiang CE, Huikuri H, Kannankeril P, Krahn A, Leenhardt A, Moss A, Schwartz PJ, Shimizu W, Tomaselli G, Tracy C, Ackerman M, Belhassen B, Estes NA, 3rd, Fatkin D, Kalman J, Kaufman E, Kirchhof P, Schulze-Bahr E, Wolpert C, Vohra J, Refaat M, Etheridge SP, Campbell RM, Martin ET, Quek SC. Executive summary: HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. *Europace* 2013;**15**:1389-1406.
892. Antz M, Weiss C, Volkmer M, Hebe J, Ernst S, Ouyang F, Kuck KH. Risk of sudden death after successful accessory atrioventricular pathway ablation in resuscitated patients with Wolff-Parkinson-White syndrome. *J Cardiovasc Electrophysiol* 2002;**13**:231-236.
893. Timmermans C, Smeets JL, Rodriguez LM, Vrouchos G, van den Dool A, Wellens HJ. Aborted sudden death in the Wolff-Parkinson-White syndrome. *Am J Cardiol* 1995;**76**:492-494.
894. Bromberg BI, Lindsay BD, Cain ME, Cox JL. Impact of clinical history and electrophysiologic characterization of accessory pathways on management strategies to reduce sudden death among children with Wolff-Parkinson-White syndrome. *J Am Coll Cardiol* 1996;**27**:690-695.
895. Al-Khatib SM, Arshad A, Balk EM, Das SR, Hsu JC, Joglar JA, Page RL. Risk stratification for arrhythmic events in patients with asymptomatic pre-excitation: A systematic review for the 2015 ACC/AHA/HRS guideline for the management of adult patients with supraventricular tachycardia: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Heart Rhythm* 2016;**13**:e222-237.
896. Maron BJ, Ommen SR, Semsarian C, Spirito P, Olivotto I, Maron MS. Hypertrophic cardiomyopathy: present and future, with translation into contemporary cardiovascular medicine. *J Am Coll Cardiol* 2014;**64**:83-99.
897. Robinson K, Frenneaux MP, Stockins B, Karatasakis G, Poloniecki JD, McKenna WJ. Atrial fibrillation in hypertrophic cardiomyopathy: a longitudinal study. *J Am Coll Cardiol* 1990;**15**:1279-1285.
898. Mozaffarian D, Furberg CD, Psaty BM, Siscovick D. Physical activity and incidence of atrial fibrillation in older adults: the cardiovascular health study. *Circulation* 2008;**118**:800-807.
899. Elosua R, Arquer A, Mont L, Sambola A, Molina L, Garcia-Moran E, Brugada J, Marrugat J. Sport practice and the risk of lone atrial fibrillation: a case-control study. *Int J Cardiol* 2006;**108**:332-337.
900. Mont L, Sambola A, Brugada J, Vacca M, Marrugat J, Elosua R, Pare C, Azqueta M, Sanz G. Long-lasting sport practice and lone atrial fibrillation. *Eur Heart J* 2002;**23**:477-482.
901. Abdulla J, Nielsen JR. Is the risk of atrial fibrillation higher in athletes than in the general population? A systematic review and meta-analysis. *Europace* 2009;**11**:1156-1159.
902. Thelle DS, Selmer R, Gjesdal K, Sakshaug S, Jugessur A, Graff-Iversen S, Tverdal A, Nystad W. Resting heart rate and physical activity as risk factors for lone atrial fibrillation: a prospective study of 309,540 men and women. *Heart* 2013;**99**:1755-1760.
903. Wilhelm M, Roten L, Tanner H, Wilhelm I, Schmid JP, Saner H. Atrial remodeling, autonomic tone, and lifetime training hours in nonelite athletes. *Am J Cardiol* 2011;**108**:580-585.
904. Guasch E, Benito B, Qi X, Cifelli C, Naud P, Shi Y, Mighiu A, Tardif JC, Tadevosyan A, Chen Y, Gillis MA, Iwasaki YK, Dobrev D, Mont L, Heximer S, Nattel S. Atrial fibrillation promotion by endurance exercise: demonstration and mechanistic exploration in an animal model. *J Am Coll Cardiol* 2013;**62**:68-77.
905. Andersen K, Farahmand B, Ahlbom A, Held C, Ljunghall S, Michaelsson K, Sundstrom J. Risk of arrhythmias in 52 755 long-distance cross-country skiers: a cohort study. *Eur Heart J* 2013;**34**:3624-3631.
906. Karjalainen J, Kujala UM, Kaprio J, Sarna S, Viitasalo M. Lone atrial fibrillation in vigorously exercising middle aged men: case-control study. *BMJ* 1998;**316**:1784-1785.
907. Biffi A, Maron BJ, Culasso F, Verdile L, Fernando F, Di Giacinto B, Di Paolo FM, Spataro A, Delise P, Pelliccia A. Patterns of ventricular tachyarrhythmias associated with training, deconditioning and retraining in elite athletes without cardiovascular abnormalities. *Am J Cardiol* 2011;**107**:697-703.
908. Calvo N, Mont L, Tamborero D, Berruezo A, Viola G, Guasch E, Nadal M, Andreu D, Vidal B, Sitges M, Brugada J. Efficacy of circumferential pulmonary vein ablation of atrial fibrillation in endurance athletes. *Europace* 2010;**12**:30-36.
