

## 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/ejcts/ezw313](https://doi.org/10.1093/ejcts/ezw313)

### 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, Deffereos, 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', *European Journal of Cardio-Thoracic Surgery*, vol. 50, no. 5, pp. e1–e88. <https://doi.org/10.1093/ejcts/ezw313>

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DOI:

[10.1093/europace/euw295](https://doi.org/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 & Authors/Task Force Members 2016, '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)' *Europace*. DOI: 10.1093/europace/euw295

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# 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)

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## 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

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180	<b>Abbreviations and acronyms</b>	
181	ABC	age, biomarkers, clinical history
182	ACE	angiotensin-converting enzyme
183	ACS	acute coronary syndromes
184	AF	atrial fibrillation
185	AFFIRM	Atrial Fibrillation Follow-up Investigation of Rhythm Management
186	AFNET	German Competence NETwork on Atrial Fibrillation
187	AHRE	atrial high rate episodes
188	ARB	angiotensin receptor blocker
189	ARISTOTLE	Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation
190	ARNI	angiotensin receptor neprilysin inhibition
191	ATRIA	AnTicoagulation and Risk factors In Atrial fibrillation
192	AXAFA	Anticoagulation using the direct factor Xa inhibitor apixaban during Atrial Fibrillation
193		catheter Ablation: Comparison to vitamin K antagonist therapy
194	BAFTA	Birmingham Atrial Fibrillation Treatment of the Aged Study
195	BMI	body mass index
196	bpm	beats per minute
197	CABANA	Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation Trial
198	CAD	coronary artery disease
199	CHA <sub>2</sub> DS <sub>2</sub> -VASc	Congestive Heart failure, hypertension, Age $\geq 75$ (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female)
200		
201	CHADS <sub>2</sub>	Cardiac failure, Hypertension, Age, Diabetes, Stroke (Doubled)
202	CI	confidence interval
203	CKD	chronic kidney disease
204	CrCl	creatinine clearance
205	CT	computed tomography
206	DIG	Digitalis Investigation Group
207	EACTS	European Association for Cardio-Thoracic Surgery
208	EAST	Early treatment of Atrial fibrillation for Stroke prevention Trial
209	ECG	electrocardiogram/electrocardiography
210	EHRA	European Heart Rhythm Association
211	ENGAGE AF-TIMI 48	Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48
212		
213	EORP	EURObservational Research Programme
214	FAST	Atrial Fibrillation Catheter Ablation vs Surgical Ablation Treatment
215	FEV1	forced expiratory volume in 1 second
216	GDF-15	growth differentiation factor 15
217	GFR	glomerular filtration rate
218	GFR	glomerular filtration rate
219	GUCH	grown up congenital heart disease
220	HARMONY	A Study to Evaluate the Effect of Ranolazine and Dronedronone When Given Alone and in Combination in Patients With Paroxysmal Atrial Fibrillation
221		
222	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)
223		
224	HFmrEF	heart failure with mid-range ejection fraction
225	HFpEF	heart failure with preserved ejection fraction
226	HFrfEF	heart failure with reduced ejection fraction
227	HR	hazard ratio
228	INR	international normalized ratio
229	LA	left atrium/atrial
230	LAA	left atrial appendage
231	LAAOS	Left Atrial Appendage Occlusion Study
232	LV	left ventricular
233	LVEF	left ventricular ejection fraction
234	LVH	left ventricular hypertrophy
235	MANTRA-PAF	Medical ANtiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation
236		
237	MERLIN	Metabolic Efficiency With Ranolazine for Less Ischemia in Non ST-Elevation Acute Coronary Syndrome
238		
239	MRI	magnetic resonance imaging

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240	NOAC	non-vitamin K antagonist oral anticoagulant
241	NYHA	New York Heart Association
242	OAC	oral anticoagulation/oral anticoagulant
243	OR	odds ratio
244	ORBIT	Outcomes Registry for Better Informed Treatment of Atrial Fibrillation
245	PCI	percutaneous coronary intervention
246	PREVAIL	Prospective Randomized Evaluation of the Watchman LAA Closure Device In Patients with AF Versus Long Term Warfarin Therapy trial
247		
248	PROTECT AF	Watchman Left Atrial Appendage System for Embolic Protection in Patients With AF trial
249	PVI	pulmonary vein isolation
250	RACE	Rate Control Efficacy in Permanent Atrial Fibrillation
251	RATE-AF	Rate Control Therapy Evaluation in Permanent Atrial Fibrillation
252	RCT	randomized controlled trial
253	RE-CIRCUIT	Randomized Evaluation of dabigatran etexilate Compared to warfarin in pulmonaRy vein ablation: assessment of different peri-proCedUral anticoagulation sTrategies
254		
255	RE-LY	Randomized Evaluation of Long-Term Anticoagulation Therapy
256	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
257		
258	RR	risk ratio
259	SD	standard deviation
260	SPAF	Stroke Prevention in Atrial Fibrillation
261	TIA	transient ischaemic attack
262	TIMI	Thrombolysis In Myocardial Infarction
263	TOE	transoesophageal echocardiography
264	TTR	time in therapeutic range
265	UFH	unfractionated heparin
266	US	United States
267	VKA	vitamin K antagonist
268	WOEST	What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing
269		
270	WPW	Wolff-Parkinson-White syndrome
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272		

## 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.

333 **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

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335  
336 **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.

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340 **2 Introduction**

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

347  
348 Reflecting the multidisciplinary input into the management of patients with AF, the Task Force includes  
349 cardiologists with varying subspecialty expertise, cardiac surgeons, stroke neurologists, and specialist nurses  
350 amongst its members. Supplementing the evidence review as outlined in the preamble, this task force identified  
351 three PICOT questions on relevant topics for the guideline. The ESC commissioned external systematic reviews  
352 to answer these three questions. These reviews informed specific recommendations.

353  
354 Further to adhering to the standards for generating recommendations that is common to all ESC guidelines (see  
355 preamble), this task force discussed each draft recommendation during web-based conference calls dedicated to  
356 specific chapters, followed by consensus modifications and an online vote on each recommendation. Only  
357 recommendations that were supported by at least 75% of the task force members were included in the guideline.

358  
359 We hope that this guideline will help to deliver good care to all patients with AF based on the current state-of-  
360 the-art evidence in 2016.

361  
362 **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.<sup>1,2</sup> One in four middle-aged adults in Europe and the United States (US) will develop AF.<sup>3-5</sup> By 2030, 14–17 million AF patients are anticipated in the European Union, with 120,000–215,000 newly diagnosed patients per year.<sup>2,6,7</sup> Estimates suggest an AF prevalence of approximately 3% in adults age 20 years or older,<sup>8,9</sup> with more AF in elderly persons<sup>1</sup> and in patients with conditions such as hypertension, heart failure, coronary artery disease (CAD), valvular heart disease, diabetes mellitus, and chronic kidney disease (CKD).<sup>7,10-15</sup> The increase in AF prevalence can be attributed to better detection of silent AF<sup>16-18</sup> and increasing age and conditions predisposing to AF.<sup>19</sup>

### 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<sup>20-22</sup> (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.<sup>23</sup> AF is also associated with increased morbidity, such as heart failure and stroke.<sup>21,24,25</sup> Contemporary studies show that 20–30% of patients with an ischaemic stroke have AF diagnosed before, during, or after the initial event.<sup>17,26,27</sup> White matter lesions in the brain, cognitive impairment,<sup>28-30</sup> decreased quality of life,<sup>31,32</sup> and depressed mood<sup>33</sup> are common in AF patients, and between 10% and 40% of AF patients are hospitalized each year.<sup>23,34,35</sup>

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,<sup>36,37</sup> 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.<sup>38,39</sup> 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.<sup>40,41</sup>



**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%.<sup>40</sup> In real life, the annual mortality can be different (both higher and lower).<sup>42</sup> 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.<sup>43, 44</sup>

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.<sup>34, 45</sup>

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

#### Recommendations relating to gender

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
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	Ila	B	55, 56

428 AF = atrial fibrillation

429 <sup>a</sup>Class of recommendation.

430 <sup>b</sup>Level of evidence.

431 <sup>c</sup>Reference(s) supporting recommendations.

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## 433 **4 Pathophysiological and genetic aspects that guide management**

### 434 **4.1. Genetic predisposition**

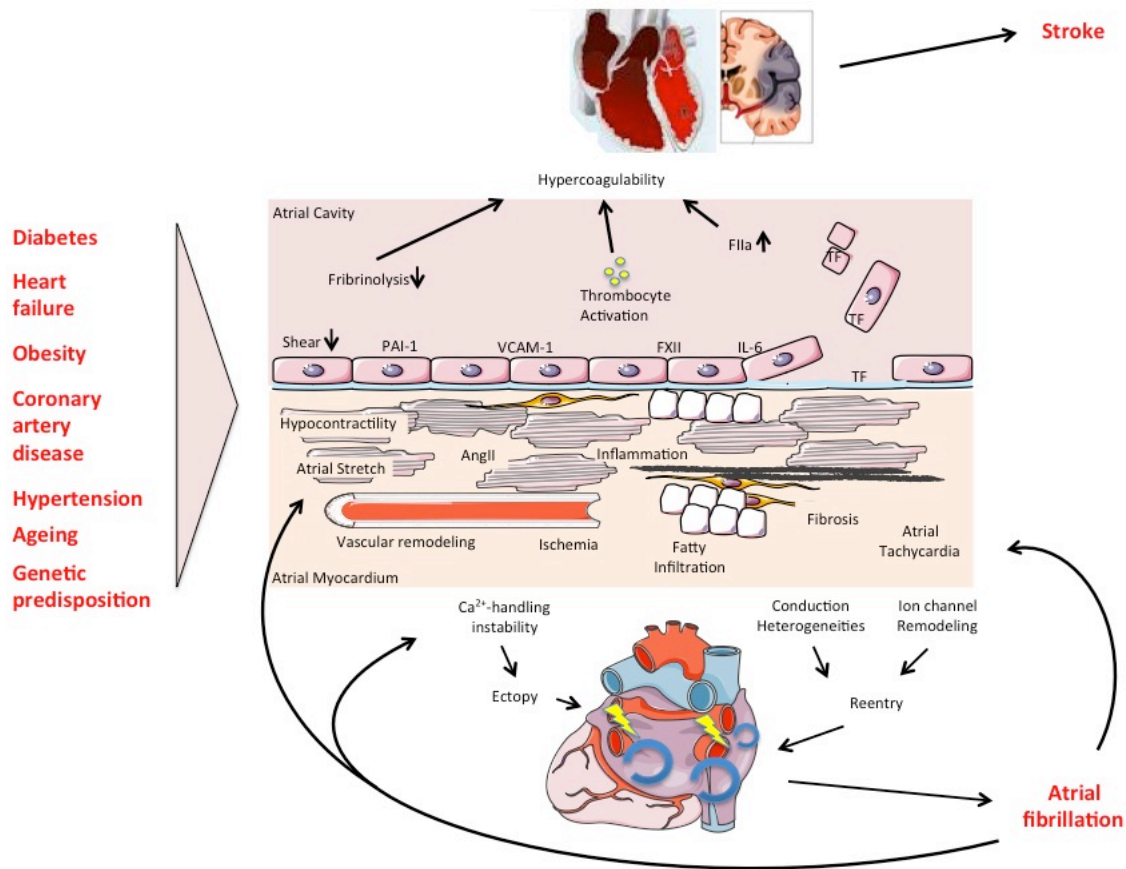
435 AF, especially early-onset AF, has a strong heritable component, independent of concomitant cardiovascular  
 436 conditions.<sup>58,59</sup> A few young AF patients suffer from inherited cardiomyopathies or channelopathies mediated  
 437 by disease-causing mutations. These monogenic diseases also convey a risk for sudden death (see Chapter 5).  
 438 Up to one-third of AF patients carry common genetic variants that predispose to AF, albeit with a relatively low  
 439 added risk. At least 14 of these common variants, often single nucleotide polymorphisms, are known to increase  
 440 the risk of prevalent AF in populations.<sup>60-62</sup> The most important variants are located close to the paired-like  
 441 homeodomain transcription factor 2 gene on chromosome 4q25.<sup>63,64</sup> These variants modify the risk of AF up to  
 442 sevenfold.<sup>64</sup> Several of the AF risk variants are also associated with cardioembolic or ischaemic stroke, possibly  
 443 due to silent AF (see section 4.1).<sup>62,65,66</sup> Changes in atrial action potential characteristics,<sup>67-70</sup> atrial remodelling,  
 444 and modified penetration of rare gene defects<sup>61</sup> have been suggested as potential mechanisms mediating  
 445 increased AF risk in carriers of common gene variants. Genetic variants could in the future become useful for  
 446 patient selection of rhythm control strategies,<sup>71-73</sup> but it is currently unknown whether common gene variants  
 447 differentially affect the efficacy of antiarrhythmic drugs or rate control medication.<sup>74</sup> While genomic analysis  
 448 may provide an opportunity to improve diagnosis and management of AF in the future,<sup>75,76</sup> routine genetic  
 449 testing for common gene variants associated with AF cannot be recommended at present.<sup>77</sup>  
 450

### 451 **4.2. Mechanisms leading to atrial fibrillation**

#### 452 **4.2.1. Remodelling of atrial structure and ion channel function**

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

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



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**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<sup>2+</sup>-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.

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**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
<i>Changes of the extracellular matrix, fibroblast function, and fat cells</i>			
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

Amyloid deposition	Ageing, heart failure, CAD (via atrial scarring), genetic factors	block Conduction disturbances	83, 93
<b><i>Ion channel alterations</i></b>			
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 <sup>2+</sup> 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
<b><i>Myocyte alterations</i></b>			
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
<b><i>Endothelial and vascular alterations</i></b>			
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
<b><i>Changes of the autonomic nervous system</i></b>			
Sympathetic hyperinnervation	Heart failure, hypertension	Enhanced propensity to ectopy	80, 105

488 AF = atrial fibrillation; CAD = coronary artery disease.

489

### 490 3.2.1. Electrophysiological mechanisms of atrial fibrillation

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

499

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

505

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

511 foci, rotors, or other stable reentry circuits) cause fibrillatory conduction remote from the source, which is  
512 difficult to distinguish from propagation sustaining AF by multiple wavelets, and either of these phenomena  
513 may generate ‘rotors’ picked up by intracardiac<sup>116,117</sup> or body surface<sup>117</sup> recordings.  
514  
515

## 516 **5 Diagnosis and timely detection of atrial fibrillation**

### 517 **5.1. Overt and silent atrial fibrillation**

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

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

530 Once the ECG diagnosis of AF has been established, further ECG monitoring can inform management  
531 in the context of: (1) a change in symptoms or new symptoms; (2) suspected progression of AF; (3) monitoring  
532 of drug effects on ventricular rate; and (4) ECG monitoring of antiarrhythmic drug effects or catheter ablation  
533 for rhythm control.  
534

### 535 **5.2. Screening for silent atrial fibrillation**

#### 536 **5.2.1. Screening for atrial fibrillation by electrocardiogram in the community**

537 Undiagnosed AF is common, especially in older populations and in patients with heart failure.<sup>130</sup> Opportunistic  
538 screening for silent AF seems cost-effective in elderly populations (e.g. > 65 years),<sup>131</sup> and similar effects have  
539 been reported using single-lead ECG screening in other at-risk populations.<sup>132, 133</sup> Screening of elderly  
540 populations (mean age 64 years) yielded a prevalence of 2.3% for chronic forms of AF in 122,571 participants  
541 using either short-term ECG or pulse palpation (followed by ECG in those with an irregular pulse).<sup>134</sup>  
542 Previously undiagnosed AF was found in 1.4% of those aged > 65 years, suggesting a number needed to screen  
543 of 70. These findings encourage the further evaluation of systematic AF screening programmes in at-risk  
544 populations.  
545

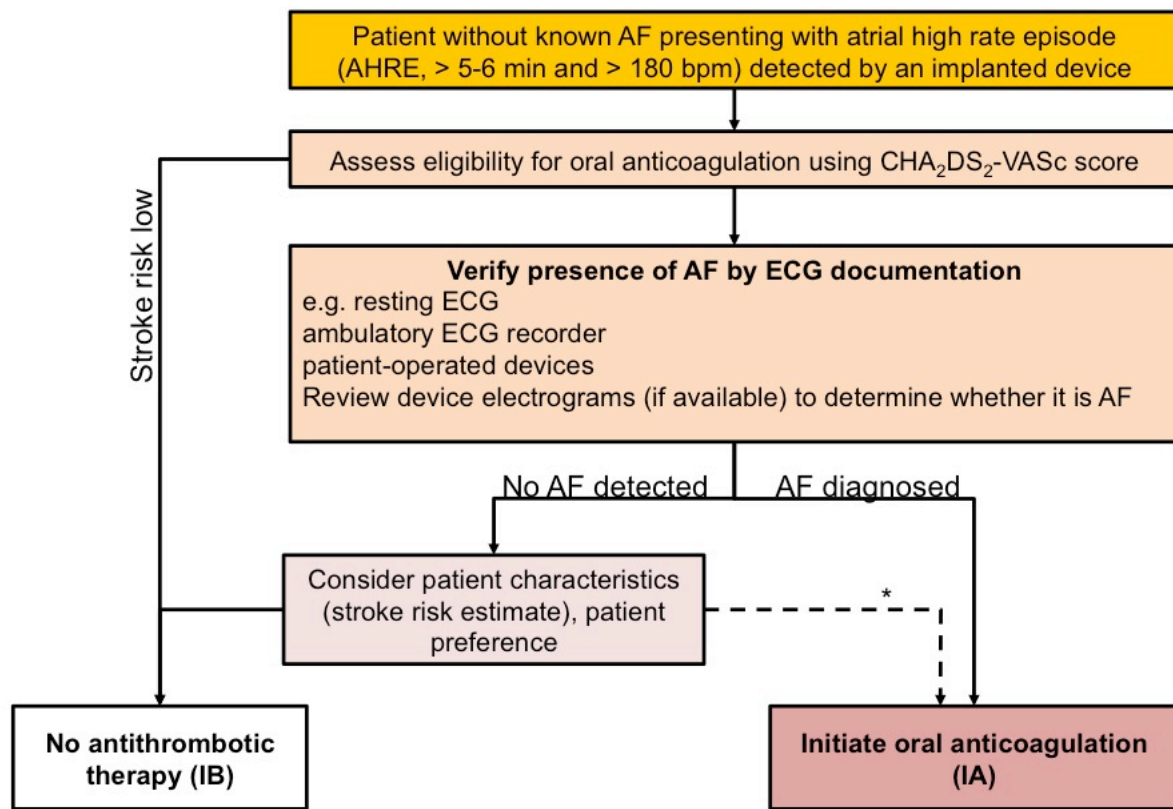
#### 546 **5.2.2. Prolonged monitoring for paroxysmal atrial fibrillation**

547 Paroxysmal AF is often missed.<sup>120</sup> Repeated daily ECG recordings increased the detection of silent,  
548 asymptomatic paroxysmal AF in an unselected Swedish population aged > 75 years.<sup>120, 135</sup> Several patient-  
549 operated devices<sup>136, 137</sup> and extended continuous ECG monitoring using skin patch recorders<sup>138</sup> have been  
550 validated for detection of paroxysmal AF.<sup>139</sup> The detection rate of asymptomatic AF by new technologies such  
551 as smartphone cases with ECG electrodes, smart watches, and blood pressure machines with AF detection  
552 algorithms, has not yet been formally evaluated against an established arrhythmia detection method.<sup>140</sup>  
553

#### 554 **5.2.3. Patients with pacemakers and implanted devices**

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

566 including ECG monitoring (Figure 3).<sup>149</sup>



\*In rare individual circumstances, oral anticoagulation may be considered in patients with AHRE, but without diagnosed AF. This clearly needs discussion with the patient and careful evaluation of perceived benefit and risk.