909. Koopman P, Nuyens D, Garweg C, La Gerche A, De Buck S, Van Casteren L, Alzand B, Willems R, Heidbuchel H. Efficacy of radiofrequency catheter ablation in athletes with atrial fibrillation. *Europace* 2011;**13**:1386-1393.
910. Heidbuchel H, Panhuyzen-Goedkoop N, Corrado D, Hoffmann E, Biffi A, Delise P, Blomstrom-Lundqvist C, Vanhees L, Ivarhoff P, Dorwarth U, Pelliccia A. Recommendations for participation in leisure-time physical activity and competitive sports in patients with arrhythmias and

potentially arrhythmogenic conditions Part I: Supraventricular arrhythmias and pacemakers. *Eur J Cardiovasc Prev Rehabil* 2006;**13**:475-484.
911. Silversides CK, Harris L, Haberer K, Sermer M, Colman JM, Siu SC. Recurrence rates of arrhythmias during pregnancy in women with previous tachyarrhythmia and impact on fetal and neonatal outcomes. *Am J Cardiol* 2006;**97**:1206-1212.
912. Salam AM, Ertekin E, van Hagen IM, Al Suwaidi J, Ruys TPE, Johnson MR, Gumbiene L, Frogoudaki AA, Sorour KA, Iserin L, Ladouceur M, van Oppen ACC, Hall R, Roos-Hesselink JW. Atrial Fibrillation or Flutter During Pregnancy in Patients With Structural Heart Disease: Data From the ROPAC (Registry on Pregnancy and Cardiac Disease). *JACC Clin Electrophysiol* 2015;**1**:284-292.
913. Baumgartner H, Bonhoeffer P, De Groot NM, de Haan F, Deanfield JE, Galie N, Gatzoulis MA, Gohlke-Baerwolf C, Kaemmerer H, Kilner P, Meijboom F, Mulder BJ, Oechslin E, Oliver JM, Serraf A, Szatmari A, Thaulow E, Vouhe PR, Walma E. ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). *Eur Heart J* 2010;**31**:2915-2957.
914. Page RL. Treatment of arrhythmias during pregnancy. *Am Heart J* 1995;**130**:871-876.
915. Magee LA, Duley L. Oral beta-blockers for mild to moderate hypertension during pregnancy. *Cochrane Database Syst Rev* 2003;**3**:CD002863.
916. Mitani GM, Steinberg I, Lien EJ, Harrison EC, Elkayam U. The pharmacokinetics of antiarrhythmic agents in pregnancy and lactation. *Clin Pharmacokinet* 1987;**12**:253-291.
917. Gowda RM, Khan IA, Mehta NJ, Vasavada BC, Sacchi TJ. Cardiac arrhythmias in pregnancy: clinical and therapeutic considerations. *Int J Cardiol* 2003;**88**:129-133.
918. Joint Formulary Committee. *British National Formulary (online)*. http://www.medicinescomplete.com. Date last accessed 02/12/2014 2014
919. Bartalena L, Bogazzi F, Braverman LE, Martino E. Effects of amiodarone administration during pregnancy on neonatal thyroid function and subsequent neurodevelopment. *J Endocrinol Invest* 2001;**24**:116-130.
920. Jaeggi ET, Carvalho JS, De Groot E, Api O, Clur SA, Rammeloo L, McCrindle BW, Ryan G, Manlhiot C, Blom NA. Comparison of transplacental treatment of fetal supraventricular tachyarrhythmias with digoxin, flecainide, and sotalol: results of a nonrandomized multicenter study. *Circulation* 2011;**124**:1747-1754.
921. Tromp CHN, Nanne ACM, Pernet PJM, Tukkie R, Bolte AC. Electrical cardioversion during pregnancy: safe or not? *Neth Heart J* 2011;**19**:134-136.
922. Ghosh N, Luk A, Derzko C, Dorian P, Chow CM. The acute treatment of maternal supraventricular tachycardias during pregnancy: a review of the literature. *J Obstet Gynaecol Can* 2011;**33**:17-23.
923. Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO, American College of Chest Physicians. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;**141**:e691S-736S.
924. Ahlsson AJ, Bodin L, Lundblad OH, Englund AG. Postoperative atrial fibrillation is not correlated to C-reactive protein. *Ann Thorac Surg* 2007;**83**:1332-1337.
925. Arsenault KA, Yusuf AM, Crystal E, Healey JS, Morillo CA, Nair GM, Whitlock RP. Interventions for preventing post-operative atrial fibrillation in patients undergoing heart surgery. *Cochrane Database Syst Rev* 2013;**1**:Cd003611.
926. Mathew JP, Fontes ML, Tudor IC, Ramsay J, Duke P, Mazer CD, Barash PG, Hsu PH, Mangano DT. A multicenter risk index for atrial fibrillation after cardiac surgery. *JAMA* 2004;**291**:1720-1729.
927. Steinberg BA, Zhao Y, He X, Hernandez AF, Fullerton DA, Thomas KL, Mills R, Klaskala W, Peterson ED, Piccini JP. Management of postoperative atrial fibrillation and subsequent outcomes in contemporary patients undergoing cardiac surgery: insights from the Society of Thoracic Surgeons CAPS-Care Atrial Fibrillation Registry. *Clin Cardiol* 2014;**37**:7-13.
928. Khan MF, Wendel CS, Movahed MR. Prevention of post-coronary artery bypass grafting (CABG) atrial fibrillation: efficacy of prophylactic beta-blockers in the modern era: a meta-analysis of latest randomized controlled trials. *Ann Noninvasive Electrocardiol* 2013;**18**:58-68.
929. Burgess DC, Kilborn MJ, Keech AC. Interventions for prevention of post-operative atrial fibrillation and its complications after cardiac surgery: a meta-analysis. *Eur Heart J* 2006;**27**:2846-2857.
930. Chatterjee S, Sardar P, Mukherjee D, Lichstein E, Aikat S. Timing and route of amiodarone for prevention of postoperative atrial fibrillation after cardiac surgery: a network regression meta-analysis. *Pacing Clin Electrophysiol* 2013;**36**:1017-1023.

931. Zhu J, Wang C, Gao D, Zhang C, Zhang Y, Lu Y, Gao Y. Meta-analysis of amiodarone versus beta-blocker as a prophylactic therapy against atrial fibrillation following cardiac surgery. *Intern Med J* 2012;**42**:1078-1087.
932. Fauchier L, Clementy N, Babuty D. Statin therapy and atrial fibrillation: systematic review and updated meta-analysis of published randomized controlled trials. *Curr Opin Cardiol* 2013;**28**:7-18.
933. Zheng H, Xue S, Hu ZL, Shan JG, Yang WG. The use of statins to prevent postoperative atrial fibrillation after coronary artery bypass grafting: a meta-analysis of 12 studies. *J Cardiovasc Pharmacol* 2014;**64**:285-292.
934. Casadei B, OTHERS. Statin Therapy In Cardiac Surgery (STICS) Trial. *N Engl J Med* 2016;**TO BE ADDED**.
935. Cook RC, Yamashita MH, Kearns M, Ramanathan K, Gin K, Humphries KH. Prophylactic magnesium does not prevent atrial fibrillation after cardiac surgery: a meta-analysis. *Ann Thorac Surg* 2013;**95**:533-541.
936. De Oliveira GS, Jr., Knautz JS, Sherwani S, McCarthy RJ. Systemic magnesium to reduce postoperative arrhythmias after coronary artery bypass graft surgery: a meta-analysis of randomized controlled trials. *J Cardiothorac Vasc Anesth* 2012;**26**:643-650.
937. Costanzo S, di Niro V, Di Castelnuovo A, Gianfagna F, Donati MB, de Gaetano G, Iacoviello L. Prevention of postoperative atrial fibrillation in open heart surgery patients by preoperative supplementation of n-3 polyunsaturated fatty acids: an updated meta-analysis. *J Thorac Cardiovasc Surg* 2013;**146**:906-911.
938. Farquharson AL, Metcalf RG, Sanders P, Stuklis R, Edwards JR, Gibson RA, Cleland LG, Sullivan TR, James MJ, Young GD. Effect of dietary fish oil on atrial fibrillation after cardiac surgery. *Am J Cardiol* 2011;**108**:851-856.
939. Heidarsdottir R, Arnar DO, Skuladottir GV, Torfason B, Edvardsson V, Gottskalksson G, Palsson R, Indridason OS. Does treatment with n-3 polyunsaturated fatty acids prevent atrial fibrillation after open heart surgery? *Europace* 2010;**12**:356-363.
940. Mariani J, Doval HC, Nul D, Varini S, Grancelli H, Ferrante D, Tognoni G, Macchia A. N-3 polyunsaturated fatty acids to prevent atrial fibrillation: updated systematic review and meta-analysis of randomized controlled trials. *J Am Heart Assoc* 2013;**2**:e005033.
941. Rodrigo R, Korantzopoulos P, Cereceda M, Asenjo R, Zamorano J, Villalabeitia E, Baeza C, Aguayo R, Castillo R, Carrasco R, Gormaz JG. A randomized controlled trial to prevent post-operative atrial fibrillation by antioxidant reinforcement. *J Am Coll Cardiol* 2013;**62**:1457-1465.
942. Saravanan P, Bridgewater B, West AL, O'Neill SC, Calder PC, Davidson NC. Omega-3 fatty acid supplementation does not reduce risk of atrial fibrillation after coronary artery bypass surgery: a randomized, double-blind, placebo-controlled clinical trial. *Circ Arrhythm Electrophysiol* 2010;**3**:46-53.
943. Wu JH, Marchioli R, Silletta MG, Macchia A, Song X, Siscovick DS, Harris WS, Masson S, Latini R, Albert C, Brown NJ, Lamarra M, Favaloro RR, Mozaffarian D. Plasma phospholipid omega-3 fatty acids and incidence of postoperative atrial fibrillation in the OPERA trial. *J Am Heart Assoc* 2013;**2**:e000397.
944. Xin W, Wei W, Lin Z, Zhang X, Yang H, Zhang T, Li B, Mi S. Fish oil and atrial fibrillation after cardiac surgery: a meta-analysis of randomized controlled trials. *PLoS One* 2013;**8**:e72913.
945. Zhang B, Zhen Y, Tao A, Bao Z, Zhang G. Polyunsaturated fatty acids for the prevention of atrial fibrillation after cardiac surgery: an updated meta-analysis of randomized controlled trials. *J Cardiol* 2014;**63**:53-59.