**Figure 3** Management of AHRE detected on an implanted device. Adapted from the report of the 3rd AFNET/EHRA consensus conference.<sup>150</sup>  
 AF = atrial fibrillation; AFNET = German Competence NETwork on Atrial Fibrillation; AHRE = atrial high rate episodes; bpm = beats per minute; CHA<sub>2</sub>DS<sub>2</sub>-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,<sup>151</sup> and in 11.5% (95% CI 8.9%–14.3%) in another meta-analysis,<sup>17</sup> 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),<sup>128</sup> but is more likely in patients with cryptogenic stroke implanted with loop recorders or who have had ECG monitors for several weeks.<sup>18, 128, 152</sup> Cryptogenic stroke is defined as a stroke in which the cause could not be identified after extensive investigations.<sup>153</sup> A broader definition is embolic stroke of undetermined source.<sup>154</sup> 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).<sup>27, 127</sup> 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 <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
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

587 AF = atrial fibrillation; AHRE = atrial high rate episodes; ECG = electrocardiogram; ICD = implantable  
 588 cardioverter defibrillator; TIA = transient ischaemic attack.

589 <sup>a</sup>Class of recommendation.

590 <sup>b</sup>Level of evidence.

591 <sup>c</sup>Reference(s) supporting recommendations.

592

### 593 5.3. Electrocardiogram detection of atrial flutter

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

602

## 603 6 Classification of atrial fibrillation

### 604 6.1. Atrial fibrillation pattern

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

610

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

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

621

622 **Table 5** Patterns of AF

AF pattern	Definition
<b>First diagnosed AF</b>	AF that has not been diagnosed before, irrespective of the duration of the arrhythmia or the presence and severity of AF-related symptoms.
<b>Paroxysmal AF</b>	Self-terminating, in most cases within 48 hours. Some AF paroxysms may continue for up to 7 days. <sup>a</sup> Most AF episodes that are cardioverted within 24-48 hours should be considered paroxysmal. <sup>a</sup>
<b>Persistent AF</b>	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.
<b>Long-standing persistent AF</b>	Continuous AF lasting for ≥ 1 year when it is decided to adopt a rhythm control strategy.
<b>Permanent AF</b>	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'.

623 AF = atrial fibrillation.

624 <sup>a</sup>The distinction between paroxysmal and persistent AF is often not made correctly without access to long-term  
625 monitoring.<sup>163</sup> Hence, this classification alone is often insufficient to select specific therapies. If both persistent  
626 and paroxysmal episodes are present, the predominant pattern should guide the classification.  
627

## 628 6.2. Atrial fibrillation types reflecting different causes of the arrhythmia

629 The risk of developing AF is increased in a variety of physiological and disease states, and the historic term  
630 'lone AF' is probably misleading and should be avoided.<sup>166</sup> Although the pattern of AF may be the same, the  
631 mechanisms underpinning AF vary substantially between patients<sup>167</sup> (Table 6). This suggests that stratifying AF  
632 patients by underlying drivers of AF could inform management, for example, considering cardiac and systemic  
633 comorbidity (e.g. diabetes and obesity<sup>168</sup>), lifestyle factors (e.g. activity level, smoking, alcohol intake<sup>169, 170</sup>),  
634 markers of cardiac structural remodelling (e.g. fibrosis<sup>171-173</sup> or electrocardiographic parameters of AF  
635 complexity<sup>174</sup>), or genetic background. Table 6 provides such a taxonomy, informed by expert consensus,<sup>76, 120,</sup>  
636 <sup>175</sup> but without much evidence to underpin its clinical use.<sup>176</sup> Systematic research defining the major drivers of  
637 AF is clearly needed to better define different types of AF.<sup>176</sup>  
638

639 **Table 6 Clinical types of AF (modified from the report on the 4<sup>th</sup> AFNET/EHRA consensus conference<sup>76</sup>)<sup>a</sup>**

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

640 AF = atrial fibrillation; LV = left ventricular; LVH = left ventricular hypertrophy.

641 <sup>a</sup>It is recognized that these types of AF will overlap in clinical practice, and that their impact for management  
642 needs to be evaluated systematically.  
643

## 644 6.3. Symptom burden in atrial fibrillation

645 Patients with AF have significantly poorer quality of life than healthy controls, experiencing a variety of  
 646 symptoms including lethargy, palpitations, dyspnoea, chest tightness, sleeping difficulties, and psychosocial  
 647 distress.<sup>32, 177-180</sup> Improved quality of life has been noted with both pharmacological and interventional  
 648 therapies,<sup>181-185</sup> but there are limited data to compare the benefit of different treatments.<sup>32, 186</sup> Assessment of  
 649 quality of life is further constrained by a lack of cross-validation of the several AF-specific quality-of-life  
 650 tools.<sup>187-191</sup> With regard to symptom assessment, the European Heart Rhythm Association (EHRA) suggested  
 651 the EHRA symptom scale (*Table 7*) to describe symptom severity in AF patients.<sup>192</sup> A similar scale (the  
 652 Canadian Cardiovascular Society Severity of Atrial Fibrillation Scale) is used in Canada.<sup>193</sup> The EHRA scale  
 653 has been used and validated.<sup>194-199</sup> A modification was proposed in 2014, subdividing EHRA class 2 into mild  
 654 (2a) or moderate (2b) impact.<sup>199</sup> As symptoms in class 2b ('troubling' symptoms) identified patients with a  
 655 health utility benefit of rhythm control in that study, this modification may provide a threshold for potential  
 656 treatment decisions, but this remains to be tested. While some AF patients had no or minimal symptoms (25–  
 657 40%), many (15–30%) reported severe or disabling symptoms.<sup>194, 196</sup> The EHRA scale should be used to guide  
 658 symptom-orientated treatment decisions and for longitudinal patient profiling.

660 **Table 7 Modified EHRA symptom scale (modified from Wynn et al<sup>199</sup>)**

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 <sup>a</sup>
2b	Moderate	Normal daily activity not affected <sup>a</sup>
3	Severe	Normal daily activity affected
4	Disabling	Normal daily activity discontinued

661 AF = atrial fibrillation; EHRA = European Heart Rhythm Association.

662 <sup>a</sup>EHRA class 2a and 2b can be differentiated by evaluating whether patients are functionally affected by their  
 663 AF symptoms. AF-related symptoms are most commonly fatigue/tiredness and exertional shortness of breath, or  
 664 less frequently palpitations and chest pain.<sup>42, 194, 200-202</sup>

#### 666 Recommendation on use of the modified EHRA symptom scale

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

667 AF = atrial fibrillation; EHRA = European Heart Rhythm Association.

668 <sup>a</sup>Class of recommendation.

669 <sup>b</sup>Level of evidence.

670 <sup>c</sup>Reference(s) supporting recommendations.

## 672 7 Detection and management of risk factors and concomitant cardiovascular diseases

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

677 **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) <sup>64</sup>	HR range 0.4–3.2

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

680 AF = atrial fibrillation; BMI = body mass index; CI = confidence interval; FEV1 = forced expiratory volume in  
681 1 second; HR = hazard ratio; OR = odds ratio; RR = risk ratio  
682

## 683 7.1. Heart failure

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

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

697  
698 **7.1.1. Patients with atrial fibrillation and heart failure with reduced ejection**  
699 **fraction**

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

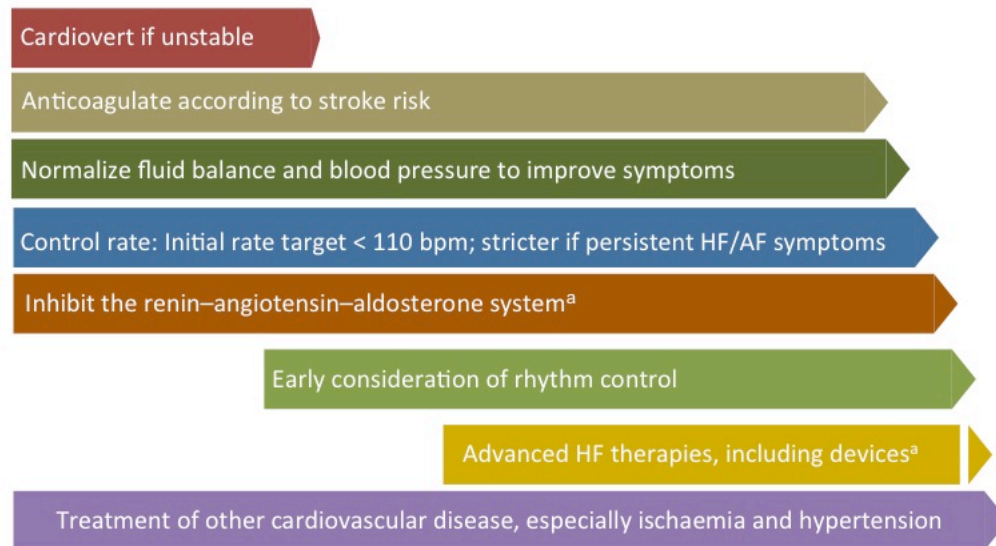
705 Rate control of AF is discussed in detail in Chapter 9. In brief, only beta-blockers and digoxin are  
706 suitable in HFrEF because of the negative inotropic potential of verapamil and diltiazem. Beta-blockers are  
707 usually the first-line option in patients with clinically stable HFrEF, although a meta-analysis using individual  
708 patient data from randomized controlled trials (RCTs) found no reduction in mortality from beta-blockers versus  
709 placebo in those with AF at baseline (HR 0.97, 95% CI 0.83–1.14).<sup>23</sup> Digoxin is commonly prescribed in  
710 clinical practice but no head-to-head RCTs in AF patients have been performed. In a meta-analysis of  
711 observational studies, digoxin had a neutral effect on mortality in patients with AF and concomitant heart failure  
712 (adjusted observational studies HR 0.90, 95% CI 0.70–1.16; propensity-matched observational studies RR 1.08,  
713 95% CI 0.93–1.26).<sup>225</sup> Initial and combination rate-control therapy for AF in HFrEF should therefore take  
714 account of individual patient characteristics and symptoms; beta-blocker initiation should be delayed in patients  
715 with acute decompensated heart failure, and digoxin has more adverse effects in patients with renal impairment  
716 (see Chapter 9).

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

## Management of patients presenting acutely with AF and heart failure

Acute management

Chronic management



**Figure 4** Initial management of newly diagnosed with AF and heart failure. Adapted from Kotecha and Piccini.<sup>218</sup>

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibition; bpm = beats per minute; HF = heart failure.

<sup>a</sup>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.<sup>230-234</sup> Natriuretic peptide levels are part of the diagnostic assessment of HFpEF,<sup>222</sup> although natriuretic peptide levels are elevated in AF patients and the optimum diagnostic cut-off is still unknown.<sup>235</sup> 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.<sup>222</sup> 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

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

755

#### 756 **7.1.4. Prevention of atrial fibrillation in heart failure**

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

766

## 767 **7.2. Hypertension**

### 768 **7.2.1. Treatment of hypertension to prevent incident atrial fibrillation**

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

774

### 775 **7.2.2. Blood pressure control in patients with atrial fibrillation**

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

783

## 784 **7.3. Valvular heart disease**

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

793

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

801

### 801 **Recommendations for patients with valvular heart disease and AF**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
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	Ila	C	
--	-----	---	--

802 AF = atrial fibrillation; LV = left ventricular.

803 <sup>a</sup>Class of recommendation.

804 <sup>b</sup>Level of evidence.

805 <sup>c</sup>Reference(s) supporting recommendations.

806

807

## 808 7.4. Diabetes mellitus

809 Diabetes and AF frequently coexist because of associations with other risk factors.<sup>277-283</sup> Diabetes is a risk factor  
 810 for stroke and other complications in AF.<sup>284</sup> In patients with AF, a longer duration of diabetes appears to confer  
 811 a higher risk of thromboembolism, albeit without greater risk of OAC-related bleeding.<sup>285</sup> Unfortunately,  
 812 intensive glycaemic control does not affect the rate of new-onset AF,<sup>284</sup> while treatment with metformin seems  
 813 to be associated with a decreased long-term risk of AF in diabetic patients<sup>286</sup> and may even lower long-term  
 814 stroke risk.<sup>13</sup> Diabetic retinopathy, a measure of disease severity, does not increase the risk of ocular bleeding in  
 815 anticoagulated patients.<sup>287</sup>  
 816

## 817 7.5. Obesity and weight loss

### 818 7.5.1. Obesity as a risk factor

819 Obesity increases the risk for AF (risk ratio 1.5–1.8),<sup>288-291</sup> with a progressive increase according to body mass  
 820 index.<sup>288, 290-292</sup> Obese patients may have more LV diastolic dysfunction, increased sympathetic activity and  
 821 inflammation, and increased fatty infiltration of the atria.<sup>293-295</sup> Obesity may also be a risk factor for ischaemic  
 822 stroke, thromboembolism, and death in AF patients.<sup>292</sup>  
 823

824

### 824 7.5.2. Weight reduction in obese patients with atrial fibrillation

825 Intensive weight-reduction management in addition to management of other cardiovascular risk factors (in the  
 826 range of 10–15 kg weight loss achieved) led to fewer AF recurrences and symptoms compared with an approach  
 827 based on general advice in obese patients with AF.<sup>203, 204, 296</sup> Improved cardiorespiratory fitness can further  
 828 decrease AF burden in obese patients with AF.<sup>297</sup> Although the findings in these studies have to be confirmed,  
 829 they underpin the positive effect of weight reduction in obese patients.  
 830

831

### 831 7.5.3. Catheter ablation in obese patients

832 Obesity may increase the rate of AF recurrence after catheter ablation,<sup>298-301</sup> with obstructive sleep apnoea as an  
 833 important potential confounder. Obesity has also been linked to a higher radiation dose and complication rate  
 834 during AF ablation.<sup>302, 303</sup> Notably, the symptomatic improvement after catheter ablation of AF in obese patients  
 835 seems comparable to the improvement in normal-weight patients.<sup>298</sup> In view of the potential to reduce AF  
 836 episodes by weight reduction (see Section 6.5.2.), AF ablation should be offered to obese patients in conjunction  
 837 with lifestyle modifications that lead to weight reduction.  
 838

839

### 839 Recommendation for obese patients with AF

840

841 AF = atrial fibrillation.

Recommendation	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
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

842

843 <sup>a</sup> Class of recommendation

844 <sup>b</sup> Level of evidence

845 <sup>c</sup> Reference(s) supporting recommendation(s)

846

## 847 7.6. Chronic obstructive pulmonary disease, sleep apnoea, and other respiratory 848 diseases

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

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

#### 865 **Recommendations for patients with AF and respiratory diseases**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
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

867 AF = atrial fibrillation.

868 <sup>a</sup>Class of recommendation.

869 <sup>b</sup>Level of evidence.

870 <sup>c</sup>Reference(s) supporting recommendations.

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#### 872 **7.7. Chronic kidney disease**

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

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#### 879 **Recommendations for patients with kidney disease and AF**

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Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
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	

881 AF = atrial fibrillation.

882 <sup>a</sup>Class of recommendation.

883 <sup>b</sup>Level of evidence.

884 <sup>c</sup>Reference(s) supporting recommendations.

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## 8 Integrated management of patients with atrial fibrillation

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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:

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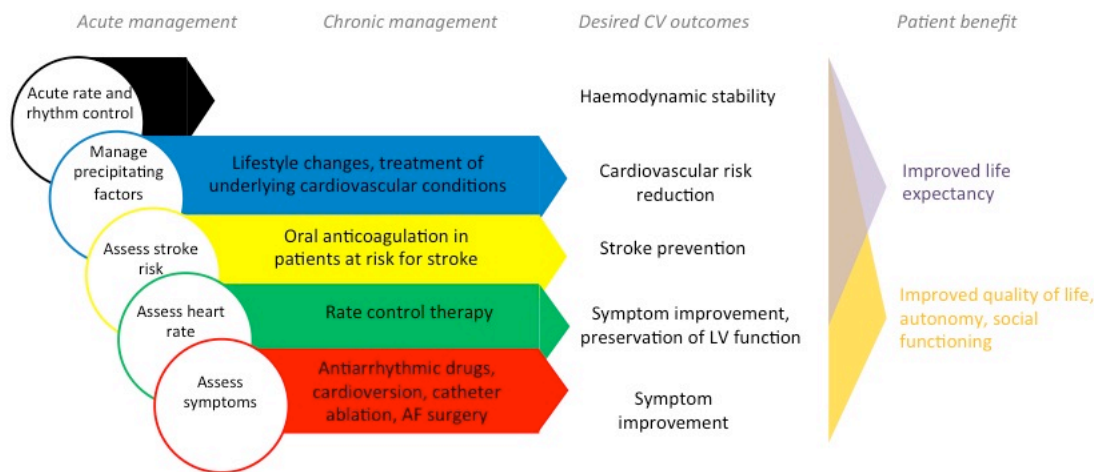
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1. Haemodynamic instability or limiting, severe symptoms
2. Presence of precipitating factors (e.g. thyrotoxicosis, sepsis, or postoperative AF) and underlying cardiovascular conditions
3. Stroke risk and need for anticoagulation
4. Heart rate and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



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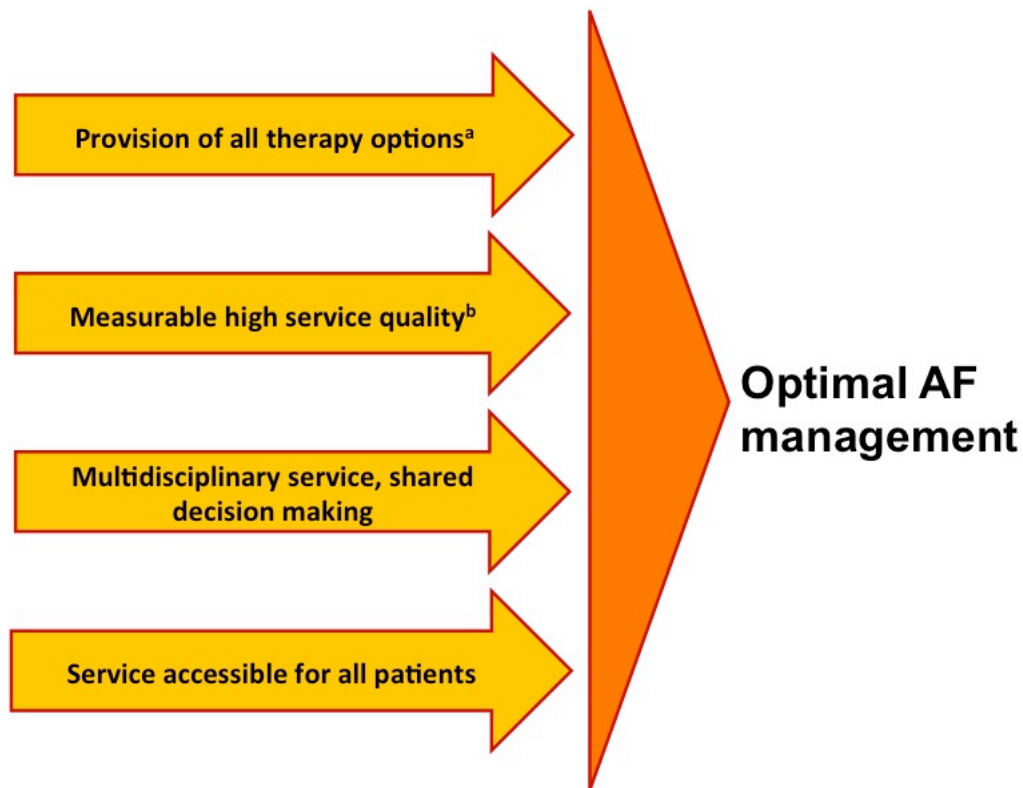
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**Figure 5** Acute and chronic management of AF patients, desired cardiovascular outcomes, and patient benefits. Adapted from the report on the 4th AFNET/EHRA consensus conference.<sup>76</sup> AF = atrial fibrillation; AFNET = German Competence NETwork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

An integrated, structured approach to AF care, as applied successfully to other domains of medicine,<sup>322-324</sup> will facilitate consistent, guideline-adherent AF management for all patients<sup>325</sup> (*Figure 6*), with the potential to improve outcomes.<sup>42, 326, 327</sup> Such approaches are consistent with the Innovative Care for Chronic Conditions Framework proposal put forward by the World Health Organization.<sup>328</sup> 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.<sup>329</sup> 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,

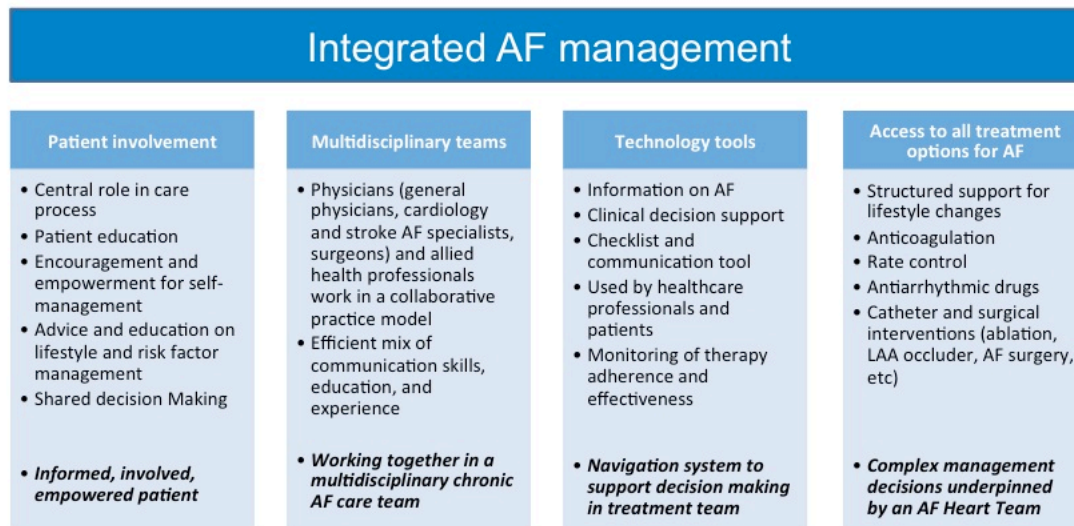
915 encompassing lifestyle interventions, treatment of underlying cardiovascular diseases and AF-specific therapy  
916 (Figure 7).