946. Imazio M, Brucato A, Ferrazzi P, Pullara A, Adler Y, Barosi A, Caforio AL, Cemin R, Chirillo F, Comoglio C, Cugola D, Cumetti D, Dyrda O, Ferrua S, Finkelstein Y, Flocco R, Gandino A, Hoit B, Innocente F, Maestroni S, Musumeci F, Oh J, Pergolini A, Polizzi V, Ristic A, Simon C, Spodick DH, Tarzia V, Trimboli S, Valenti A, Belli R, Gaita F, COPPS-2 Investigators. Colchicine for prevention of postpericardiotomy syndrome and postoperative atrial fibrillation: the COPPS-2 randomized clinical trial. *JAMA* 2014;**312**:1016-1023.
947. Cappabianca G, Rotunno C, de Luca Tupputi Schinosa L, Ranieri VM, Paparella D. Protective effects of steroids in cardiac surgery: a meta-analysis of randomized double-blind trials. *J Cardiothorac Vasc Anesth* 2011;**25**:156-165.
948. Viviano A, Kanagasabay R, Zakkar M. Is perioperative corticosteroid administration associated with a reduced incidence of postoperative atrial fibrillation in adult cardiac surgery? *Interact Cardiovasc Thorac Surg* 2014;**18**:225-229.
949. Kaleda VI, McCormack DJ, Shipolini AR. Does posterior pericardiotomy reduce the incidence of atrial fibrillation after coronary artery bypass grafting surgery? *Interact Cardiovasc Thorac Surg* 2012;**14**:384-389.

950. Dunning J, Treasure T, Versteegh M, Nashef SA. Guidelines on the prevention and management of de novo atrial fibrillation after cardiac and thoracic surgery. *Eur J Cardiothorac Surg* 2006;**30**:852-872.
951. LaPar DJ, Speir AM, Crosby IK, Fonner E, Jr., Brown M, Rich JB, Quader M, Kern JA, Kron IL, Ailawadi G, Investigators for the Virginia Cardiac Surgery Quality Initiative. Postoperative atrial fibrillation significantly increases mortality, hospital readmission, and hospital costs. *Ann Thorac Surg* 2014;**98**:527-533; discussion 533.
952. Saxena A, Dinh DT, Smith JA, Shardey GC, Reid CM, Newcomb AE. Usefulness of postoperative atrial fibrillation as an independent predictor for worse early and late outcomes after isolated coronary artery bypass grafting (multicenter Australian study of 19,497 patients). *Am J Cardiol* 2012;**109**:219-225.
953. Gialdini G, Nearing K, Bhave PD, Bonuccelli U, Iadecola C, Healey JS, Kamel H. Perioperative atrial fibrillation and the long-term risk of ischemic stroke. *JAMA* 2014;**312**:616-622.
954. Ahlsson A, Bodin L, Fengsrud E, Englund A. Patients with postoperative atrial fibrillation have a doubled cardiovascular mortality. *Scand Cardiovasc J* 2009;**43**:330-336.
955. Ahlsson A, Fengsrud E, Bodin L, Englund A. Postoperative atrial fibrillation in patients undergoing aortocoronary bypass surgery carries an eightfold risk of future atrial fibrillation and a doubled cardiovascular mortality. *Eur J Cardiothorac Surg* 2010;**37**:1353-1359.
956. Mariscalco G, Klersy C, Zanobini M, Banach M, Ferrarese S, Borsani P, Cantore C, Biglioli P, Sala A. Atrial fibrillation after isolated coronary surgery affects late survival. *Circulation* 2008;**118**:1612-1618.
957. Villareal RP, Hariharan R, Liu BC, Kar B, Lee VV, Elayda M, Lopez JA, Rasekh A, Wilson JM, Massumi A. Postoperative atrial fibrillation and mortality after coronary artery bypass surgery. *J Am Coll Cardiol* 2004;**43**:742-748.
958. Phan K, Ha HS, Phan S, Medi C, Thomas SP, Yan TD. New-onset atrial fibrillation following coronary bypass surgery predicts long-term mortality: a systematic review and meta-analysis. *Eur J Cardiothorac Surg* 2015;**48**:817-824.
959. El-Chami MF, Kilgo P, Thourani V, Lattouf OM, Delurgio DB, Guyton RA, Leon AR, Puskas JD. New-onset atrial fibrillation predicts long-term mortality after coronary artery bypass graft. *J Am Coll Cardiol* 2010;**55**:1370-1376.
960. Anderson E, Dyke C, Levy JH. Anticoagulation strategies for the management of postoperative atrial fibrillation. *Clin Lab Med* 2014;**34**:537-561.
961. Heldal M, Atar D. Pharmacological conversion of recent-onset atrial fibrillation: a systematic review. *Scand Cardiovasc J Suppl* 2013;**47**:2-10.
962. Gillinov AM, Bagiella E, Moskowitz AJ, Raiten JM, Groh MA, Bowdish ME, Ailawadi G, Kirkwood KA, Perrault LP, Parides MK, Smith Ii RL, Kern JA, Dussault G, Hackmann AE, Jeffries NO, Miller MA, Taddei-Peters WC, Rose EA, Weisel RD, Williams DL, Mangusan RF, Argenziano M, Moquete EG, O'Sullivan KL, Pellerin M, Shah KJ, Gammie JS, Mayer ML, Voisine P, Gelijns AC, O'Gara PT, Mack MJ, CTSN. Rate Control versus Rhythm Control for Atrial Fibrillation after Cardiac Surgery. *N Engl J Med* 2016:[Epub ahead of print].