917  
918 **Figure 6** Achieving optimal management of AF patients.  
919 AF = atrial fibrillation.

920 <sup>a</sup>On-site or through institutionalized cooperation.

921 <sup>b</sup>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.<sup>a</sup>

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

<sup>a</sup>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.<sup>330</sup> Integrated AF management appeared cost-effective in that study.<sup>331</sup> 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.<sup>332</sup> Two observational studies of integrated AF care found fewer hospitalizations,<sup>333, 334</sup> one study showed fewer cases of stroke,<sup>333</sup> 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.<sup>335</sup> 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

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

### 955 **8.2.2. Multidisciplinary atrial fibrillation teams**

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

### 964 **8.2.3. Role of non-specialists**

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

### 972 **8.2.4. Technology use to support atrial fibrillation care**

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

### 979 **Recommendations for an integrated approach to care**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
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

980 AF = atrial fibrillation

981 <sup>a</sup>Class of recommendation.

982 <sup>b</sup>Level of evidence.

983 <sup>c</sup>Reference(s) supporting recommendations.

984

## 985 **8.3. Diagnostic workup of atrial fibrillation patients**

986 AF is often found in patients with other, at times undiagnosed, cardiovascular conditions. Thus, all AF patients  
 987 will benefit from a comprehensive cardiovascular assessment.<sup>339</sup>

988

### 989 **8.3.1. Recommended evaluation in all atrial fibrillation patients**

990 A complete medical history should be taken and all patients should undergo clinical evaluation that includes  
 991 thorough assessment for concomitant conditions, establishing the AF pattern, estimation of stroke risk and AF-  
 992 related symptoms, and assessment of arrhythmia-related complications such as thromboembolism or LV  
 993 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.<sup>339, 340</sup> 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.<sup>341-343</sup>

### 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.<sup>344</sup> 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,<sup>345-347</sup> T1 mapping using cardiac MRI,<sup>347</sup> and intracardiac echo<sup>348</sup> 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.<sup>325, 330</sup> 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 <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
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	Ila	C	

AF = atrial fibrillation; ECG = electrocardiogram.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>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

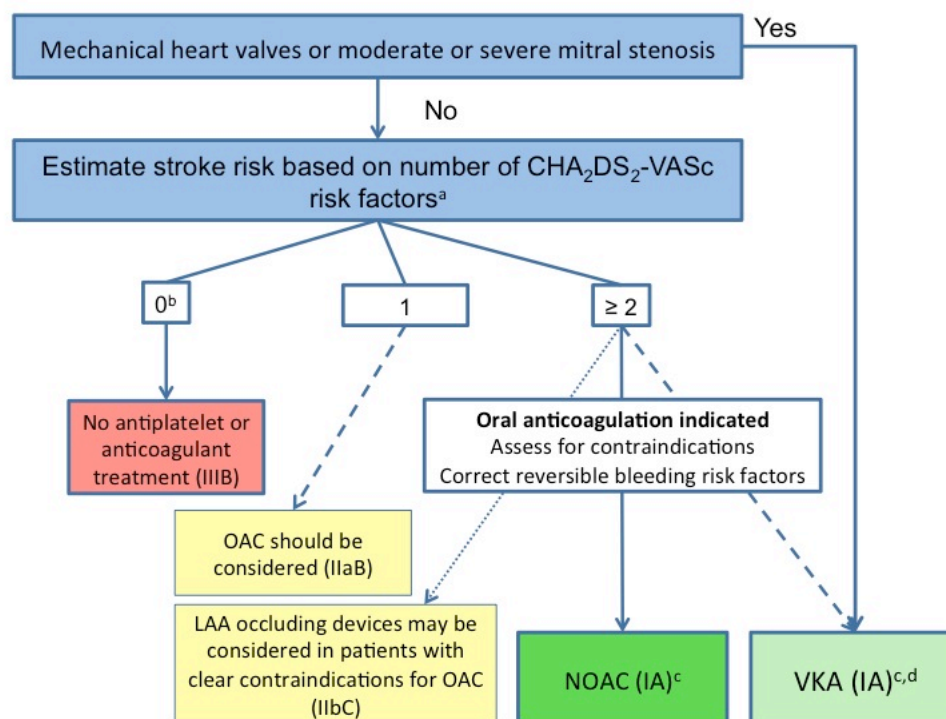
Category	Intervention	Follow-up aspects	Performance indicator (examples)
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Prognostic	Comorbidity control (relevant examples given)	Obesity	Weight loss
		Arterial hypertension	Blood pressure control
		Heart failure	Heart failure therapy
		Coronary artery 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
Symptomatic at present	Rhythm control	Symptoms vs. side-effects Exclusion of proarrhythmia (PR; QRS; QTc interval)	Hospitalization Therapy complications
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

1035 bpm = beats per minute; EHRA = European Heart Rhythm Association; GP = general practitioner; INR =  
1036 international normalized ratio; LV = left ventricular; NOAC = non-vitamin K antagonist oral anticoagulant;  
1037 VKA = vitamin K antagonist.  
1038

## 1039 **9 Stroke prevention therapy in atrial fibrillation patients**

1040 OAC therapy can prevent the majority of ischaemic strokes in AF patients and can prolong life.<sup>38, 39, 42, 194, 201, 329,</sup>  
1041 <sup>350-352</sup> It is superior to no treatment or aspirin in patients with different profiles for stroke risk.<sup>353, 354</sup> The net  
1042 clinical benefit is almost universal, with the exception of patients at very low stroke risk, and OAC should  
1043 therefore be used in most patients with AF (*Figure 8*). Despite this evidence, underuse or premature termination  
1044 of OAC therapy is still common. Bleeding events, both severe and nuisance bleeds, a perceived 'high risk of  
1045 bleeding' on anticoagulation, and the efforts required to monitor and dose-adjust VKA therapy are among the  
1046 most common reasons for withholding or ending OAC.<sup>352, 355-359</sup> However, the considerable stroke risk without  
1047 OAC often exceeds the bleeding risk on OAC, even in the elderly, in patients with cognitive dysfunction, or in  
1048 patients with frequent falls or frailty.<sup>360, 361</sup> The bleeding risk on aspirin is not different to the bleeding risk on  
1049 VKA<sup>362</sup> or NOAC therapy,<sup>354, 363</sup> while VKA and NOACs, but not aspirin, effectively prevent strokes in AF  
1050 patients.<sup>38, 354, 362, 363</sup>  
1051



**Figure 8** Stroke prevention in AF.

AF = atrial fibrillation; CHA<sub>2</sub>DS<sub>2</sub>-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.

<sup>a</sup>Congestive heart failure, hypertension, age ≥75 years (2 points), diabetes, prior stroke/TIA/embolus (2 points), vascular disease, age 65–74, female sex.

<sup>b</sup>Includes women without other stroke risk factors.

<sup>c</sup>IIaB for women with only one additional stroke risk factor,

<sup>d</sup>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.<sup>364-368</sup> The introduction of the CHA<sub>2</sub>DS<sub>2</sub>-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,<sup>369</sup> it has been widely used.<sup>370</sup> We recommend estimating stroke risk in AF patients based on the CHA<sub>2</sub>DS<sub>2</sub>-VASc score.<sup>368</sup> In general, patients without clinical stroke risk factors do not need antithrombotic therapy, while patients with stroke risk factors (i.e. CHA<sub>2</sub>DS<sub>2</sub>-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<sub>2</sub>DS<sub>2</sub>-VASc score.

CHA <sub>2</sub> DS <sub>2</sub> -VASc risk factor	Points
<b>Congestive heart failure</b>	+1
Signs/symptoms of heart failure or objective evidence of reduced left-ventricular ejection fraction	

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

1076 CHA<sub>2</sub>DS<sub>2</sub>-VASc = Congestive Heart failure, hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled),  
1077 Vascular disease, Age 65–74, and Sex (female).

1078  
1079 Other, less established risk factors for stroke include unstable international normalized ratio (INR) and low time  
1080 in therapeutic range (TTR) in patients treated with VKAs; previous bleed or anaemia; alcohol excess and other  
1081 markers for decreased therapy adherence; CKD; elevated high-sensitivity troponin T; and elevated N-terminal  
1082 pro-B-type natriuretic peptide.

### 1084 9.1.2. Anticoagulation in patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 1 in men and 2 1085 in women

1086 Controlled trials studying OAC in AF patients have been enriched for patients at high risk of stroke,<sup>38, 39, 42, 194,</sup>  
1087 <sup>201, 329, 351, 352</sup> and hence there is strong evidence that patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc risk score of 2 or more in  
1088 men, and 3 or more in women benefit from OAC. Fortunately, we now have a growing evidence-base regarding  
1089 stroke risk in patients with one clinical risk factor (i.e. CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 1 for men, and 2 for women),  
1090 although this relies largely on observed stroke rates in patients not receiving OAC. In many of these patients,  
1091 anticoagulation seems to provide a clinical benefit.<sup>371-375</sup> The rates of stroke and thromboembolism vary  
1092 considerably in patients with CHA<sub>2</sub>DS<sub>2</sub>-VASc scores of 1 or 2 due to differences in outcomes, populations, and  
1093 anticoagulation status (*Web Addenda Table 1*).<sup>371, 376, 377, 1041</sup> OAC should be considered for men with a  
1094 CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 1 and women with a score of 2, balancing the expected stroke reduction, bleeding  
1095 risk, and patient preference. Importantly, age (65 years and older) conveys a relatively high and continuously  
1096 increasing stroke risk that also potentiates other risk factors (such as heart failure and sex). Hence, an  
1097 individualized weighing of risk, as well as patient preferences, should inform the decision to anticoagulate  
1098 patients with only one CHA<sub>2</sub>DS<sub>2</sub>-VASc risk factor, apart from female sex. Female sex does not appear to  
1099 increase stroke risk in the absence of other stroke risk factors (*Web Addenda Table 1*).<sup>378, 379</sup>

1100 Measurement of cardiac troponin (high-sensitivity troponin T or I) and N-terminal pro-B-type  
1101 natriuretic peptide may provide additional prognostic information in selected AF patients.<sup>380-382</sup> Biomarker-  
1102 based risk scores may in the future prove helpful to better stratify patients (e.g. those at a truly low risk of  
1103 stroke).<sup>75, 382</sup>

### 1104 1105 9.1.3. Clinical risk scores for bleeding

1106 Several bleeding risk scores have been developed, mainly in patients on VKAs. These include HAS-BLED  
1107 (hypertension, abnormal renal/liver function [1 point each], stroke, bleeding history or predisposition, labile  
1108 INR, elderly [>65 years], drugs/alcohol concomitantly [1 point each]), ORBIT (Outcomes Registry for Better  
1109 Informed Treatment of Atrial Fibrillation), and more recently, the ABC (age, biomarkers, clinical history)  
1110 bleeding score, which also makes use of selected biomarkers.<sup>383-385</sup> Stroke and bleeding risk factors overlap  
1111 (compare *Table 11* and *Table 12*). For example, older age is one of the most important predictors of both  
1112 ischaemic stroke and bleeding in AF patients.<sup>386, 387</sup> A high bleeding risk score should generally not result in  
1113 withholding OAC. Rather, bleeding risk factors should be identified and treatable factors corrected (see Section  
1114 8.5). *Table 12* provides details of modifiable bleeding risk factors.

1115  
1116 **Table 12** Modifiable and non-modifiable risk factors for bleeding in anticoagulated patients based on  
1117 bleeding risk scores.

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

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

- 1118 ABC = age, biomarkers, clinical history; ATRIA = AnTicoagulation and Risk factors In Atrial fibrillation; CKD  
 1119 = chronic kidney disease; CrCl = creatinine clearance; HAS-BLED = hypertension, abnormal renal/liver  
 1120 function (1 point each), stroke, bleeding history or predisposition, labile INR, elderly (>65 years), drugs/alcohol  
 1121 concomitantly (1 point each); INR = international normalized ratio; ORBIT = Outcomes Registry for Better  
 1122 Informed Treatment of Atrial Fibrillation; TTR = time in therapeutic range; VKA = vitamin K antagonist.  
 1123 <sup>a</sup>Derived from the HAS-BLED score.<sup>384</sup>  
 1124 <sup>b</sup>Derived from the HEMORR<sub>2</sub>HAGES score.<sup>383</sup>  
 1125 <sup>c</sup>Derived from the ATRIA score.<sup>385</sup>  
 1126 <sup>d</sup>Derived from the ORBIT score.<sup>388</sup>  
 1127 <sup>e</sup>Derived from the ABC bleeding score.<sup>387</sup>

## 1128

### 1129 Recommendations for prediction of stroke and bleeding risk

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
The CHA <sub>2</sub> DS <sub>2</sub> -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

- 1130 AF = atrial fibrillation; CHA<sub>2</sub>DS<sub>2</sub>-VASc = Congestive Heart failure, hypertension, Age ≥75 (doubled),  
 1131 Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female); OAC = oral anticoagulation.  
 1132 <sup>a</sup>Class of recommendation.  
 1133 <sup>b</sup>Level of evidence.  
 1134 <sup>c</sup>Reference(s) supporting recommendations.  
 1135

## 1136 9.2. Stroke prevention

### 1137 9.2.1. Vitamin K antagonists

- 1138 Warfarin and other VKAs were the first anticoagulants used in AF patients. VKA therapy reduces risk of stroke  
 1139 by two-thirds and mortality by one-quarter compared with control (aspirin or no therapy).<sup>38</sup> VKAs have been  
 1140 used in many patients throughout the world with good outcomes,<sup>394-396</sup> and this is reflected in the warfarin arms  
 1141 of the NOAC trials (see Section 8.2.2.). The use of VKAs is limited by the narrow therapeutic interval,  
 1142 necessitating frequent monitoring and dose adjustments, but VKAs, when delivered with adequate TTR, are

1143 effective for stroke prevention in AF patients. Clinical parameters can help to identify patients who are likely to  
1144 achieve a decent TTR on VKA therapy.<sup>397</sup> These have been summarized in the SAME-TT<sub>2</sub>R<sub>2</sub> score. Patients who  
1145 fare well on this score, when treated with a VKA, have on average a higher TTR than patients who do not fare  
1146 well on the score.<sup>398, 399</sup> VKAs are currently the only treatment with established safety in AF patients with  
1147 rheumatic mitral valve disease and/or a mechanical heart valve prosthesis.<sup>400</sup>

### 1148 1149 **9.2.2. Non-vitamin K antagonist oral anticoagulants**

1150 NOACs, including the direct thrombin inhibitor dabigatran and the factor Xa inhibitors apixaban, edoxaban, and  
1151 rivaroxaban, are suitable alternatives to VKAs for stroke prevention in AF (*Table 13*). Their use in clinical  
1152 practice is increasing rapidly.<sup>401</sup> All NOACs have a predictable effect (onset and offset) without need for regular  
1153 anticoagulation monitoring. The phase III trials have been conducted with carefully selected doses of the  
1154 NOACs, including clear rules for dose reduction that should be followed in clinical practice (*Table 13*).

#### 1155 *Apixaban*

1156 In the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial  
1157 Fibrillation) trial,<sup>319</sup> apixaban reduced stroke or systemic embolism by 21% compared with warfarin, combined  
1158 with a 31% reduction in major bleeding and an 11% reduction in all-cause mortality (all statistically significant).  
1159 Rates of haemorrhagic stroke and intracranial haemorrhage, but not of ischaemic stroke, were lower on  
1160 apixaban. Rates of gastrointestinal bleeding were similar between the two treatment arms.<sup>402</sup>

1161 Apixaban is the only NOAC that has been compared with aspirin in AF patients: apixaban significantly  
1162 reduced stroke or systemic embolism by 55% compared with aspirin, with no significant difference in rates of  
1163 major bleeding or intracranial haemorrhage.<sup>354, 403</sup>

#### 1164 *Dabigatran*

1165 In the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) study,<sup>318, 404</sup> dabigatran 150 mg  
1166 twice daily reduced stroke and systemic embolism by 35% compared with warfarin without a significant  
1167 difference in major bleeding events. Dabigatran 110 mg twice daily was non-inferior to warfarin for prevention  
1168 of stroke and systemic embolism, with 20% fewer major bleeding events. Both dabigatran doses significantly  
1169 reduced haemorrhagic stroke and intracranial haemorrhage. Dabigatran 150 mg twice daily significantly  
1170 reduced ischaemic stroke by 24% and vascular mortality by 12%, while gastrointestinal bleeding was  
1171 significantly increased by 50%. There was a non-significant numerical increase in the rate of myocardial  
1172 infarction with both dabigatran doses,<sup>318, 404</sup> which has not been replicated in large post-authorization  
1173 analyses.<sup>396</sup> These data have also replicated the benefit of dabigatran over VKAs found in the RE-LY trial in  
1174 patients enriched for the higher dabigatran dose (150 mg twice daily).<sup>396</sup>

#### 1175 *Edoxaban*

1176 In the ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–  
1177 Thrombolysis in Myocardial Infarction 48) trial,<sup>321</sup> edoxaban 60 mg once daily and edoxaban 30 mg once daily  
1178 (with dose reductions in certain patients according to *Table 13*), were compared with adjusted-dose warfarin.<sup>405</sup>  
1179 Edoxaban 60 mg once daily was non-inferior to warfarin (primary outcome, HR 0.87; 97.5% CI 0.73–1.04; *P* =  
1180 0.08). In an on-treatment analysis, edoxaban 60 mg once daily significantly reduced stroke or systemic  
1181 embolism by 21% and significantly reduced major bleeding events by 20% compared with warfarin, while  
1182 edoxaban 30 mg once daily was non-inferior to warfarin for prevention of stroke and systemic embolism but  
1183 significantly reduced major bleeding events by 53%. Cardiovascular death was reduced in patients randomized  
1184 to edoxaban 60 mg once daily or edoxaban 30 mg once daily compared with warfarin. Only the higher dose  
1185 regimen has been approved for stroke prevention in AF.