963. Triedman JK. Arrhythmias in adults with congenital heart disease. *Heart* 2002;**87**:383-389.
964. Ammash NM, Phillips SD, Hodge DO, Connolly HM, Grogan MA, Friedman PA, Warnes CA, Asirvatham SJ. Outcome of direct current cardioversion for atrial arrhythmias in adults with congenital heart disease. *Int J Cardiol* 2012;**154**:270-274.
965. Greason KL, Dearani JA, Theodoro DA, Porter CB, Warnes CA, Danielson GK. Surgical management of atrial tachyarrhythmias associated with congenital cardiac anomalies: Mayo Clinic experience. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu* 2003;**6**:59-71.
966. Payne L, Zeigler VL, Gillette PC. Acute cardiac arrhythmias following surgery for congenital heart disease: mechanisms, diagnostic tools, and management. *Crit Care Nurs Clin North Am* 2011;**23**:255-272.
967. Koyak Z, Harris L, de Groot JR, Silversides CK, Oechslin EN, Bouma BJ, Budts W, Zwinderman AH, Van Gelder IC, Mulder BJ. Sudden cardiac death in adult congenital heart disease. *Circulation* 2012;**126**:1944-1954.
968. Jensen AS, Idorn L, Norager B, Vejlstrup N, Sondergaard L. Anticoagulation in adults with congenital heart disease: The who, the when and the how? *Heart* 2014.
969. Fujita S, Takahashi K, Takeuchi D, Manaka T, Shoda M, Hagiwara N, Kurosawa H, Nakanishi T. Management of late atrial tachyarrhythmia long after Fontan operation. *J Cardiol* 2009;**53**:410-416.
970. Feltes TF, Friedman RA. Transesophageal echocardiographic detection of atrial thrombi in patients with nonfibrillation atrial tachyarrhythmias and congenital heart disease. *J Am Coll Cardiol* 1994;**24**:1365-1370.

971. Nagao K, Tsuchihashi K, Tanaka S, Iimura O. [Studies on atrial arrhythmias in atrial septal defect. The influences of aging on atrial fibrillation]. *Nihon Ronen Igakkai Zasshi* 1995;**32**:27-32.
972. Giamberti A, Chessa M, Abella R, Butera G, Negura D, Foresti S, Carminati M, Cappato R, Frigiola A. Surgical treatment of arrhythmias in adults with congenital heart defects. *Int J Cardiol* 2008;**129**:37-41.
973. Roos-Hesselink JW, Meijboom FJ, Spitaels SE, van Domburg R, van Rijen EH, Utens EM, Bogers AJ, Simoons ML. Excellent survival and low incidence of arrhythmias, stroke and heart failure long-term after surgical ASD closure at young age. A prospective follow-up study of 21-33 years. *Eur Heart J* 2003;**24**:190-197.
974. Yamada T, McElderry HT, Muto M, Murakami Y, Kay GN. Pulmonary vein isolation in patients with paroxysmal atrial fibrillation after direct suture closure of congenital atrial septal defect. *Circ J* 2007;**71**:1989-1992.
975. Van De Bruaene A, Delcroix M, Pasquet A, De Backer J, Paelinck B, Morissens M, Budts W. The importance of pulmonary artery pressures on late atrial arrhythmia in transcatheter and surgically closed ASD type secundum. *Int J Cardiol* 2011;**152**:192-195.
976. de Salle P, Goenen M, Lecron J, Jaumin P, Tremouroux J. [Rhythm disorders occurring after surgical closure of the interatrial communication]. *Acta Cardiol* 1975;**30**:239-249.
977. Scaglione M, Caponi D, Ebrille E, Di Donna P, Di Clemente F, Battaglia A, Raimondo C, Appendino M, Gaita F. Very long-term results of electroanatomic-guided radiofrequency ablation of atrial arrhythmias in patients with surgically corrected atrial septal defect. *Europace* 2014;**16**:1800-1807.
978. Kanter RJ, Garson A, Jr. Atrial arrhythmias during chronic follow-up of surgery for complex congenital heart disease. *Pacing Clin Electrophysiol* 1997;**20**:502-511.
979. Porter CJ, Garson A. Incidence and management of dysrhythmias after Fontan procedure. *Herz* 1993;**18**:318-327.
980. Gelatt M, Hamilton RM, McCrindle BW, Gow RM, Williams WG, Trusler GA, Freedom RM. Risk factors for atrial tachyarrhythmias after the Fontan operation. *J Am Coll Cardiol* 1994;**24**:1735-1741.
981. Peters NS, Somerville J. Arrhythmias after the Fontan procedure. *Br Heart J* 1992;**68**:199-204.
982. Kwak JG, Kim WH, Lee JR, Kim YJ. Surgical therapy of arrhythmias in single-ventricle patients undergoing Fontan or Fontan conversion. *J Card Surg* 2009;**24**:738-741.
983. Backer CL, Tsao S, Deal BJ, Mavroudis C. Maze procedure in single ventricle patients. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu* 2008:44-48.
984. Deal BJ, Mavroudis C, Backer CL. The role of concomitant arrhythmia surgery in patients undergoing repair of congenital heart disease. *Pacing Clin Electrophysiol* 2008;**31 Suppl 1**:S13-16.
985. Gandhi SK. Atrial arrhythmia surgery in congenital heart disease. *J Interv Card Electrophysiol* 2007;**20**:119-125.