#### 1186 *Rivaroxaban*

1187 In the ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K  
1188 Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial,<sup>320</sup> patients were  
1189 randomized to rivaroxaban 20 mg once daily or VKA, with a dose adjustment to 15 mg daily for those with  
1190 estimated CrCl 30–49 mL/min by the Cockcroft–Gault formula. Rivaroxaban was non-inferior to warfarin for the  
1191 prevention of stroke and systemic embolism in the intent-to-treat analysis, while the per-protocol on-treatment  
1192 analysis achieved statistical superiority with a 21% reduction in stroke or systemic embolism compared with  
1193 warfarin. Rivaroxaban did not reduce the rates of mortality, ischaemic stroke, or major bleeding events  
1194 compared to VKA. There was an increase in gastrointestinal bleeding events, but a significant reduction in  
1195 haemorrhagic stroke and intracranial haemorrhage with rivaroxaban compared with warfarin. Comparable event  
1196 rates have been reported in post-authorization analyses, which are part of the post-approval risk-management  
1197 process.<sup>406, 407</sup>

1202 **Table 13** NOACs compared with warfarin in controlled trials

	<b>Dabigatran (RE-LY)</b>	<b>Rivaroxaban (ROCKET-AF)</b>	<b>Apixaban (ARISTOTLE)</b>	<b>Edoxaban (ENGAGE AF-TIMI 48)</b>
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 <sub>2</sub> score (mean)	2.1	3.5	2.1	2.8

1203

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

1204 AF = atrial fibrillation; CHADS<sub>2</sub> = Cardiac failure, Hypertension, Age, Diabetes, Stroke (Doubled); CrCl = creatinine clearance; HR = hazard ratio; IQR = interquartile range (25<sup>th</sup> to 75<sup>th</sup> quartiles); RR = risk ratio; SD = standard deviation.

1206 RRs and HRs compared to warfarin therapy are presented with 95% confidence intervals and *P*-values.

1207

1208 **9.2.3. Non-vitamin K antagonist oral anticoagulants or vitamin K antagonists**

1209 Both VKAs and NOACs are effective for the prevention of stroke in AF. A meta-analysis<sup>39</sup> based on the high-  
 1210 dose treatment groups of the pivotal studies of warfarin versus NOACs included 42,411 patients receiving a  
 1211 NOAC and 29,272 receiving warfarin. NOACs in these dosages significantly reduced stroke or systemic  
 1212 embolic events by 19% compared with warfarin (RR 0.81; 95% CI 0.73–0.91;  $P < 0.0001$ ), mainly driven by a  
 1213 reduction in haemorrhagic stroke (RR 0.49; 95% CI 0.38–0.64;  $P < 0.0001$ ). Mortality was 10% lower in  
 1214 patients randomized to NOAC therapy (RR 0.90; 95% CI 0.85–0.95;  $P = 0.0003$ ) and intracranial haemorrhage  
 1215 was halved (RR 0.48; 95% CI 0.39–0.59;  $P < 0.0001$ ), while gastrointestinal bleeding events were more  
 1216 frequent (RR 1.25; 95% CI 1.01–1.55;  $P = 0.04$ ).<sup>39</sup> The stroke reduction with NOACs was consistent in all  
 1217 evaluated subgroups, while there was a suggestion of greater relative reduction in bleeding with NOACs at  
 1218 centres with poor INR control (interaction  $P = 0.022$ ). Notably, the substantial reduction in intracranial  
 1219 haemorrhage by NOACs compared with warfarin seems unrelated to poor or good INR control.<sup>408, 409</sup>

1220

1221 **9.2.4. Oral anticoagulation in atrial fibrillation patients with chronic kidney disease**

1222

1223 CKD is associated with stroke and bleeding in large data sets.<sup>410, 411</sup> Anticoagulation can be safely used in AF  
 1224 patients with moderate or moderate-to-severe CKD (glomerular filtration rate [GFR]  $\geq 15$  mL/min): the SPAF  
 1225 (Stroke Prevention in Atrial Fibrillation) III trial randomized 805/1936 participants with stage 3 CKD (estimated  
 1226 GFR  $< 59$  mL/min/1.73 m<sup>2</sup>), and reported good outcomes on warfarin (INR 2–3).<sup>412</sup> This finding is supported by  
 1227 a large Swedish database, in which stroke risk was lower in CKD patients with AF treated with warfarin  
 1228 (adjusted HR 0.76; 95% CI 0.72–0.80),<sup>413</sup> while bleeding was also slightly increased, especially during therapy  
 1229 initiation.<sup>414</sup> In a meta-analysis of the major NOAC trials, patients with mild or moderate CKD suffered fewer  
 1230 strokes, systemic emboli, or major bleeding events on NOACs than on warfarin.<sup>415</sup> Kidney function should be  
 1231 regularly monitored in AF patients on OAC to allow dose adaptation for those on NOACs (Table 14) and to  
 1232 refine risk estimation.<sup>416</sup>

1233

1234 **Table 14 Inclusion criteria, dose adjustments, and outcomes in patients with chronic kidney disease in the**  
 1235 **four major randomized trials comparing NOACs with warfarin in patients with AF. Adapted from Hart**  
 1236 ***et al.***<sup>316</sup>

	Dabigatran (RE-LY) <sup>318, 425</sup>	Rivaroxaban (ROCKET-AF) <sup>320, 426</sup>	Apixaban (ARISTOTLE) <sup>319, 427</sup>	Edoxaban (ENGAGE AF- TIMI 48) <sup>321</sup>
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 $\geq 1.5$ mg/dL plus age $\geq 80$ years or weight $\leq 60$ 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			
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1237 AF = atrial fibrillation; CKD = chronic kidney disease; CrCl = creatinine clearance; GFR = glomerular filtration  
1238 rate; NA = not available; NOAC = non-vitamin K antagonist oral anticoagulant.

1239

### 1240 9.2.5. Oral anticoagulation in atrial fibrillation patients on dialysis

1241 Approximately one in eight dialysis patient suffers from AF, with an incidence rate of 2.7/100 patient-years.<sup>417</sup>  
1242 AF is associated with increased mortality in patients on dialysis.<sup>417</sup> There are no randomized trials assessing  
1243 OAC in haemodialysis patients,<sup>418</sup> and no controlled trials of NOACs in patients with severe CKD (CrCl < 25–  
1244 30 mL/min).<sup>318-321</sup> Warfarin use was associated either with a neutral or increased risk of stroke in database  
1245 analyses of patients on dialysis,<sup>419-421</sup> including a population-based analysis in Canada (adjusted HR for stroke  
1246 1.14; 95% CI 0.78–1.67, adjusted HR for bleeding 1.44; 95% CI 1.13–1.85).<sup>422</sup> In contrast, data from Denmark  
1247 suggest a benefit of OAC in patients on renal replacement therapy.<sup>423</sup> Hence, controlled studies of  
1248 anticoagulants (both VKAs and NOACs) in AF patients on dialysis are needed.<sup>424</sup>

1249

### 1250 9.2.6. Patients with atrial fibrillation requiring kidney transplantation

1251 There are no randomized trials assessing OAC in patients after kidney transplantation. The prescription of  
1252 NOAC therapy should be guided by the estimated GFR of the transplanted kidney. Potential pharmacokinetic  
1253 interactions of OAC with immunosuppressive agents should be considered.

1254

1255

### 1256 9.2.7. Antiplatelet therapy as an alternative to oral anticoagulants

1257 The evidence supporting antiplatelet monotherapy for stroke prevention in AF is very limited.<sup>38, 428-430</sup> VKA  
1258 therapy prevents stroke, non-central nervous system embolus, myocardial infarction, and vascular death better  
1259 than single or dual antiplatelet therapy with aspirin and clopidogrel (annual risk of 5.6% for aspirin and  
1260 clopidogrel vs. 3.9% with VKA therapy).<sup>431</sup> Even greater benefits were seen in VKA-treated patients with a high  
1261 TTR.<sup>432</sup> Antiplatelet therapy increases bleeding risk, especially dual antiplatelet therapy (2.0% vs. 1.3% with  
1262 antiplatelet monotherapy;  $P < 0.001$ ),<sup>433</sup> with bleeding rates that are similar to those on OAC.<sup>354, 362, 431, 434</sup> Thus,  
1263 antiplatelet therapy cannot be recommended for stroke prevention in AF patients.

1264

### 1265 Recommendations for stroke prevention in patients with AF

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
<b>Oral anticoagulation therapy to prevent thromboembolism is recommended for all male AF patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 2 or more</b>	I	A	38, 318-321, 354, 404
<b>Oral anticoagulation therapy to prevent thromboembolism is recommended in all female AF patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 3 or more</b>	I	A	38, 318-321, 354, 404
<b>Oral anticoagulation therapy to prevent thromboembolism should be considered in male AF patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 1, considering individual characteristics and patient preferences</b>	IIa	B	371, 375-377
<b>Oral anticoagulation therapy to prevent thromboembolism should be considered in female AF patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 2, considering individual characteristics and patient preferences</b>	IIa	B	371, 376, 377
<b>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</b>	I	B	274, 435-440
<b>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</b>	I	A	39, 318-321, 404
<b>When patients are treated with a vitamin K antagonist, time</b>	I	A	395, 432, 441-444

<b>in therapeutic range (TTR) should be kept as high as possible and closely monitored</b>			
<b>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)</b>	IIb	A	39, 318, 319, 404, 408
<b>Combinations of oral anticoagulants and platelet inhibitors increase bleeding risk and should be avoided in AF patients without another indication for platelet inhibition</b>	III (harm)	B	429, 445
<b>In male or female AF patients without additional stroke risk factors, anticoagulant or antiplatelet therapy is not recommended for stroke prevention</b>	III (harm)	B	368, 371, 376, 377
<b>Antiplatelet monotherapy is not recommended for stroke prevention in AF patients, regardless of stroke risk</b>	III (harm)	A	38, 429, 430
<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)</b>	III (harm)	B/C	318-321, 400, 404

1266 AF = atrial fibrillation; CHA<sub>2</sub>DS<sub>2</sub>-VASc = Congestive Heart failure, hypertension, Age ≥75 (doubled),  
 1267 Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female); INR = international normalized  
 1268 ratio; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulation; TTR = time in  
 1269 therapeutic range; VKA = vitamin K antagonist.

1270 <sup>a</sup>Class of recommendation.

1271 <sup>b</sup>Level of evidence.

1272 <sup>c</sup>Reference(s) supporting recommendations.

1273

### 1274 9.3. Left atrial appendage occlusion and exclusion

#### 1275 9.3.1. Left atrial appendage occlusion devices

1276 Interventional LAA occlusion,<sup>446-449</sup> and limited experience with percutaneous LAA ligation, has mainly been  
 1277 reported in observational studies and registries. Only one device (Watchman®) has been compared with VKA  
 1278 therapy in randomized trials (PROTECT AF [Watchman Left Atrial Appendage System for Embolic Protection  
 1279 in Patients With AF trial], see *Web Addenda Table 2*; and PREVAIL [Prospective Randomized Evaluation of  
 1280 the Watchman LAA Closure Device In Patients with AF Versus Long Term Warfarin Therapy trial]).<sup>449-451</sup> In  
 1281 these data sets, LAA occlusion was non-inferior to VKA treatment for the prevention of stroke in AF patients  
 1282 with moderate stroke risk, with a possibility of lower bleeding rates in the patients who continued follow-up.<sup>452</sup>  
 1283 <sup>453</sup> These data were confirmed in a patient-level meta-analysis of the two trials and their associated registries.<sup>453</sup>  
 1284 LAA occlusion may also reduce stroke risk in patients with contraindications to OAC.<sup>454, 455</sup> The implantation  
 1285 procedure can cause serious complications,<sup>446, 456-458</sup> with high event rates reported in analyses from insurance  
 1286 databases and systematic reviews, possibly identifying a certain degree of reporting bias.<sup>446, 456</sup> A large recent  
 1287 European registry reported a high rate of implantation success (98%), with an acceptable procedure-related  
 1288 complication rate of 4% at 30 days.<sup>459</sup> Most patients who historically would be considered unsuitable for OAC  
 1289 therapy seem to do relatively well on contemporarily managed OAC.<sup>396, 407, 460</sup> Adequately powered controlled  
 1290 trials are urgently needed to inform the best use of these devices, including LAA occluders in patients who are  
 1291 truly unsuitable for OAC or in patients who suffer a stroke on OAC, randomized comparisons of LAA occluders  
 1292 with NOACs, and assessment of the minimal antiplatelet therapy acceptable after LAA occlusion.

1293

#### 1294 9.3.2. Surgical left atrial appendage occlusion or exclusion

1295 Surgical LAA occlusion or exclusion concomitant to cardiac surgery has been performed for many decades and  
 1296 with various techniques. Multiple observational studies indicate the feasibility and safety of surgical LAA  
 1297 occlusion/exclusion, but only limited controlled trial data are available.<sup>461-464</sup> Residual LAA flow or incomplete  
 1298 LAA exclusion can increase stroke risk.<sup>465</sup> In most studies, LAA occlusion/exclusion was performed during  
 1299 other open heart surgery, and more recently in combination with surgical ablation of AF<sup>463</sup> or as a stand-alone  
 1300 thoracoscopic procedure. One randomized trial evaluating the role of concomitant AF surgery and LAA  
 1301 occlusion reported in 2015, without a clear benefit of LAA exclusion for stroke prevention in the subgroup  
 1302 undergoing AF surgery.<sup>466</sup> A large randomized trial is currently underway.<sup>467</sup>

1303

#### 1304 Recommendations for occlusion or exclusion of the LAA

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
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

1305 AF = atrial fibrillation; LAA = left atrial appendage.

1306 <sup>a</sup>Class of recommendation.

1307 <sup>b</sup>Level of evidence.

1308 <sup>c</sup>Reference(s) supporting recommendations.

1309

## 1310 9.4. Secondary stroke prevention

1311 The most important risk factors for stroke in patients with AF are advanced age and previous cardioembolic  
1312 stroke or TIA,<sup>382</sup> emphasizing the need for OAC in these patients. The highest risk of recurrent stroke is in the  
1313 early phase after a first stroke or TIA.<sup>469, 470</sup>

1314

### 1315 9.4.1. Treatment of acute ischaemic stroke

1316 Systemic thrombolysis with recombinant tissue plasminogen activator (rtPA) is an effective and approved  
1317 medical treatment for acute ischaemic stroke in patients presenting within 4.5 hours of symptom onset.<sup>471</sup>

1318 Systemic thrombolysis is contraindicated in patients on therapeutic OAC.<sup>472, 473</sup> Recombinant tissue  
1319 plasminogen activator can be given in patients treated with a VKA if the INR is below 1.7,<sup>474</sup> or in dabigatran-  
1320 treated patients with a normal activated partial thromboplastin time and last intake of drug > 48 hours previously  
1321 (based on expert consensus).<sup>472</sup> Whether specific NOAC antidotes<sup>475</sup> could be used followed by systemic  
1322 thrombolysis needs to be investigated. Thrombectomy can be performed in anticoagulated patients with distal  
1323 occlusion of the internal carotid artery or middle cerebral artery in a 6-hour window.<sup>476</sup>

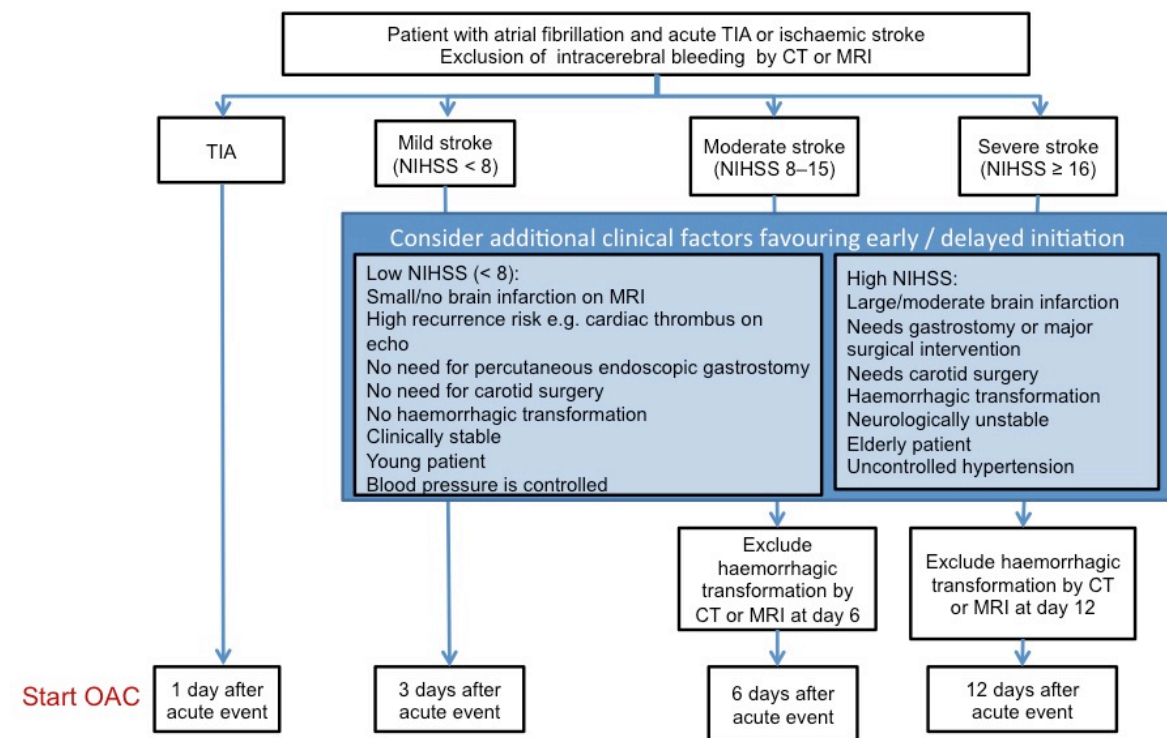
1324

### 1325 9.4.2. Initiation of anticoagulation after transient ischaemic attack or ischaemic 1326 stroke

1327 Data on the optimal use of anticoagulants (heparin, low-molecular-weight heparin, heparinoid, VKA, NOAC) in  
1328 the first days after a stroke are scarce. Parenteral anticoagulants seem to be associated with a non-significant  
1329 reduction in recurrent ischaemic stroke when administered 7 to 14 days after the acute stroke (odds ratio [OR]  
1330 0.68; 95% CI 0.44–1.06), with a significant increase in symptomatic intracranial bleeding (OR 2.89; 95% CI  
1331 1.19–7.01), and a similar rate of death or disability at final follow-up.<sup>477</sup> It seems likely that the bleeding risk on  
1332 parenteral anticoagulation exceeds the stroke prevention benefit in the first days after a large stroke, whereas  
1333 patients with a TIA or a small stroke may benefit from early (immediate) initiation or continuation of  
1334 anticoagulation. Therefore, we propose to initiate anticoagulation in AF patients between 1 and 12 days after an  
1335 ischaemic stroke, depending on its severity (*Figure 9*).<sup>478</sup> We suggest repeat brain imaging to determine the  
1336 optimal initiation of anticoagulation in patients with a large stroke at risk for haemorrhagic transformation.  
1337 Long-term OAC with a VKA<sup>363, 479–481</sup> or NOAC<sup>482</sup> conveys benefits in AF patients who survived a stroke.  
1338 NOACs seem to convey slightly better outcomes, mainly driven by fewer intracranial haemorrhages and  
1339 haemorrhagic strokes (OR 0.44, 95% CI 0.32–0.62).<sup>482</sup> Detailed data for edoxaban have not yet been  
1340 published.<sup>321</sup> If a patient suffers a stroke or TIA whilst taking an anticoagulant, switching to another  
1341 anticoagulant should be considered.

1342

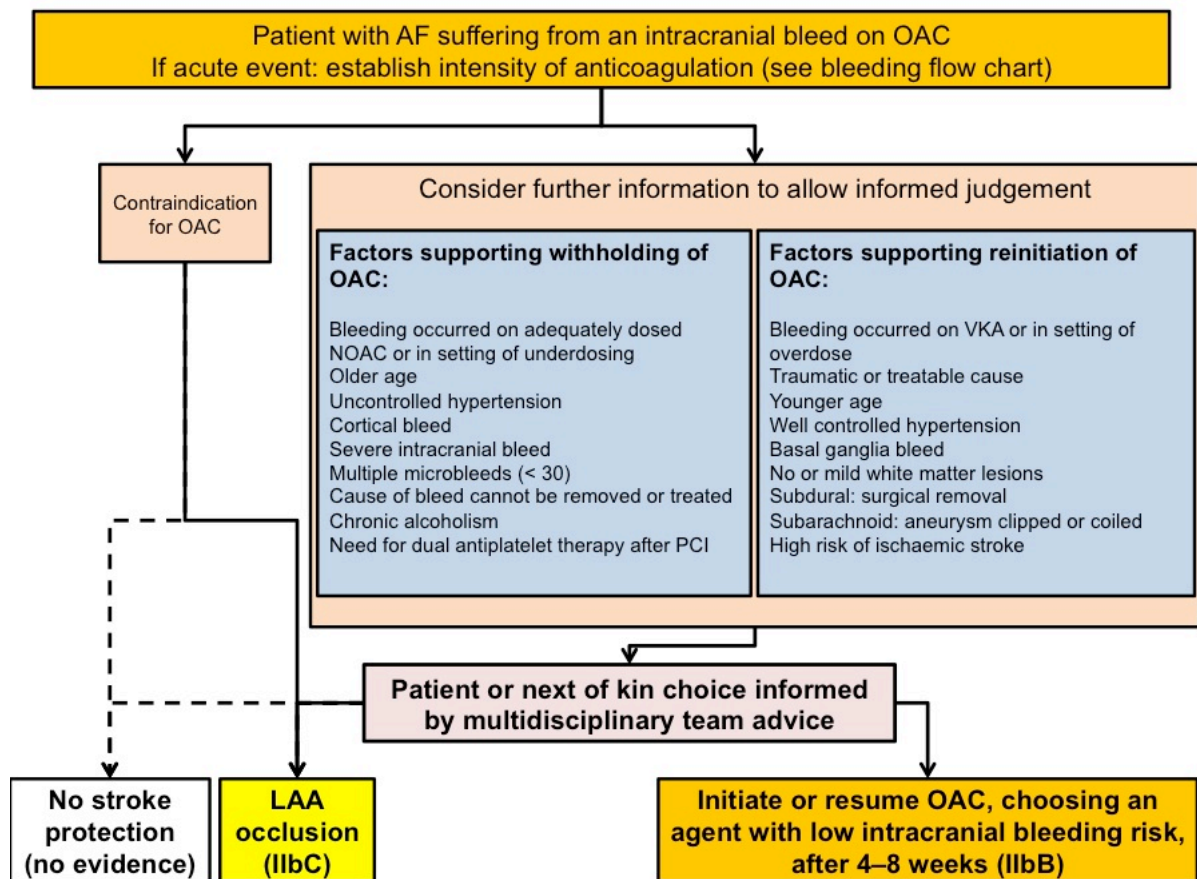
1343 **Figure 9** Initiation or continuation of anticoagulation in AF patients after a stroke or TIA. This approach is  
 1344 based on consensus rather than prospective data.



1345 AF = atrial fibrillation; CT = computed tomography; MRI = magnetic resonance imaging; NIHSS = National  
 1346 Institutes of Health stroke severity scale (available at [http://www.strokecenter.org/wp-](http://www.strokecenter.org/wp-content/uploads/2011/08/NIH_Stroke_Scale.pdf)  
 1347 [content/uploads/2011/08/NIH\\_Stroke\\_Scale.pdf](http://www.strokecenter.org/wp-content/uploads/2011/08/NIH_Stroke_Scale.pdf)); OAC = oral anticoagulation; TIA = transient ischaemic  
 1348 attack.  
 1349

### 1350 9.4.3. Initiation of anticoagulation after intracranial haemorrhage

1352 No prospective studies have investigated the benefit or risk of the initiation of OAC after intracranial  
 1353 haemorrhage,<sup>483</sup> and patients with a history of intracranial bleeding were excluded from the randomized trials  
 1354 comparing NOACs with VKAs. The available evidence indicates that anticoagulation in patients with AF can be  
 1355 reinitiated after 4–8 weeks, especially when the cause of bleeding or the relevant risk factor (e.g. uncontrolled  
 1356 hypertension) has been treated, and that such treatment leads to fewer recurrent (ischaemic) strokes and lower  
 1357 mortality.<sup>460, 484</sup> If anticoagulation is resumed, it seems reasonable to consider anticoagulants with a low  
 1358 bleeding risk.<sup>39</sup> *Figure 10* depicts a consensus opinion on the initiation or resumption of OAC after an  
 1359 intracranial haemorrhage. We recommend a multidisciplinary decision with input from stroke  
 1360 physicians/neurologists, cardiologists, neuroradiologists, and neurosurgeons.



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### Recommendations for secondary stroke prevention

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
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

1369

1370

1371 AF = atrial fibrillation; INR = international normalized ratio; NOAC = non-vitamin K antagonist oral  
1372 anticoagulant; OAC = oral anticoagulation; TIA = transient ischaemic attack; VKA = vitamin K antagonist.

1373 <sup>a</sup>Class of recommendation.

1374 <sup>b</sup>Level of evidence.

1375 <sup>c</sup>Reference(s) supporting recommendations.

1376

## 1377 **9.5. Strategies to minimize bleeding on anticoagulant therapy**

1378 In a meta-analysis of 47 studies, the overall incidence of major bleeding with VKAs was 2.1 (range 0.9–3.4) per  
1379 100 patient-years in controlled trials and 2.0 (range 0.2–7.6) per 100 patient-years for observational data sets.<sup>488</sup>

1380 Minimizing treatable bleeding risk factors (see *Table 12*) seems paramount to reduce the bleeding rate on  
1381 anticoagulants.

1382

### 1383 **9.5.1. Uncontrolled hypertension**

1384 Uncontrolled blood pressure increases the risk of bleeding on OAC.<sup>53</sup> Hence, keeping systolic blood pressure  
1385 well controlled is of particular relevance in anticoagulated patients with AF. Treatment according to current  
1386 guidelines is recommended in patients with known hypertension.<sup>489</sup>

1387

### 1388 **9.5.2. Previous bleeding event**

1389 History of bleeding events and the presence of anaemia are important parts of the assessment of all patients  
1390 receiving OAC. The majority of bleeding events are gastrointestinal. Compared with warfarin, the risk of  
1391 gastrointestinal bleeds was increased for dabigatran 150 mg twice daily,<sup>396, 490</sup> rivaroxaban 20 mg once daily,<sup>491</sup>  
1392 and edoxaban 60 mg once daily.<sup>321</sup> The risk of gastrointestinal bleeds was comparable to warfarin on dabigatran  
1393 110 mg twice daily<sup>490</sup> and on apixaban 5 mg twice daily.<sup>319</sup> Recent observational analyses do not replicate these  
1394 findings, suggesting a smaller effect.<sup>396, 492, 493</sup> In patients in whom the source of bleeding has been identified and  
1395 corrected, OAC can be reinitiated. This also appears true for patients who have had an intracranial haemorrhage,  
1396 once modifiable bleeding risk factors (e.g. uncontrolled hypertension) have been corrected.<sup>460, 484</sup>

1397

### 1398 **9.5.3. Labile international normalized ratio and adequate non-vitamin K 1399 antagonist oral anticoagulant dosing**

1400 TTR on VKA therapy is an important predictor of major haemorrhage.<sup>432, 441, 494</sup> Therefore we recommend  
1401 targeting the INR between 2.0 and 3.0 in patients on VKAs, maintaining a high TTR (e.g.  $\geq 70\%$ <sup>494</sup>), and to  
1402 consider switching to a NOAC when a high TTR cannot be sustained.<sup>444</sup> NOAC dosing should follow the dose-  
1403 reduction criteria evaluated in the clinical trials, considering renal function, age, and weight. Patient information  
1404 and empowerment, best delivered through integrated AF management, seem paramount to achieve this goal.

1405

### 1406 **9.5.4. Alcohol abuse**

1407 Alcohol excess is a risk factor for bleeding in anticoagulated patients,<sup>384</sup> mediated by poor adherence, liver  
1408 disease, variceal bleeding, and risk of major trauma. Severe alcohol abuse and binge drinking habits should be  
1409 corrected in patients eligible for OAC.

1410

### 1411 **9.5.5. Falls and dementia**

1412 Falls and dementia are associated with increased mortality in AF patients,<sup>495</sup> without evidence that these  
1413 conditions markedly increase the risk of intracranial haemorrhage.<sup>495, 496</sup> Hence, anticoagulation should only be  
1414 withheld from patients with severe uncontrolled falls (e.g. epilepsy or advanced multisystem atrophy with  
1415 backwards falls), or in selected patients with dementia where compliance and adherence cannot be ensured by a  
1416 caregiver.

1417

### 1418 **9.5.6. Genetic testing**

1419 In addition to food and drug interactions, multiple genetic variations affect the metabolism of VKAs.<sup>497</sup> The  
1420 systematic use of genetic information for adjustment of VKA dosage has been evaluated in several controlled  
1421 clinical studies.<sup>498-500</sup> Genetic testing has little effect on TTR or bleeding risk on warfarin, and is not  
1422 recommended for clinical use at present.<sup>501</sup>

1423

### 1424 **9.5.7. Bridging periods off oral anticoagulation**

1425 Most cardiovascular interventions (e.g. percutaneous coronary intervention or pacemaker implantation) can be  
1426 performed safely on continued OAC. When interruption of OAC is required, bridging does not seem to be  
1427 beneficial, except in patients with mechanical heart valves. In a randomized trial of 1884 patients with AF,  
1428 interruption of anticoagulation was non-inferior to heparin administration for the outcome of arterial  
1429 thromboembolism (incidence of 0.4% and 0.3%, respectively) and resulted in a lower risk of major bleeding  
1430 (1.3% and 3.2%, respectively).<sup>502</sup> A short interruption or continued OAC should be considered in patients at  
1431 highest risk of stroke.

1432

## 1433 **9.6. Management of bleeding events in anticoagulated patients with atrial fibrillation**

### 1434 **9.6.1. Management of minor, moderate, and severe bleeding**

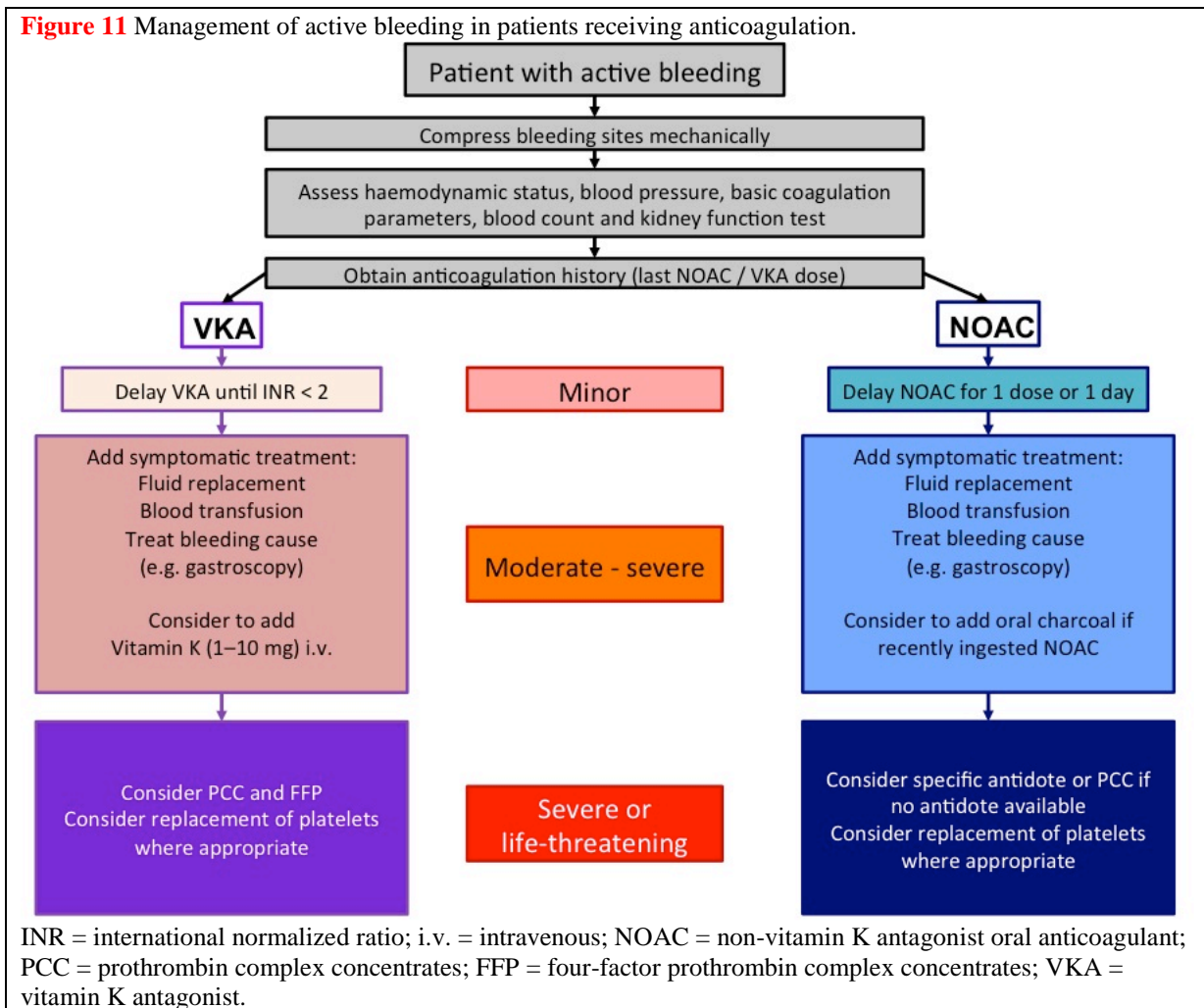
1435 General assessment of an anticoagulated patient with AF experiencing a bleeding event should include  
1436 assessment of bleeding site, onset, and severity of the bleeding, the time-point of last intake of OAC and other  
1437 antithrombotic drugs, and other factors influencing bleeding risk such as CKD, alcohol abuse, and concurrent  
1438 medications. Laboratory tests should include haemoglobin, haematocrit, platelet count, renal function, and for  
1439 VKA patients, prothrombin time, activated partial thromboplastin time, and INR. Coagulation tests do not  
1440 provide much information in patients on NOACs, except for activated partial thromboplastin time in the case of  
1441 dabigatran. More specific coagulation tests do exist, including diluted thrombin time (HEMOCLLOT) for  
1442 dabigatran and calibrated quantitative anti-factor Xa assays for factor Xa inhibitors.<sup>503</sup> However, these tests are  
1443 not always readily available and are often unnecessary for bleeding management.<sup>504</sup>

1444 We propose a simple scheme to manage bleeding events in patients on OAC (*Figure 11*). Minor  
1445 bleeding events should be treated with supportive measures such as mechanical compression or minor surgery to  
1446 achieve haemostasis. In patients receiving VKAs, the next dose of VKA can be postponed. NOACs have a short  
1447 plasma half-life of approximately 12 hours and improved haemostasis is expected within 12–24 hours after a  
1448 delayed or omitted dose. Treatment of moderate bleeding events may require blood transfusions and fluid  
1449 replacement. Specific diagnostic and treatment interventions directed against the cause of the bleeding (e.g.  
1450 gastroscopy) should be performed promptly. If the intake of NOAC was recent (< 2–4 h), charcoal  
1451 administration and/or gastric lavage will reduce further exposure. Dialysis clears dabigatran but is not effective  
1452 for the other NOACs.

1453 Immediate reversal of the antithrombotic effect is indicated in severe or life-threatening bleeding  
1454 events. An agreed, the institutional procedure for the management of life-threatening bleeds should be  
1455 documented and accessible at all times to ensure adequate initial management. For VKAs, administration of  
1456 fresh frozen plasma restores coagulation more rapidly than vitamin K, and prothrombin complex concentrates  
1457 achieve even faster blood coagulation.<sup>505</sup> Registry data suggest that the combination of plasma and prothrombin  
1458 complex concentrates is associated with the lowest case fatality following intracranial haemorrhage on VKA  
1459 treatment with an INR  $\geq 1.3$ .<sup>506</sup> In a multicentre randomized trial of 188 patients, four-factor prothrombin  
1460 complex concentrates achieved more rapid INR reversal and effective haemostasis than plasma in patients  
1461 undergoing urgent surgical or invasive procedures.<sup>507</sup> Administration of prothrombin complex concentrates may  
1462 also be considered for severe bleeding on NOAC treatment if specific antidotes are not available.

1463 Several antidotes to NOACs are under development. Idarucizumab (approved in 2015 by the US Food  
1464 and Drug Administration and the European Medicines Agency) is a clinically available humanized antibody  
1465 fragment that binds dabigatran and rapidly and dose-dependently reverses the effects without over-correction or  
1466 thrombin generation.<sup>475</sup> Andexanet alpha, a modified recombinant human factor Xa that lacks enzymatic  
1467 activity, reverses the anticoagulant activity of apixaban and rivaroxaban in healthy probands within minutes  
1468 after administration and for the duration of infusion, with a transient increase in markers of coagulation activity  
1469 of uncertain clinical relevance.<sup>508</sup> Another agent under development is ciraparantag (PER977), an antidote  
1470 targeted to reverse both direct thrombin and factor Xa inhibitors as well as the indirect inhibitor enoxaparin.<sup>509</sup>  
1471 The clinical usefulness of these specific antidotes needs further evaluation.

1472

1473 **Figure 11** Management of active bleeding in patients receiving anticoagulation.

1478

### 1479 9.6.2. Oral anticoagulation in atrial fibrillation patients at risk of or having a 1480 bleeding event

1481 While anticoagulation therapy should be paused to control active bleeding, absolute contraindications to long-  
1482 term OAC after a bleeding episode are rare. When nuisance bleeds are the reason to stop OAC, a change from  
1483 one anticoagulant to another seems reasonable. Many causes or triggers of major bleeding events can be treated  
1484 and/or eliminated, including uncontrolled hypertension, gastrointestinal ulcers, and intracranial aneurysms.  
1485 Reinitiation of anticoagulation after a bleeding event is often clinically justified.<sup>460, 510</sup> Difficult decisions,  
1486 including the discontinuation and recommencement of OAC, should be taken by a multidisciplinary team,  
1487 balancing estimated risk of recurrent stroke and bleeding, and considering the bleeding risk of different stroke  
1488 prevention therapies. LAA exclusion or occlusion might be an alternative in selected patients.

1489

#### 1490 Recommendations for management of bleeding

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
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	<sup>497</sup>
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	<sup>460</sup>
In AF patients with severe active bleeding events, it is recommended to interrupt OAC therapy until the underlying cause is resolved	I	C	

1491 AF = atrial fibrillation; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulation;

1492 VKA = vitamin K antagonist

1493 <sup>a</sup>Class of recommendation.

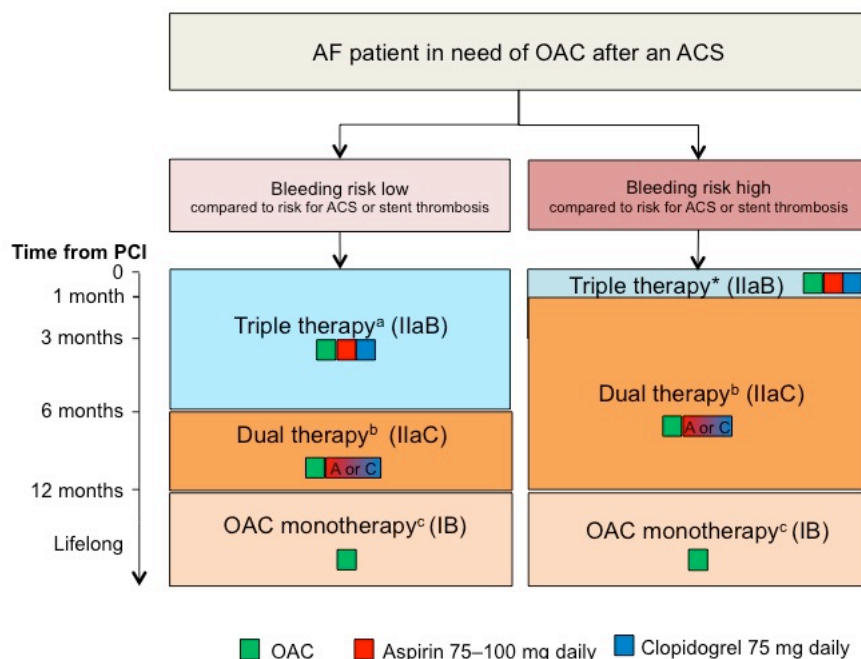
1494 <sup>b</sup>Level of evidence.

1495 <sup>c</sup>Reference(s) supporting recommendations.