986. Correa R, Sherwin ED, Kovach J, Mah DY, Alexander ME, Cecchin F, Walsh EP, Triedman JK, Abrams DJ. Mechanism and ablation of arrhythmia following total cavopulmonary connection. *Circ Arrhythm Electrophysiol* 2015;**8**:318-325.
987. Khairy P, Aboulhosn J, Gurvitz MZ, Opotowsky AR, Mongeon FP, Kay J, Valente AM, Earing MG, Lui G, Gersony DR, Cook S, Ting JG, Nickolaus MJ, Webb G, Landzberg MJ, Broberg CS, Alliance for Adult Research in Congenital Cardiology. Arrhythmia burden in adults with surgically repaired tetralogy of Fallot: a multi-institutional study. *Circulation* 2010;**122**:868-875.
988. Kobayashi J, Yamamoto F, Nakano K, Sasako Y, Kitamura S, Kosakai Y. Maze procedure for atrial fibrillation associated with atrial septal defect. *Circulation* 1998;**98**:II399-402.
989. Shim H, Yang JH, Park PW, Jeong DS, Jun TG. Efficacy of the maze procedure for atrial fibrillation associated with atrial septal defect. *Korean J Thorac Cardiovasc Surg* 2013;**46**:98-103.
990. Gutierrez SD, Earing MG, Singh AK, Tweddell JS, Bartz PJ. Atrial tachyarrhythmias and the Cox-maze procedure in congenital heart disease. *Congenit Heart Dis* 2013;**8**:434-439.
991. Sherwin ED, Triedman JK, Walsh EP. Update on interventional electrophysiology in congenital heart disease: evolving solutions for complex hearts. *Circ Arrhythm Electrophysiol* 2013;**6**:1032-1040.
992. Wellens HJ. Contemporary management of atrial flutter. *Circulation* 2002;**106**:649-652.
993. Bertaglia E, Zoppo F, Bonso A, Proclemer A, Verlato R, Coro L, Mantovan R, D'Este D, Zerbo F, Pascotto P. Long term follow up of radiofrequency catheter ablation of atrial flutter: clinical course and predictors of atrial fibrillation occurrence. *Heart* 2004;**90**:59-63.

994. Seara JG, Roubin SR, Gude Sampedro F, Barreiro VB, Sande JM, Manero MR, Grandio PC, Alvarez B, Juanatey JG. Risk of atrial fibrillation, stroke, and death after radiofrequency catheter ablation of typical atrial flutter. *Clin Res Cardiol* 2014;**103**:543-552.
995. Brembilla-Perrot B, Girerd N, Sellal JM, Olivier A, Manenti V, Villemin T, Beurrier D, de Chillou C, Louis P, Selton O, de la Chaise AT. Risk of atrial fibrillation after atrial flutter ablation: impact of AF history, gender, and antiarrhythmic drug medication. *J Cardiovasc Electrophysiol* 2014;**25**:813-820.
996. Bronis K, Metaxa S, Koulouris S, Manolis AS. Vernakalant: review of a novel atrial selective antiarrhythmic agent and its place in current treatment of atrial fibrillation. *Hosp Chronicles* 2012;**7**:171-181.
997. Nair M, George LK, Koshy SK. Safety and efficacy of ibutilide in cardioversion of atrial flutter and fibrillation. *J Am Board Fam Med* 2011;**24**:86-92.
998. Reisinger J, Gstrein C, Winter T, Zeindlhofer E, Hollinger K, Mori M, Schiller A, Winter A, Geiger H, Siostrzonek P. Optimization of initial energy for cardioversion of atrial tachyarrhythmias with biphasic shocks. *Am J Emerg Med* 2010;**28**:159-165.
999. Pinski SL, Sgarbossa EB, Ching E, Trohman RG. A comparison of 50-J versus 100-J shocks for direct-current cardioversion of atrial flutter. *Am Heart J* 1999;**137**:439-442.
1000. Manolis AS, Dragazis I, Kapelakis I, Papadimitriou P, Sakellaris N. Transesophageal overdrive pacing: A simple and versatile tool. *Hosp Chronicles* 2013;**8**:143-145.
1001. Poulidakis E, Manolis AS. Transvenous temporary cardiac pacing. *Rhythmos* 2014;**9**:20-27.
1002. Spector P, Reynolds MR, Calkins H, Sondhi M, Xu Y, Martin A, Williams CJ, Sledge I. Meta-analysis of ablation of atrial flutter and supraventricular tachycardia. *Am J Cardiol* 2009;**104**:671-677.
1003. Schmieder S, Ndrepepa G, Dong J, Zrenner B, Schreieck J, Schneider MA, Karch MR, Schmitt C. Acute and long-term results of radiofrequency ablation of common atrial flutter and the influence of the right atrial isthmus ablation on the occurrence of atrial fibrillation. *Eur Heart J* 2003;**24**:956-962.
1004. Bandini A, Golia P, Caroli E, Biancoli S, Galvani M. Atrial fibrillation after typical atrial flutter ablation: a long-term follow-up. *J Cardiovasc Med (Hagerstown)* 2011;**12**:110-115.
1005. Dewland TA, Glidden DV, Marcus GM. Healthcare utilization and clinical outcomes after catheter ablation of atrial flutter. *PLoS One* 2014;**9**:e100509.