1496

### 1497 **9.7. Combination therapy with oral anticoagulants and antiplatelets**

1498 Approximately 15% of AF patients in contemporary trials<sup>513</sup> and registries<sup>514-516</sup> have a history of myocardial  
 1499 infarction. Between 5% and 15% of AF patients will require stenting at some point in their lives. This scenario  
 1500 requires careful consideration of antithrombotic therapy, balancing bleeding risk, stroke risk, and risk of acute  
 1501 coronary syndromes (ACS).<sup>516</sup> Co-prescription of OAC with antiplatelet therapy, in particular triple therapy,  
 1502 increases the absolute risk of major haemorrhage.<sup>445, 517, 518</sup> A recent meta-analysis involving 30,866 patients  
 1503 with a recent ACS evaluated the effects of adding NOAC therapy to single (4135 patients) or dual (26,731  
 1504 patients) antiplatelet therapy.<sup>519</sup> The addition of a NOAC increased the bleeding risk by 79–134%, while  
 1505 reducing recurrent ischaemic events only marginally in patients without AF. OAC monotherapy, and not  
 1506 combination therapy with antiplatelets, is recommended in AF patients with stable CAD but without an ACS  
 1507 and/or coronary intervention in the previous 12 months. In patients treated for ACS and in those receiving a  
 1508 coronary stent, short-term triple combination therapy of OAC, clopidogrel, and aspirin seems warranted (*Figure*  
 1509 *12*).



1510

1511 **Figure 12** Antithrombotic therapy after an ACS in AF patients requiring anticoagulation.

1512 ACS = acute coronary syndrome; AF = atrial fibrillation; OAC = oral anticoagulation (using vitamin K

1513 antagonists or non-vitamin K antagonist oral anticoagulants); PCI = percutaneous coronary intervention.

1514 <sup>a</sup>Dual therapy with OAC and aspirin or clopidogrel may be considered in selected patients, especially those not

1515 receiving a stent or patients at a longer time from the index event.

1516 <sup>b</sup>OAC plus single antiplatelet.1517 <sup>c</sup>Dual therapy with OAC and an antiplatelet agent (aspirin or clopidogrel) may be considered in patients at high

1518 risk of coronary events.

1519

1520

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1522

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

1523 The optimal combination antithrombotic therapy or duration of combination therapy for AF patients undergoing

1524 percutaneous coronary intervention is not known, but the continued bleeding risk suggests a short duration.

1525 Expert consensus,<sup>520</sup> reviewed and reconsidered by this Task Force, suggests the following principles: AF

1526 patients at risk for stroke, patients with mechanical valves, and patients with recent or recurrent deep vein

1527 thrombosis or pulmonary embolism should continue OAC during and after stenting. In general, a short period of

1528 triple therapy (OAC, aspirin, clopidogrel) is recommended, followed by a period of dual therapy (OAC plus a

1529 single antiplatelet) (Figure 13). When a NOAC is used, the consensus recommendation is that the lowest dose

1530 effective for stroke prevention in AF should be considered. Dose reduction beyond the dosing regimens tested in

1531 the phase III trials is not currently recommended, and awaits assessment in ongoing controlled trials. The

1532 combination of aspirin, clopidogrel, and low-dose rivaroxaban (2.5 mg twice daily) is not recommended for

1533 stroke prevention in AF.<sup>521</sup>

1534 The use of prasugrel or ticagrelor as part of triple therapy should be avoided unless there is a clear need

1535 for these agents (e.g. stent thrombosis on aspirin plus clopidogrel), given the lack of evidence and the greater

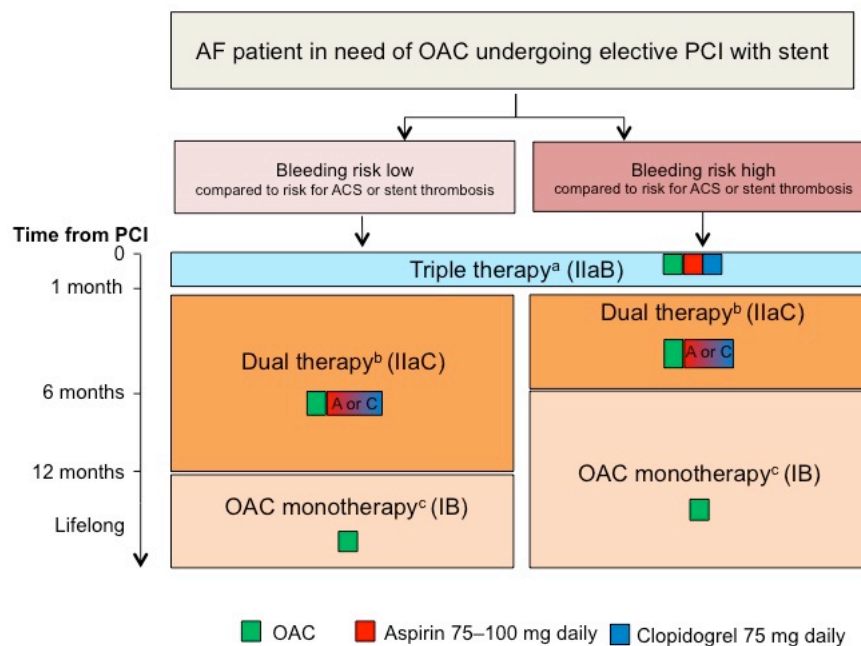
1536 risk of major bleeding compared with clopidogrel.<sup>522, 523</sup> Ongoing trials will inform about such combination

1537 therapies in the future.

1538 The omission of aspirin while maintaining clopidogrel and OAC has been evaluated in the WOEST

1539 (What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary

1540 StenTing) trial, in which 573 anticoagulated patients undergoing percutaneous coronary intervention (70% with  
 1541 AF) were randomized to either dual therapy with OAC and clopidogrel (75 mg once daily) or to triple therapy  
 1542 with OAC, clopidogrel, and aspirin.<sup>524</sup> Bleeding was lower in the dual versus triple therapy arm, driven by fewer  
 1543 minor bleeding events. The rates of myocardial infarction, stroke, target vessel revascularization, and stent  
 1544 thrombosis did not differ (albeit with low event numbers), but all-cause mortality was lower in the dual therapy  
 1545 group at 1 year (2.5% vs. triple 6.4%). Although the trial was too small to assess ischaemic outcomes, dual  
 1546 therapy with OAC and clopidogrel may emerge in the future as an alternative to triple therapy in patients with  
 1547 AF and ACS and/or coronary intervention.<sup>525</sup>



1548  
 1549 **Figure 13** Antithrombotic therapy after percutaneous intervention in AF patients requiring anticoagulation.  
 1550 ACS = acute coronary syndrome; AF = atrial fibrillation; OAC = oral anticoagulation (using vitamin K  
 1551 antagonists or non-vitamin K antagonist oral anticoagulants); PCI = percutaneous coronary intervention.

1552 <sup>a</sup>Dual therapy with OAC and aspirin or clopidogrel may be considered in selected patients.

1553 <sup>b</sup>OAC plus single antiplatelet.

1554 <sup>c</sup>Dual therapy with OAC and an antiplatelet agent (aspirin or clopidogrel) may be considered in patients at high  
 1555 risk of coronary events.

1556

### 1557 Recommendations for combination therapy with oral anticoagulants and antiplatelets

1558

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
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

1559 ACS = acute coronary syndromes; AF = atrial fibrillation

1560 <sup>a</sup>Class of recommendation.

1561 <sup>b</sup>Level of evidence.

1562 <sup>c</sup>Reference(s) supporting recommendations.

1563

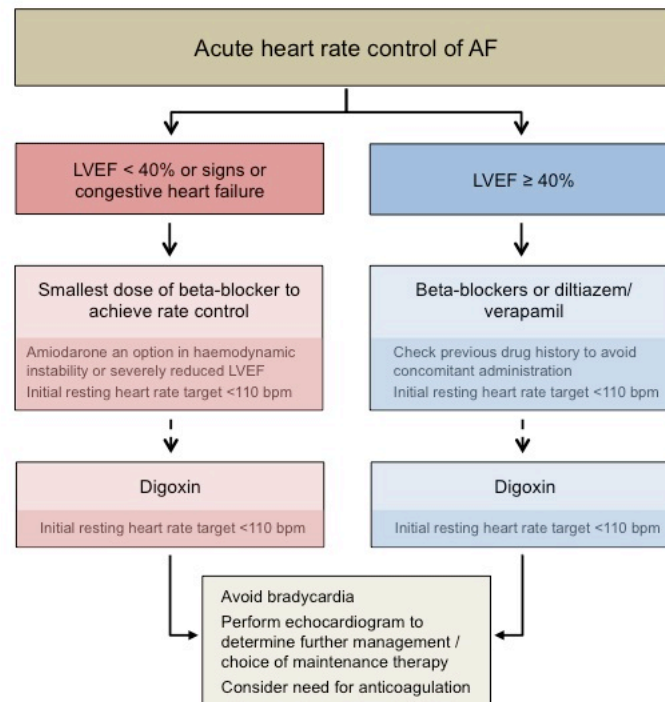
## 1564 **10 Rate control therapy in AF**

1565 Rate control is an integral part of the management of AF patients, and is often sufficient to improve AF-related  
 1566 symptoms. Compared with stroke prevention and rhythm control, very little robust evidence exists to inform the  
 1567 best type and intensity of rate control treatment, with the majority of data derived from short-term crossover  
 1568 trials and observational studies.<sup>41, 526-528</sup> Pharmacological rate control can be achieved for acute or long-term rate  
 1569 control with beta-blockers, digoxin, the calcium channel blockers diltiazem and verapamil, or combination  
 1570 therapy (*Table 15*). A number of antiarrhythmic drugs also have rate-limiting properties (amiodarone,  
 1571 dronedarone, sotalol, and to some extent propafenone), but they should only be used in patients needing rhythm  
 1572 control therapy (see Chapter 10).

1573

### 1574 **10.1. Acute rate control**

1575 In the setting of acute new-onset AF, patients are often in need of heart rate control. Physicians should evaluate  
 1576 underlying causes of elevated heart rate, such as infection, endocrine imbalance, anaemia, and pulmonary  
 1577 embolism. For acute rate control, beta-blockers and diltiazem/verapamil are preferred over digoxin because of  
 1578 their rapid onset of action and effectiveness at high sympathetic tone.<sup>528-532</sup> The choice of drug (*Table 15*) and  
 1579 target heart rate will depend on patient characteristics, symptoms, LVEF and haemodynamics, but a lenient  
 1580 initial approach to heart rate seems acceptable. Combination therapy may be required (*Figure 14*). In patients  
 1581 with evidence of HFrEF, beta-blockers, digitalis (digoxin or digitoxin), or their combination should be used,<sup>218,</sup>  
 1582 <sup>533</sup> as diltiazem and verapamil can have negative inotropic effects in patients with LVEF < 40%.<sup>222, 534, 535</sup> In  
 1583 critically ill patients and those with severely impaired LV systolic function, intravenous amiodarone can be used  
 1584 where excess heart rate is leading to haemodynamic instability.<sup>536-538</sup> Urgent cardioversion should be considered  
 1585 in unstable patients (see Chapter 10.2).



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1590

**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.

## 1591 10.2. Long-term pharmacological rate control

### 1592 10.2.1. Beta-blockers

1593 Beta-adrenoreceptor blocker monotherapy is often the first-line rate-controlling agent,<sup>539</sup> largely based on  
1594 observations of better acute heart rate control than digoxin. Interestingly, the prognostic benefit of beta-blockers  
1595 seen in HFrEF patients with sinus rhythm is lost in those with AF. In an individual patient-level meta-analysis  
1596 of RCTs, beta-blockers did not reduce all-cause mortality compared to placebo in those with AF at baseline (HR  
1597 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;  
1598 95% CI 0.67–0.80;  $P < 0.001$ ).<sup>23</sup> The study, which included 3066 participants with HFrEF and AF, showed  
1599 consistency across all subgroups and outcomes, with no heterogeneity between the 10 RCTs included ( $I^2 = 0\%$ ).  
1600 Despite this lack of prognostic benefit in HFrEF, this Task Force still considers beta-blockers as a useful first-  
1601 line rate control agent across all AF patients, based on the potential for symptomatic and cardiac function  
1602 improvement as a result of rate control, the lack of harm from published studies, and the good tolerability profile  
1603 across all ages in sinus rhythm and in AF.<sup>23, 540</sup>

1604

### 1605 10.2.2. Non-dihydropyridine calcium channel blockers

1606 Verapamil or diltiazem provides reasonable rate control in AF patients.<sup>541</sup> They should be avoided in patients  
1607 with HFrEF because of their negative inotropic effects.<sup>222, 534, 535</sup> Verapamil or diltiazem can improve  
1608 arrhythmia-related symptoms,<sup>526</sup> in comparison with beta-blockers, which reduced exercise capacity and  
1609 increased B-type natriuretic peptide in one small trial of low-risk patients with preserved LVEF.<sup>542</sup>

1610

### 1611 10.2.3. Digitalis

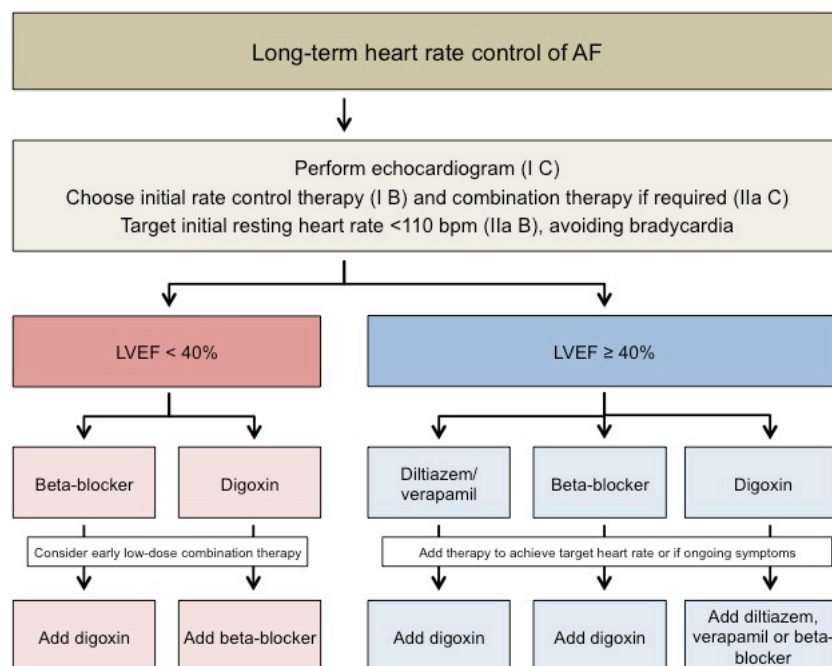
1612 Cardiac glycosides such as digoxin and digitoxin have been in use for over two centuries, although prescriptions  
1613 have been declining steadily over the past 15 years.<sup>543</sup> In the randomized Digitalis Investigation Group (DIG)  
1614 trial, digoxin had no effect on mortality compared to placebo in HFrEF patients in sinus rhythm (RR 0.99; 95%

1615 CI 0.91–1.07), but reduced hospital admissions (RR 0.72; 95% CI 0.66–0.79).<sup>544, 545</sup> There have been no head-  
 1616 to-head RCTs of digoxin in AF patients.<sup>546</sup> Observational studies have associated digoxin use with excess  
 1617 mortality in AF patients,<sup>547-549</sup> but this association is likely due to selection and prescription biases rather than  
 1618 harm caused by digoxin,<sup>550-553</sup> particularly as digoxin is commonly prescribed to sicker patients.<sup>225</sup> In a  
 1619 crossover mechanistic trial of 47 patients with HFrEF and AF, there were no differences in heart rate, blood  
 1620 pressure, walking distance, or LVEF between carvedilol and digoxin, although beta-blockers did result in higher  
 1621 B-type natriuretic peptide levels, combination carvedilol/digoxin improved LVEF, and digoxin withdrawal  
 1622 reduced LVEF.<sup>554</sup> Comparisons with other rate control therapies are based on small, short-duration studies that  
 1623 identify no or marginal differences in exercise capacity, quality of life, or LVEF compared to digoxin.<sup>526, 554-558</sup>  
 1624 Lower doses of digoxin ( $\leq 250$   $\mu\text{g}$  once daily), corresponding to serum digoxin levels of 0.5–0.9 ng/mL, may be  
 1625 associated with better prognosis.<sup>225</sup>

#### 1627 10.2.4. Amiodarone

1628 Amiodarone can be useful for rate control as a last resort. The wide array of extracardiac adverse effects  
 1629 associated with amiodarone renders it a reserve agent in patients whose heart rate cannot be controlled with  
 1630 combination therapy (e.g. beta-blocker or verapamil/diltiazem combined with digoxin).

1631  
 1632 In summary, there is equipoise for the use of different rate control agents in AF. The choice of beta-blocker,  
 1633 diltiazem/verapamil, digoxin, or combination therapy should be made on an individual basis, after consideration  
 1634 of patient characteristics and patient preference. All available therapies have the potential for adverse effects and  
 1635 patients should initially be treated with a low dose and uptitrated to achieve symptom improvement. In practice,  
 1636 achieving a heart rate  $< 110$  bpm will often require combination therapy (*Figure 15*). The benefit of different  
 1637 rate control strategies on symptoms, quality of life, and other intermediate outcomes is under investigation.<sup>559</sup>



1638

1639 **Figure 15** Long-term heart rate control of AF.

1640 See *Table 15* for medication dosage. Digitoxin is a suitable alternative to digoxin, where available.

1641 AF = atrial fibrillation; bpm = beats per minute; LVEF = left ventricular ejection fraction.

1642

### 1643 10.3. Heart rate targets in atrial fibrillation

1644 The optimal heart rate target in AF patients is unclear. The RACE (Rate Control Efficacy in Permanent Atrial  
 1645 Fibrillation) II study randomized 614 patients with permanent AF to either a target heart rate < 80 bpm at rest  
 1646 and < 110 bpm during moderate exercise, or to a lenient heart rate target of < 110 bpm. There was no difference  
 1647 in a composite of clinical events (14.9% in the strict rate control group, 12.9% in the lenient group),<sup>560</sup> NYHA  
 1648 class, or hospitalizations.<sup>560, 561</sup> Similar results were found in a pooled analysis of the AFFIRM (Atrial  
 1649 Fibrillation Follow-up Investigation of Rhythm Management) and RACE trials (1091 participants), albeit with  
 1650 smaller heart rate differences and without randomization.<sup>562</sup> It is worthwhile to note that many ‘adequately rate-  
 1651 controlled’ patients (resting heart rate 60–100 bpm) are severely symptomatic, calling for additional  
 1652 management.<sup>194</sup> Nonetheless, lenient rate control is an acceptable initial approach, regardless of heart failure  
 1653 status, unless symptoms call for stricter rate control.  
 1654

#### 1655 10.4. Atrioventricular node ablation and pacing

1656 Ablation of the atrioventricular node/His bundle and implantation of a VVI pacemaker can control ventricular  
 1657 rate when medications fail to control rate and symptoms. It is a relatively simple procedure with a low  
 1658 complication rate and low long-term mortality risk,<sup>563, 564</sup> especially when the pacemaker is implanted a few  
 1659 weeks before the AV nodal ablation and the initial pacing rate after ablation is set at 70–90 bpm.<sup>565, 566</sup> The  
 1660 procedure does not worsen LV function<sup>567</sup> and may even improve LVEF in selected patients.<sup>568-570</sup> In some  
 1661 patients in heart failure treated with biventricular pacing (cardiac resynchronization therapy), AF can  
 1662 terminate,<sup>571</sup> although such a ‘rhythm control’ effect of cardiac resynchronization therapy is likely to be small  
 1663 and clearly needs confirmation.<sup>572</sup> AV nodal ablation renders patients pacemaker-dependent for the rest of their  
 1664 lives, limiting AV nodal ablation and pacing to patients whose symptoms cannot be managed by rate controlling  
 1665 medication or by reasonable rhythm control interventions. The choice of pacing therapy (right ventricular or  
 1666 biventricular pacing with or without an implantable defibrillator) will depend on individual patient  
 1667 characteristics, including LVEF.<sup>573, 574</sup>  
 1668

#### 1669 Recommendations for rate control

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
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

1670 AF = atrial fibrillation; bpm = beats per minute; LVEF = left ventricular ejection fraction.

1671 Digitoxin is a suitable alternative to digoxin, where available. In patients with heart failure with reduced ejection  
 1672 fraction (LVEF < 40%), recommended beta-blockers are bisoprolol, carvedilol, long-acting metoprolol, and  
 1673 nebivolol.

1674 <sup>a</sup>Class of recommendation.

1675 <sup>b</sup> Level of evidence.1676 <sup>c</sup> Reference(s) supporting recommendations.

1677

1678 **Table 15 Rate control therapy in AF**

Therapy	Acute intravenous rate control	Long-term oral rate control	Side-effect profile	Comments
<b>Beta-blockers<sup>a</sup></b>				
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			
<b>Calcium-channel blockers</b>				
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)		
<b>Cardiac glycosides</b>				
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		
<b>Specific indications</b>				
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)<sup>b</sup>

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

1679 AF = atrial fibrillation; CKD = chronic kidney disease; LV = left ventricular; LVEF = left ventricular ejection  
1680 fraction.

1681 <sup>a</sup>A number of other beta-blockers are also available, but are not recommended as specific rate control therapy in  
1682 AF. These include atenolol (25–100 mg once daily with a short biological half-life), propranolol (non-selective,  
1683 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  
1684 labetalol (non-selective, 1–2 mg/min [acute]).

1685 <sup>b</sup>If ongoing requirement for amiodarone, follow with 900 mg intravenous over 24 hours diluted in 500–1000 mL  
1686 via a central venous cannula.

1687

## 1688 **11 Rhythm control therapy in atrial fibrillation**

1689 Restoring and maintaining sinus rhythm is an integral part of AF management. Antiarrhythmic drugs  
1690 approximately double the rate of sinus rhythm compared with placebo.<sup>580-584</sup> Catheter ablation or combination  
1691 therapy is often effective when antiarrhythmic drugs fail.<sup>226, 585-587</sup> Although many clinicians believe that  
1692 maintaining sinus rhythm can improve outcomes in AF patients,<sup>588</sup> all trials that have compared rhythm control  
1693 to rate control (with appropriate anticoagulation) therapy have resulted in neutral outcomes.<sup>41, 578, 579, 582, 589-593</sup>

1694 Whether modern rhythm control management involving catheter ablation, combination therapy, and early  
1695 therapy leads to a reduction in major cardiovascular events (e.g. stroke and cardiovascular death) is currently  
1696 under investigation (e.g. in the EAST [Early treatment of Atrial fibrillation for Stroke prevention Trial] –  
1697 AFNET 4<sup>40</sup> and CABANA [Catheter Ablation vs Anti-arrhythmic Drug Therapy for Atrial Fibrillation Trial]<sup>594</sup>  
1698 trials). For now, rhythm control therapy is indicated to improve symptoms in AF patients who remain  
1699 symptomatic on adequate rate control therapy.

1700

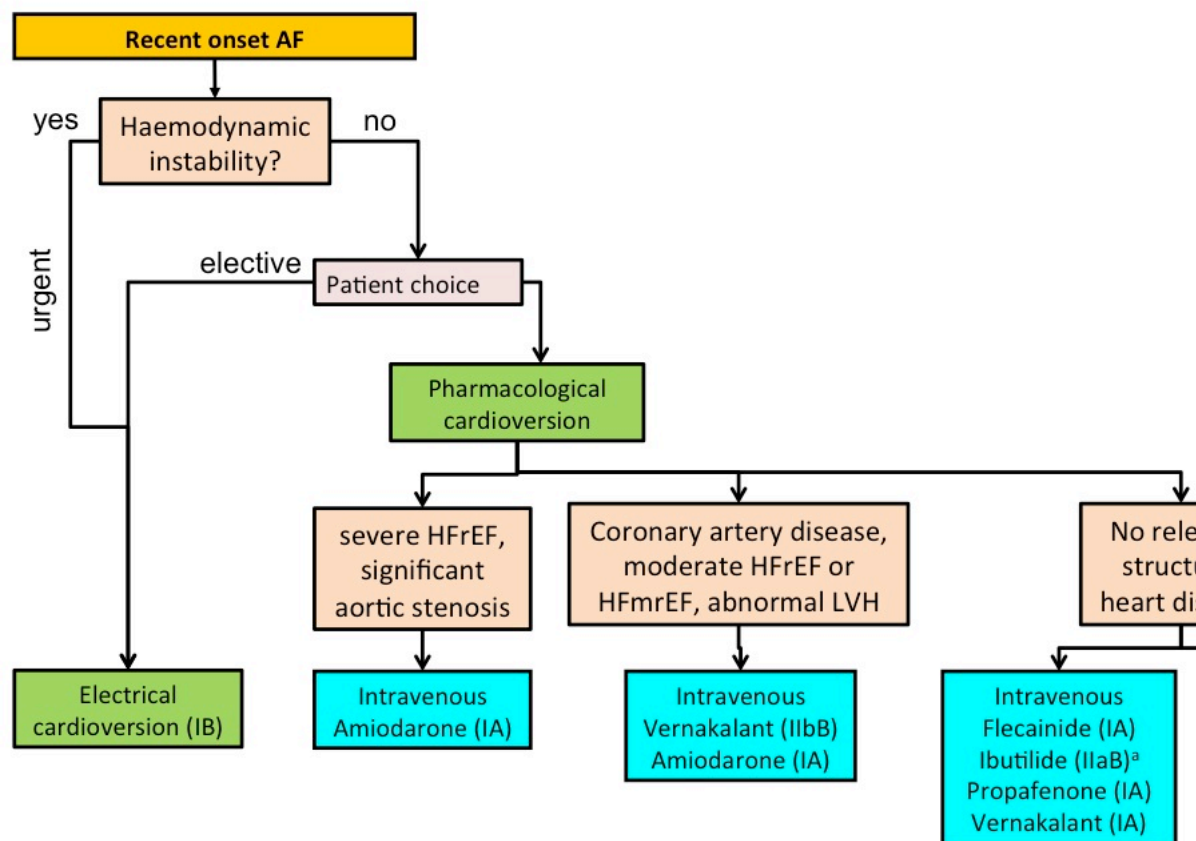
### 1701 **11.1. Acute restoration of sinus rhythm**

#### 1702 **11.1.1. Antiarrhythmic drugs for acute restoration of sinus rhythm**

##### 1703 **(‘pharmacological cardioversion’)**

1704 Antiarrhythmic drug can restore sinus rhythm in patients with AF (pharmacological cardioversion) as  
1705 shown in small controlled trials, meta-analyses,<sup>41, 584, 595, 596</sup> and in a few larger controlled trials.<sup>597-605</sup>  
1706 Outside of Europe, dofetilide is available and can convert recent-onset AF.<sup>606</sup> Pharmacological cardioversion  
1707 restores sinus rhythm in approximately 50% of patients with recent-onset AF (*Table 16*).<sup>607-609</sup> In the short term,  
1708 electrical cardioversion restores sinus rhythm quicker and more effectively than pharmacological cardioversion  
1709 and is associated with shorter hospitalization.<sup>609-613</sup> Pharmacological cardioversion, conversely, does not require  
1710 sedation or fasting (*Figure 16*).

1711 Flecainide and propafenone are effective for pharmacological cardioversion,<sup>595, 602-605, 614, 615</sup> but their  
1712 use is restricted largely to patients without structural heart disease. Ibutilide is an alternative where available,  
1713 but carries a risk of torsades de pointes.<sup>615</sup> Vernakalant<sup>602-605</sup> can be given to patients with mild heart failure  
1714 (NYHA Class I or II), including those with ischaemic heart disease, provided they do not present with  
1715 hypotension or severe aortic stenosis.<sup>616-618</sup> Amiodarone can be used in patients with heart failure and in patients  
1716 with ischaemic heart disease (although patients with severe heart failure were excluded in most of the AF  
1717 cardioversion trials).<sup>596</sup> Amiodarone also slows heart rate by 10–12 bpm after 8–12 hours when given  
1718 intravenously.<sup>596</sup> Both amiodarone and flecainide appear more effective than sotalol in restoring sinus  
1719 rhythm.<sup>600, 601, 619</sup>



1720

1721 **Figure 16** Rhythm control management of acute AF.1722 AF = atrial fibrillation; HFmrEF = heart failure with mid-range ejection fraction; HFrEF = heart failure with  
1723 reduced ejection fraction.1724 <sup>a</sup>Ibutilide should not be used in patients with long QT interval.

1725

1726 **11.1.2. 'Pill in the pocket' cardioversion performed by patients**

1727 In selected patients with infrequent symptomatic episodes of paroxysmal AF, a single bolus of oral flecainide  
1728 (200–300 mg) or propafenone (450–600 mg) can be self-administered by the patient at home ('pill in the pocket'  
1729 therapy) to restore sinus rhythm, after safety has been established in the hospital setting.<sup>620</sup> This approach seems  
1730 marginally less effective than hospital-based cardioversion,<sup>621</sup> but is practical and provides control and  
1731 reassurance to selected patients.

1732

1733 **Table 16** Antiarrhythmic drugs for pharmacological cardioversion

Drug	Route	First dose	Follow-up dose	Risks	References
<b>Flecainide</b>	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			
<b>Amiodarone</b>	IV <sup>a</sup>	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
<b>Propafenone</b>	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)	
<b>Ibutilide<sup>b</sup></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
<b>Vernakalant</b>	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

1734 ACS = acute coronary syndromes; IHD = ischaemic heart disease; IV = intravenous; LVH = left ventricular  
 1735 hypertrophy; NYHA = New York Heart Association.

1736 <sup>a</sup>Use a large peripheral vessel and change to oral amiodarone within 24 h of IV (central line) administration.

1737 <sup>b</sup>Ibutilide is only available in selected European countries.

1738

### 1739 11.1.3. Electrical cardioversion

1740 Synchronized direct current electrical cardioversion quickly and effectively converts AF to sinus rhythm and is  
 1741 the method of choice in severely haemodynamically compromised patients with new-onset AF (*Figure 16*).<sup>626-</sup>  
 1742 <sup>628</sup> Electrical cardioversion can be performed safely in sedated patients treated with intravenous midazolam  
 1743 and/or propofol. Continuous monitoring of blood pressure and oximetry during the procedure is important.<sup>629</sup>  
 1744 Skin burns may occasionally be observed. Intravenous atropine or isoproterenol or temporary transcutaneous  
 1745 pacing should be available to mitigate post-cardioversion bradycardia. Biphasic defibrillators are more effective  
 1746 than monophasic waveforms, and have become industry standard.<sup>626, 628</sup> Anterior–posterior electrode positions  
 1747 generate a stronger shock field in the left atrium than anterolaterally positioned electrodes, and restore sinus  
 1748 rhythm more effectively.<sup>626, 627, 630</sup>

1749 Pretreatment with amiodarone (requiring a few weeks of therapy),<sup>631, 632</sup> sotalol,<sup>631</sup> ibutilide,<sup>633</sup> or  
 1750 vernakalant<sup>634</sup> can improve efficacy of electrical cardioversion, and similar effects are likely for flecainide<sup>584</sup>  
 1751 and propafenone.<sup>635</sup> Beta-blockers,<sup>636</sup> verapamil, diltiazem,<sup>637-639</sup> and digoxin<sup>640, 641</sup> do not reliably terminate AF  
 1752 or facilitate electrical cardioversion. When antiarrhythmic drug therapy is planned to maintain sinus rhythm  
 1753 after cardioversion, it seems prudent to start therapy 1–3 days before cardioversion (amiodarone: a few weeks)  
 1754 to promote pharmacological conversion and to achieve effective drug levels.<sup>584, 601</sup>

1755

### 1756 11.1.4. Anticoagulation in patients undergoing cardioversion

1757 Cardioversion carries an inherent risk of stroke in non-anticoagulated patients,<sup>642</sup> which is reduced substantially  
 1758 by the administration of anticoagulation.<sup>643</sup> Immediate initiation of anticoagulation is important in all patients  
 1759 scheduled for cardioversion.<sup>644-646</sup> Patients who have been in AF for longer than 48 hours should start OAC at  
 1760 least 3 weeks before cardioversion and continue it for 4 weeks afterwards (in patients without a need for long-  
 1761 term anticoagulation), and continue it indefinitely in patients at risk of stroke. This practice has never been  
 1762 evaluated in controlled trials, but seemed safe in a large observational data set from Finland.<sup>647</sup> When early  
 1763 cardioversion is desired, TOE can exclude the majority of left atrial thrombi, allowing immediate  
 1764 cardioversion.<sup>648, 649</sup> Ongoing studies will inform about the safety and efficacy of newly initiated anticoagulation  
 1765 using NOACs in patients scheduled for electrical cardioversion.

1766

## 1767 11.2. Long-term antiarrhythmic drug therapy

1768 The aim of antiarrhythmic drug therapy is improvement in AF-related symptoms.<sup>41, 580</sup> Hence, the decision to  
 1769 initiate long-term antiarrhythmic drug therapy needs to balance symptom burden, possible adverse drug  
 1770 reactions, and patient preferences. The principles of antiarrhythmic drug therapy outlined in the 2010 ESC AF  
 1771 guidelines<sup>369</sup> are still relevant and should be observed:

- 1772 1. Treatment is aimed at reducing AF-related symptoms;
- 1773 2. Efficacy of antiarrhythmic drugs to maintain sinus rhythm is modest;

- 1774 3. Clinically successful antiarrhythmic drug therapy may reduce rather than eliminate the recurrence of  
1775 AF;  
1776 4. If one antiarrhythmic drug ‘fails’, a clinically acceptable response may be achieved with another agent;  
1777 5. Drug-induced proarrhythmia or extra-cardiac side-effects are frequent;  
1778 6. Safety rather than efficacy considerations should primarily guide the choice of antiarrhythmic drug.  
1779

1780 Antiarrhythmic drug therapy approximately doubles sinus rhythm maintenance compared with no therapy.<sup>580</sup>  
1781 There is no appreciable effect on mortality or cardiovascular complications, but rhythm control therapy can  
1782 slightly increase the risk of hospitalizations (often for AF).<sup>41, 578, 579, 582, 589-593</sup> To reduce the risk of side-  
1783 effects,<sup>201, 580</sup> a shorter duration of antiarrhythmic drug therapy seems desirable. As an example, short-term  
1784 treatment (4 weeks) with flecainide for 4 weeks after cardioversion of AF was well-tolerated and prevented  
1785 most (80%) AF recurrences when compared with long-term treatment.<sup>584</sup> Short-term antiarrhythmic drug  
1786 therapy is also used to avoid early AF recurrences after catheter ablation<sup>650</sup> and may be reasonable in patients  
1787 deemed at increased risk of antiarrhythmic drug side-effects or in those with a low perceived risk of recurrent  
1788 AF.

1789 In addition to antiarrhythmic drug therapy and catheter ablation (see Section 10.3), management of  
1790 concomitant cardiovascular conditions can reduce symptom burden in AF and facilitate maintenance of sinus  
1791 rhythm.<sup>203, 204, 296, 312</sup> This includes weight reduction, blood pressure control, heart failure treatment, increasing  
1792 cardiorespiratory fitness, and other measures (see Chapter 6).  
1793

### 1794 11.2.1. Selection of antiarrhythmic drugs for long-term therapy: Safety first!

1795 Usually, the safety of antiarrhythmic drug therapy determines the initial choice of antiarrhythmic drugs (*Figure*  
1796 *17*). The following major antiarrhythmic drugs are available to prevent AF:  
1797

1798 **Amiodarone** is an effective multichannel blocker, reduces ventricular rate, and is safe in patients with heart  
1799 failure.<sup>582, 651</sup> Torsades de pointes proarrhythmia can occur, and QT interval and TU waves should be monitored  
1800 on therapy (see *Table 17*).<sup>652</sup> Amiodarone often causes extracardiac side-effects, especially on long-term  
1801 therapy,<sup>653, 654</sup> rendering it a second-line treatment in patients who are suitable for other antiarrhythmic drugs.  
1802 Amiodarone appears less suitable to episodic short-term therapy (unless after catheter ablation),<sup>655</sup> probably  
1803 because of its long biological half-life.  
1804

1805 **Dronedarone** maintains sinus rhythm, reduces ventricular rate, and prevents cardiovascular hospitalizations  
1806 (mostly due to AF) and cardiovascular death in patients with paroxysmal or persistent AF or flutter who had at  
1807 least one relevant cardiovascular comorbidity.<sup>583, 588, 656</sup> Dronedarone increases mortality in patients with  
1808 recently decompensated heart failure (with or without AF)<sup>657</sup> and in patients with permanent AF in whom sinus  
1809 rhythm is not restored.<sup>658</sup> Dronedarone moderately increases serum creatinine, reflecting a reduction in  
1810 creatinine excretion rather than a decline in kidney function.<sup>659</sup>  
1811

1812 **Flecainide** and **propafenone** are effective in preventing recurrent AF.<sup>581, 584, 620</sup> They should only be used in  
1813 patients without significant ischaemic heart disease or heart failure to avoid the risk of life-threatening  
1814 ventricular arrhythmias.<sup>660</sup> High ventricular rates resulting from the conversion of AF into atrial flutter with 1:1  
1815 conduction by flecainide or propafenone can be prevented by preadministering a beta-blocker, verapamil, or  
1816 diltiazem.  
1817

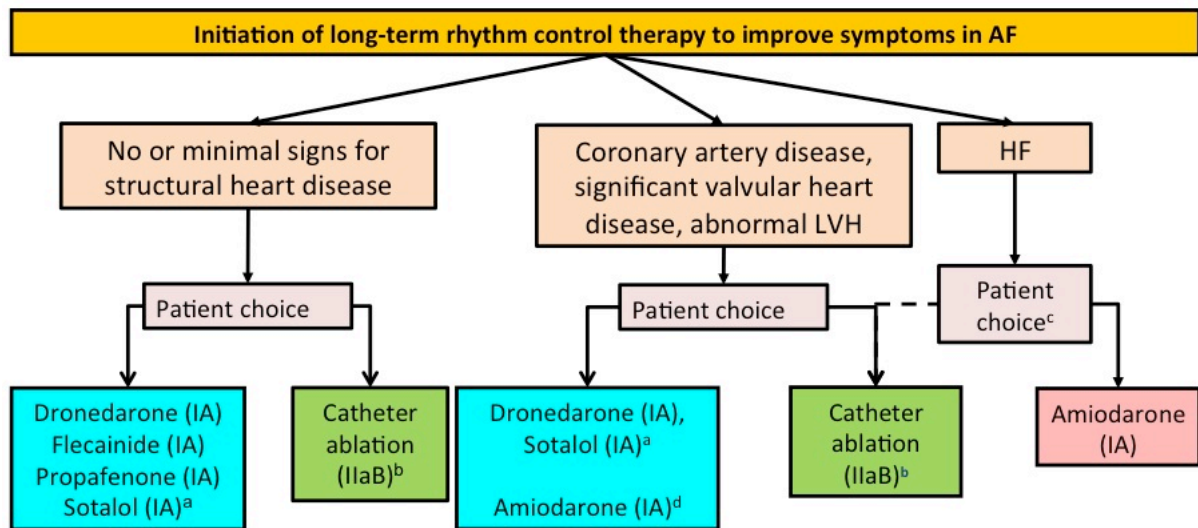
1818 **Quinidine** and **disopyramide** have been associated with an increase in all-cause mortality (OR 2.39; 95% CI  
1819 1.03–5.59; number needed to harm 109; 95% CI 34–4985) at 1-year follow-up,<sup>580, 661</sup> likely due to ventricular  
1820 arrhythmias (torsades de pointes).<sup>580, 661</sup> Although this proarrhythmic effect is more common at higher doses,  
1821 they are less commonly used for rhythm control in AF. Disopyramide may be useful in ‘vagally mediated’ AF  
1822 (e.g. AF occurring in athletes and/or during sleep<sup>76</sup>), and has been shown to reduce LV outflow gradient and  
1823 improve symptoms in patients with hypertrophic cardiomyopathy.<sup>662-664</sup>  
1824

1825 **Sotalol** has a relevant risk of torsades de pointes (1% in the Prevention of Atrial Fibrillation After Cardioversion  
1826 [PAFAC] trial<sup>118</sup>). Its d-enantiomer is associated with an increased mortality compared to placebo in patients  
1827 with LV dysfunction post-myocardial infarction,<sup>665</sup> probably due to ventricular arrhythmias (OR 2.47; 95% CI  
1828 1.2–5.05; number needed to harm 166; 95% CI 61–1159).<sup>580, 665</sup> On the other hand, d,l sotalol has been used in  
1829 AF patients without safety signals in two controlled trials.<sup>581, 601</sup>  
1830

1831 **Dofetilide** is another potassium channel blocker that is mainly available outside of Europe. Dofetilide restores  
1832 and maintains sinus rhythm in heart failure patients<sup>666</sup> and occasionally in patients refractory to other  
1833 antiarrhythmic drugs.<sup>667</sup>

1834

1835 Overall, it seems prudent to limit the use of quinidine, disopyramide, dofetilide, and sotalol to specific  
 1836 situations. Similarly, combinations of QT-prolonging antiarrhythmic drugs should generally be avoided (*Table*  
 1837 *17*).