1006. Esato M, Hindricks G, Sommer P, Arya A, Gaspar T, Bode K, Bollmann A, Wetzel U, Hilbert S, Kircher S, Eitel C, Piorkowski C. Color-coded three-dimensional entrainment mapping for analysis and treatment of atrial macroreentrant tachycardia. *Heart Rhythm* 2009;**6**:349-358.
1007. Huo Y, Schoenbauer R, Richter S, Rolf S, Sommer P, Arya A, Rastan A, Doll N, Mohr FW, Hindricks G, Piorkowski C, Gaspar T. Atrial Arrhythmias Following Surgical AF Ablation: Electrophysiological Findings, Ablation Strategies, and Clinical Outcome. *J Cardiovasc Electrophysiol* 2014;**25**:725-738.
1008. Institute of Medicine Committee on Quality of Health Care in America. *Crossing the Quality Chasm: A New Health System for the 21st Century*. Washington (DC): National Academies Press (US); 2001.
1009. Bodenheimer T, Wagner EH, Grumbach K. Improving primary care for patients with chronic illness. *JAMA* 2002;**288**:1775-1779.
1010. Hibbard JH, Greene J. What the evidence shows about patient activation: better health outcomes and care experiences; fewer data on costs. *Health Aff (Millwood)* 2013;**32**:207-214.
1011. McCabe PJ. Self-management of atrial fibrillation: a new frontier for nursing research. *Prog Cardiovasc Nurs* 2008;**23**:37-40.
1012. Lip GY, Kamath S, Jafri M, Mohammed A, Bareford D. Ethnic differences in patient perceptions of atrial fibrillation and anticoagulation therapy: the West Birmingham Atrial Fibrillation Project. *Stroke* 2002;**33**:238-242.
1013. Clarkesmith DE, Pattison HM, Lane DA. Educational and behavioural interventions for anticoagulant therapy in patients with atrial fibrillation. *Cochrane Database Syst Rev* 2013;**6**:Cd008600.
1014. 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.
1015. 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.
1016. Smith MB, Christensen N, Wang S, Strohecker J, Day JD, Weiss JP, Crandall BG, Osborn JS, Anderson JL, Horne BD, Muhlestein JB, Lappe DL, Moss H, Oliver J, Viau K, Bunch TJ. Warfarin

6103 knowledge in patients with atrial fibrillation: implications for safety, efficacy, and education strategies.
6104 *Cardiology* 2010;**116**:61-69.
6105 1017. Aliot E, Breithardt G, Brugada J, Camm J, Lip GY, Vardas PE, Wagner M, Atrial Fibrillation
6106 AWareness and Risk Education group [comprising the Atrial Fibrillation Association (AFA), the
6107 European Heart Rhythm Association (EHRA), Stroke Alliance for Europe (SAFE), and the World Heart
6108 Federation (WHF)]. An international survey of physician and patient understanding, perception, and
6109 attitudes to atrial fibrillation and its contribution to cardiovascular disease morbidity and mortality.
6110 *Europace* 2010;**12**:626-633.
6111 1018. Hendriks JM, Crijns HJ, Tieleman RG, Vrijhoef HJ. The atrial fibrillation knowledge scale:
6112 development, validation and results. *Int J Cardiol* 2013;**168**:1422-1428.
6113 1019. McCabe PJ. What patients want and need to know about atrial fibrillation. *J Multidiscip*
6114 *Healthc* 2011;**4**:413-419.
6115 1020. Lorig KR, Holman H. Self-management education: history, definition, outcomes, and
6116 mechanisms. *Ann Behav Med* 2003;**26**:1-7.
6117 1021. Stiggelbout AM, Van der Weijden T, De Wit MP, Frosch D, Legare F, Montori VM, Trevena L,
6118 Elwyn G. Shared decision making: really putting patients at the centre of healthcare. *BMJ*
6119 2012;**344**:e256.
6120 1022. Stacey D, Legare F, Col NF, Bennett CL, Barry MJ, Eden KB, Holmes-Rovner M, Llewellyn-
6121 Thomas H, Lyddiatt A, Thomson R, Trevena L, Wu JH. Decision aids for people facing health
6122 treatment or screening decisions. *Cochrane Database Syst Rev* 2014;**1**:CD001431.
6123 1023. Elwyn G, Frosch D, Thomson R, Joseph-Williams N, Lloyd A, Kinnersley P, Cording E,
6124 Tomson D, Dodd C, Rollnick S, Edwards A, Barry M. Shared decision making: a model for clinical
6125 practice. *J Gen Intern Med* 2012;**27**:1361-1367.
6126 1024. Van Wagoner DR, Piccini JP, Albert CM, Anderson ME, Benjamin EJ, Brundel B, Califf RM,
6127 Calkins H, Chen PS, Chiamvimonvat N, Darbar D, Eckhardt LL, Ellinor PT, Exner DV, Fogel RI, Gillis
6128 AM, Healey J, Hohnloser SH, Kamel H, Lathrop DA, Lip GY, Mehra R, Narayan SM, Olgin J, Packer
6129 D, Peters NS, Roden DM, Ross HM, Sheldon R, Wehrens XH. Progress toward the prevention and
6130 treatment of atrial fibrillation: A summary of the Heart Rhythm Society Research Forum on the
6131 Treatment and Prevention of Atrial Fibrillation, Washington, DC, December 9-10, 2013. *Heart Rhythm*
6132 2015;**12**:e5-e29.
6133 1025. van Nieuwenhuizen KM, van der Worp HB, Algra A, Kappelle LJ, Rinkel GJ, van Gelder IC,
6134 Schutgens RE, Klijn CJ, APACHE-AF Investigators. Apixaban versus Antiplatelet drugs or no
6135 antithrombotic drugs after anticoagulation-associated intraCerebral HaEmorrhage in patients with
6136 Atrial Fibrillation (APACHE-AF): study protocol for a randomised controlled trial. *Trials* 2015;**16**:393.
6137 1026. Gronberg T, Nuotio I, Nikkinen M, Ylitalo A, Vasankari T, Hartikainen JE, Airaksinen KE.
6138 Arrhythmic complications after electrical cardioversion of acute atrial fibrillation: the FinCV study.
6139 *Europace* 2013;**15**:1432-1435.
6140 1027. Tse HF, Lau CP. Does sinus rhythm beget sinus rhythm? Effects of prompt cardioversion on
6141 the frequency and persistence of recurrent atrial fibrillation. *Card Electrophysiol Rev* 2003;**7**:359-365.
6142 1028. Van Gelder IC, Hemels ME. The progressive nature of atrial fibrillation: a rationale for early
6143 restoration and maintenance of sinus rhythm. *Europace* 2006;**8**:943-949.
6144 1029. Liu ZJ, Fu WG, Guo ZY, Shen LG, Shi ZY, Li JH. Updated systematic review and meta-
6145 analysis of randomized clinical trials comparing carotid artery stenting and carotid endarterectomy in
6146 the treatment of carotid stenosis. *Ann Vasc Surg* 2012;**26**:576-590.
6147 1030. Taylor DW, Barnett HJM, Haynes RB, Ferguson GG, Sackett DL, Thorpe KE, Simard D,
6148 Silver FL, Hachinski V, Clagett GP, barnes R, Spence JD, ASA and Carotid Endarterectomy (ACE)
6149 trial collaborators. Low-dose and high-dose acetylsalicylic acid for patients undergoing carotid
6150 endarterectomy: a randomised controlled trial. *Lancet* 1999;**353**:2179-2184.
6151 1031. Watanabe M, Chaudhry SA, Adil MM, Alqadri SL, Majidi S, Semaan E, Qureshi AI. The effect
6152 of atrial fibrillation on outcomes in patients undergoing carotid endarterectomy or stent placement in
6153 general practice. *J Vasc Surg* 2015;**61**:927-932.
6154 1032. Breithardt G, Baumgartner H, Berkowitz SD, Hellkamp AS, Piccini JP, Stevens SR,
6155 Lokhnygina Y, Patel MR, Halperin JL, Singer DE, Hankey GJ, Hacke W, Becker RC, Nessel CC,
6156 Mahaffey KW, Fox KA, Califf RM, ROCHET AF Steering Committee & Investigators. Clinical
6157 characteristics and outcomes with rivaroxaban vs. warfarin in patients with non-valvular atrial
6158 fibrillation but underlying native mitral and aortic valve disease participating in the ROCKET AF trial.
6159 *Eur Heart J* 2014;**35**:3377-3385.
6160 1033. Philippart R, Brunet-Bernard A, Clementy N, Bourguignon T, Mirza A, Babuty D, Angoulvant
6161 D, Lip GY, Fauchier L. Prognostic value of CHA2DS2-VASc score in patients with 'non-valvular atrial

6162 fibrillation' and valvular heart disease: the Loire Valley Atrial Fibrillation Project. *Eur Heart J*
6163 2015;**36**:1822-1830.
6164 1034. Breithardt G, Baumgartner H. Valvular heart disease among non-valvular atrial fibrillation: a
6165 misnomer, in search of a new term. *Eur Heart J* 2015;**36**:1794-1797.
6166 1035. Wolf RK, Schneeberger EW, Osterday R, Miller D, Merrill W, Flege JB, Jr., Gillinov AM.
6167 Video-assisted bilateral pulmonary vein isolation and left atrial appendage exclusion for atrial
6168 fibrillation. *J Thorac Cardiovasc Surg* 2005;**130**:797-802.
6169 1036. Yilmaz A, Van Putte BP, Van Boven WJ. Completely thoracoscopic bilateral pulmonary vein
6170 isolation and left atrial appendage exclusion for atrial fibrillation. *J Thorac Cardiovasc Surg*
6171 2008;**136**:521-522.
6172 1037. Salzberg SP, Plass A, Emmert MY, Desbiolles L, Alkadhi H, Grunenfelder J, Genoni M. Left
6173 atrial appendage clip occlusion: early clinical results. *J Thorac Cardiovasc Surg* 2010;**139**:1269-1274.
6174 1038. Papworth Hospital NHS Foundation Trust. *A randomised controlled trial to investigate the*
6175 *clinical and cost effectiveness of adding an ablation device-based maze procedure as a routine*
6176 *adjunct to elective cardiac surgery for patients with pre-existing atrial fibrillation*.
6177 http://www.isrctn.com/ISRCTN82731440. Date last accessed 5 May 2016 ISRCTN82731440
6178 1039. Efficacy and safety of ablation for patients with non-paroxysmal atrial fibrillation. doi:
6179 10.1002/14651858.CD012088.pub2
6180 1040. Concomitant atrial fibrillation surgery for people undergoing cardiac surgery. doi:
6181 10.1002/14651858.CD011814.pub2
6182 1041. Hemingway CPRD data (when published)
6183 1042. MANTRA-PAF 5 yr outcomes (when published)