1838

1839 **Figure 17** Initiation of rhythm control therapy in symptomatic patients.

1840 AF = atrial fibrillation; HF = heart failure; LVH = left ventricular hypertrophy;

1841 <sup>a</sup>Sotalol requires careful evaluation of proarrhythmic risk.

1842 <sup>b</sup>Catheter ablation should isolate pulmonary veins and can be performed using radiofrequency or cryoballoon catheters.

1844 <sup>c</sup>Catheter ablation as a first-line therapy is usually reserved for heart failure patients with tachycardiomyopathy.

1845 <sup>d</sup>Amiodarone is a second-choice therapy in many patients because of its extracardiac side-effects.

1846

### 1847 11.2.2. Twelve-lead electrocardiogram as a tool to identify patients at risk of 1848 proarrhythmia

1849 Identifying patients at risk of proarrhythmia can help to mitigate the proarrhythmic risk of antiarrhythmic  
 1850 drugs.<sup>668</sup> In addition to the clinical characteristics mentioned above, monitoring PR, QT, and QRS durations  
 1851 during initiation of antiarrhythmic drug therapy can identify patients at higher risk of drug-induced  
 1852 proarrhythmia on longer-term treatment.<sup>669-671</sup> In addition, the presence of ‘abnormal TU waves’ is a sign of  
 1853 imminent torsades de pointes.<sup>652</sup> Periodic ECG analysis for proarrhythmia signs has been used successfully in  
 1854 recent antiarrhythmic drug trials.<sup>118, 584, 672</sup> Specifically, ECG monitoring was used systematically on days 1–3 in  
 1855 patients receiving flecainide, propafenone, or sotalol to identify those at risk of proarrhythmia.<sup>118, 584, 601</sup> Based  
 1856 on this evaluated practice, we suggest to record an ECG in all patients before initiation of antiarrhythmic drugs.  
 1857 Scheduled ECGs during the initiation period seem reasonable (*Table 17*).

1858

1859 **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.	QRS duration increases > 25% above baseline	None	Baseline, day 1, day 2–3
Flecainide slow release	200 mg once daily	Caution in the presence of sinoatrial node or atrioventricular node or conduction system disease. CYP2D6 inhibitors (e.g. fluoxetine, tricyclic) increase plasma concentration			
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

1860 AF = atrial fibrillation; bpm = beats per minute; CrCl = creatinine clearance; ECG = electrocardiogram; IHD =  
 1861 ischaemic heart disease; LV = left ventricular; LVEF = left ventricular ejection fraction; NYHA = New York  
 1862 Heart Association; VKA = vitamin K antagonist.

1863

### 1864 11.2.3. New antiarrhythmic drugs

1865 Several compounds that inhibit the ultrarapid potassium current ( $I_{Kur}$ ) and other inhibitors of atypical ion  
 1866 channels are in clinical development.<sup>673-675</sup> They are not available for clinical use at present. The antianginal  
 1867 compound ranolazine inhibits potassium and sodium currents and increases glucose metabolism at the expense  
 1868 of free fatty acid metabolism, thereby enhancing efficient use of oxygen.<sup>676, 677</sup> Ranolazine was safe in patients  
 1869 with non-ST-segment elevation myocardial infarction and unstable angina evaluated in the MERLIN  
 1870 (Metabolic Efficiency With Ranolazine for Less Ischemia in Non ST-Elevation Acute Coronary Syndrome)  
 1871 trial.<sup>678</sup> In a post-hoc analysis of continuous ECG recordings obtained during the first 7 days after  
 1872 randomization, patients assigned to ranolazine had a trend towards fewer episodes of AF than those on placebo  
 1873 (75 [2.4%] vs. 55 [1.7%] patients;  $P = 0.08$ ).<sup>679</sup> In the HARMONY (A Study to Evaluate the Effect of  
 1874 Ranolazine and Dronedaron When Given Alone and in Combination in Patients With Paroxysmal Atrial  
 1875 Fibrillation) trial, the highest tested dose of a combination of ranolazine (750 mg twice daily) and dronedarone  
 1876 (225 mg twice daily) slightly reduced AF burden in 134 subjects with paroxysmal AF and dual-chamber  
 1877 pacemakers.<sup>680</sup> Small, open-label studies suggest that ranolazine might enhance the antiarrhythmic effect of  
 1878 amiodarone for cardioversion,<sup>681-683</sup> whereas the results from a controlled trial of ranolazine and the ranolazine-  
 1879 dronedarone combination to prevent AHRE in pacemaker patients were ambiguous.<sup>684</sup> At present, there is  
 1880 insufficient evidence to recommend ranolazine as an antiarrhythmic drug, alone or in combination with other  
 1881 antiarrhythmic drugs. Of note, the ‘funny channel blocker’ ivabradine, which is used for angina and heart  
 1882 failure, increases the risk of AF.<sup>685</sup>

1883

### 1884 11.2.4. Antiarrhythmic effects of non-antiarrhythmic drugs

1885 ACE inhibitors or ARBs appear to prevent new-onset AF in patients with LV dysfunction and in hypertensive  
 1886 patients with LV hypertrophy.<sup>219, 236, 237, 239, 246, 250, 686</sup> Nephilysin inhibition needs to be studied further, but does  
 1887 not seem to enhance this effect.<sup>224</sup> A Danish cohort study also suggested that initial treatment of uncomplicated  
 1888 hypertension with ACE inhibitors or ARBs reduces incident AF compared with other hypertensive agents.<sup>245</sup>  
 1889 ARB therapy did not reduce the AF burden in patients with AF without structural heart disease.<sup>241</sup> Thus, ACE  
 1890 inhibitors or ARBs are unlikely to have a relevant direct antiarrhythmic effect. However, it might be justified to  
 1891 consider adding ACE inhibitors or ARB therapy to antiarrhythmic drugs to reduce AF recurrences after  
 1892 cardioversion.<sup>248, 249, 687</sup>

1893

1894 Compared with placebo, beta-blockers are associated with a reduced risk of new-onset AF in patients  
 1895 with reduced ejection fraction and sinus rhythm.<sup>23</sup> Beta-blockers have also been reported to reduce symptomatic  
 1896 AF recurrences,<sup>580, 636, 688</sup> but this finding may be driven by the beneficial effect of rate control, which will  
 1897 render AF more often asymptomatic.

1898

1899 Perioperative statin therapy appeared to reduce the risk of postoperative AF in a number of small  
 1900 RCTs<sup>689, 690</sup>; however, an adequately powered placebo-controlled trial has shown no effect of perioperative  
 1901 rosuvastatin therapy on postoperative AF.<sup>691</sup> Statin treatment does not prevent AF in other settings.<sup>692, 693</sup>  
 1902 Similarly, polyunsaturated fatty acids failed to show convincing benefit.<sup>241, 694-698</sup> The role of aldosterone  
 1903 antagonists in the management of AF has not been extensively investigated in humans; although preliminary  
 1904 evidence from trials of eplerenone is encouraging for primary prevention,<sup>243</sup> at present there is no robust  
 1905 evidence to make any recommendation for the use of aldosterone antagonists for secondary prevention of AF.<sup>699-  
 1906 701</sup>

1904

1905

### 1906 Recommendations for rhythm control therapy

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>d</sup>
<b>General recommendations</b>			
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			
<b>Cardioversion of AF</b>			
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	Ila	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	Ila	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	Ila	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)	Ilb	B	602-605, 616, 618
<b>Stroke prevention in patients designated for cardioversion of AF</b>			
Anticoagulation with heparin or a NOAC should be initiated as soon as possible before every cardioversion of AF or atrial flutter	Ila	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	Ila	B	648
In patients at risk for stroke (e.g. presence of CHA <sub>2</sub> DS <sub>2</sub> -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	Ila	C	
<b>Antiarrhythmic drugs for the long-term maintenance of sinus rhythm/prevention of recurrent AF</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	41, 580
Dronedaron, 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
Dronedaron 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
<b>Antiarrhythmic effects of non-antiarrhythmic drugs</b>			
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

1907 ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; CHA<sub>2</sub>DS<sub>2</sub>-  
1908 VASc = Congestive Heart failure, hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular  
1909 disease, Age 65–74, and Sex (female); ECG = electrocardiogram; NOAC = non-vitamin K antagonist oral  
1910 anticoagulant; TOE = transoesophageal echocardiography.

1911 <sup>a</sup>Class of recommendation.

1912 <sup>b</sup>Level of evidence.

1913 <sup>c</sup>Reference(s) supporting recommendations.

1914

1915 **11.3. Catheter ablation**

1916 Since the initial description of triggers in the pulmonary veins that initiate paroxysmal AF,<sup>108</sup> catheter ablation  
 1917 of AF has developed from a specialized, experimental procedure into a common treatment to prevent recurrent  
 1918 AF.<sup>587, 715</sup> This is primarily achieved through isolation of the pulmonary veins, probably requiring complete  
 1919 isolation for full effectiveness,<sup>716</sup> and additional ablation in the posterior left atrial wall. AF ablation, when  
 1920 performed in experienced centres by adequately trained teams, is more effective than antiarrhythmic drug  
 1921 therapy in maintaining sinus rhythm, and the complication rate, though not negligible, is similar to the  
 1922 complication rate for antiarrhythmic drugs.<sup>585, 717, 1042</sup>

### 1924 11.3.1. Indications

1925 Catheter ablation of AF is effective in restoring and maintaining sinus rhythm in patients with symptomatic  
 1926 paroxysmal, persistent, and probably long-standing persistent AF – in general as second-line treatment after  
 1927 failure of or intolerance to antiarrhythmic drug therapy. In such patients, catheter ablation is more effective than  
 1928 antiarrhythmic drug therapy.<sup>185, 586, 713, 717-720</sup> As first-line treatment for paroxysmal AF, randomized trials  
 1929 showed only modestly improved rhythm outcome with catheter ablation compared to antiarrhythmic drug  
 1930 therapy.<sup>585, 721-723</sup> Complication rates were similar, but ablation was performed in expert centres, justifying  
 1931 catheter ablation as first-line therapy in selected patients with paroxysmal AF who ask for interventional  
 1932 therapy. Fewer data are available reporting the effectiveness and safety of catheter ablation in patients with  
 1933 persistent or long-standing persistent AF, but all point to lower recurrence rates after catheter ablation compared  
 1934 to antiarrhythmic drug therapy with or without cardioversion.<sup>185, 717, 723-726, 1039</sup> In patients who experience  
 1935 symptomatic recurrences of AF despite antiarrhythmic drug therapy, all RCTs showed better sinus rhythm  
 1936 maintenance with catheter ablation than on antiarrhythmic drugs.<sup>586, 713, 727, 728</sup> There is no current indication for  
 1937 catheter ablation to prevent cardiovascular outcomes (or desired withdrawal of anticoagulation), or to reduce  
 1938 hospitalization.<sup>40, 594</sup>

### 1940 11.3.2. Techniques and technologies

1941 Complete pulmonary vein isolation (PVI) on an atrial level is the best documented target for catheter  
 1942 ablation,<sup>716, 729-731</sup> achievable by point-by-point radiofrequency ablation, linear lesions encircling the pulmonary  
 1943 veins, or cryoballoon ablation, with similar outcomes.<sup>732-734</sup> Complete isolation of the pulmonary veins has  
 1944 better rhythm outcomes than incomplete isolation.<sup>716</sup> PVI was initially tested in patients with paroxysmal AF,  
 1945 but appears to be non-inferior to more extensive ablation in persistent AF as well.<sup>729, 735</sup> More extensive  
 1946 ablations have been used in patients with persistent AF, but there are insufficient data to guide the use of these at  
 1947 present.<sup>117, 718, 719, 735-737</sup> Extended ablation procedures (beyond PVI) consistently require longer procedures and  
 1948 more ionizing radiation, potentially creating risk for patients. Left atrial macro-reentrant tachycardia is relatively  
 1949 uncommon after PVI ( $\approx 5\%$ ). It also seems even less common after cryoballoon ablation,<sup>734</sup> but may occur in up  
 1950 to 25% of patients after left atrial substrate modification ablation, often due to incomplete ablation lines. Thus,  
 1951 for patients with persistent AF, ablation of complex fractionated electrograms, ablation of rotors, or routine  
 1952 deployment of linear lesions or other additional ablations does not seem justified in the first procedure.<sup>735, 738, 739</sup>  
 1953 However, additional ablation on top of complete PVI<sup>716</sup> may be considered in patients with recurrent AF after  
 1954 the initial ablation procedure.<sup>719, 740, 741</sup> In patients with documented right atrial isthmus-dependent flutter  
 1955 undergoing AF ablation, right atrial isthmus ablation is recommended. Adenosine testing to identify patients in  
 1956 need of additional ablation remains controversial after evaluation in several reports.<sup>739, 742-744</sup> Ablation of so-  
 1957 called ‘rotors’ guided by body surface mapping or endocardial mapping is under evaluation and cannot be  
 1958 recommended for routine clinical use at present.

### 1960 11.3.3. Outcome and complications

1961 The rhythm outcome after catheter ablation of AF is difficult to predict in individual patients.<sup>173, 227, 713, 728</sup> Most  
 1962 patients require more than one procedure to achieve symptom control.<sup>713, 726, 728</sup> In general, better rhythm  
 1963 outcome and lower procedure-related complications can be expected in younger patients with a short history of  
 1964 AF and frequent, short AF episodes in the absence of significant structural heart disease.<sup>745</sup> Catheter ablation is  
 1965 more effective than antiarrhythmic drug therapy in maintaining sinus rhythm (*Web Addenda Figure 2*).<sup>746, 1039</sup>  
 1966 Sinus rhythm without severely symptomatic recurrences of AF is found in up to 70% of patients with  
 1967 paroxysmal AF, and around 50% in persistent AF.<sup>713, 728, 735, 1042</sup> Very late recurrence of AF after years of sinus  
 1968 rhythm is not uncommon and may reflect disease progression, with important implications for continuation of  
 1969 AF therapies.<sup>728</sup> Multiple variables have been identified as risk factors for recurrence after catheter ablation of  
 1970 AF, but their predictive power is weak. The decision for catheter ablation thus should be based on a shared  
 1971 decision-making process<sup>747</sup> (see Chapter 7), following thorough explanation of the potential benefits and risks,  
 1972 and of the alternatives such as antiarrhythmic drug or acceptance of current symptoms without rhythm control  
 1973 therapy.<sup>175</sup>

1974 *Complications of catheter ablation for AF*

1975 There is a clear need to systematically capture complications in clinical practice to improve the quality of AF  
 1976 ablation procedures.<sup>175</sup> The median length of hospital stay in AF patients undergoing their first ablation as part  
 1977 of the EURObservational Research Programme (EORP) was 3 days (interquartile range 2–4 days), based on  
 1978 data from 1391 patients from hospitals performing at least 50 ablations per year. Five to seven per cent of  
 1979 patients will suffer severe complications after catheter ablation of AF, and 2–3% will experience life-threatening  
 1980 but usually manageable complications.<sup>727, 748-750</sup> Intraprocedural death has been reported, but is rare (< 0.2%).<sup>751</sup>  
 1981 The most important severe complications are stroke/TIA (< 1%), cardiac tamponade (1–2%), pulmonary vein  
 1982 stenosis, and severe oesophageal injury leading to atrio-oesophageal fistula weeks after ablation (*Table 18*).  
 1983 ‘Silent strokes’ (i.e. white matter lesions detectable by brain MRI), have been observed in around 10% of  
 1984 patients treated with radiofrequency and cryoballoon ablation.<sup>752</sup> The clinical relevance of this observation is  
 1985 unclear.<sup>749</sup> Post-procedure complications include stroke, with the highest risk within the first week,<sup>753</sup> late  
 1986 pericardial tamponade several days after catheter ablation,<sup>751</sup> and oesophageal fistulas, which usually become  
 1987 apparent 7–30 days after ablation. Timely detection of atrio-oesophageal fistulas can be life-saving and should  
 1988 be based on the typical triad of infection without a clear focus, retrosternal pain, and stroke or TIA.<sup>748</sup>  
 1989

1990 **Table 18** Complications related to catheter ablation of AF

Complication severity	Complication type	Rate <sup>727, 748, 750, 754-759</sup>
Life-threatening complications	Periprocedural death	< 0.2%
	Oesophageal injury (perforation/fistula) <sup>a</sup>	< 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) <sup>b</sup>	5–20%
	Radiation exposure	

1991 AF = atrial fibrillation; TIA = transient ischaemic attack.

1992 <sup>a</sup>Oesophageal fistula should be suspected in patients presenting with the triad of unspecific signs of infection,  
 1993 chest pain, and stroke or TIA in the first weeks after an ablation procedure. It requires immediate therapy.

1994 <sup>b</sup>< 10% for cryoablation or radiofrequency ablation, > 20% for phased radiofrequency ablation

1995

1996 **11.3.4. Anticoagulation – before, during, and after ablation**

1997 Patients anticoagulated with VKAs should continue therapy during ablation (with an INR of 2–3).<sup>760</sup>

1998 Anticoagulation with NOACs is an alternative to warfarin.<sup>478, 761-765</sup> There is no safety signal from observational  
 1999 cohorts treated with uninterrupted NOAC therapy undergoing catheter ablation in experienced centres.<sup>761, 763, 766,</sup>

2000 <sup>767</sup> The first controlled trial, enrolling around 200 patients, has recently been published,<sup>768</sup> as well as several  
 2001 observational data sets.<sup>761, 769, 770</sup> Ongoing studies compare uninterrupted VKA with NOAC therapy in AF

2002 patients undergoing ablation (e.g. AXAFA – AFNET 5 [Apixaban During Atrial Fibrillation Catheter Ablation:  
 2003 Comparison to Vitamin K Antagonist Therapy – Anticoagulation using the direct factor Xa inhibitor apixaban

2004 during Atrial Fibrillation catheter Ablation: Comparison to vitamin K antagonist therapy; NCT02227550] and  
 2005 RE-CIRCUIT [Randomized Evaluation of dabigatran etexilate Compared to warfarin in pulmonaRy vein

2006 ablation: assessment of different peri-procedural anticoagulation strategies; NCT02348723]). During ablation,  
 2007 heparin should be given to maintain an activated clotting time > 300 seconds. Anticoagulation should be  
 2008 maintained for at least 8 weeks after ablation for all patients. The true incidence of thromboembolic events after  
 2009 catheter ablation has never been systematically studied and the expected stroke risk has been adopted from non-  
 2010 ablation AF cohorts. Although observational studies suggest a relatively low stroke rate in the first few years  
 2011 after catheter ablation of AF,<sup>737, 771-776</sup> the long-term risk of recurrent AF and the safety profile of  
 2012 anticoagulation in ablated patients need to be considered. In the absence of controlled trial data, OAC after  
 2013 catheter ablation should follow general anticoagulation recommendations, regardless of the presumed rhythm  
 2014 outcome.

### 2016 **11.3.5. Ablation of atrial fibrillation in heart failure patients**

2017 Catheter ablation, compared with amiodarone therapy, significantly reduces recurrent AF in AF patients with  
 2018 HFrEF.<sup>777</sup> Selected patients with HFrEF and AF can achieve recovery of LV systolic function after catheter  
 2019 ablation (probably reflecting tachycardiomyopathy). Several smaller trials suggest improved LV function after  
 2020 catheter ablation in HFrEF patients<sup>185, 226-228, 778, 779</sup> and reduced hospitalizations,<sup>720, 777</sup> especially in patients  
 2021 without a previous myocardial infarction.<sup>780</sup> Larger trials are warranted to confirm these findings. Catheter  
 2022 ablation can be demanding in these patients. Thus, indications for catheter ablation in HFrEF patients should be  
 2023 carefully balanced, and the procedures performed in experienced centres.

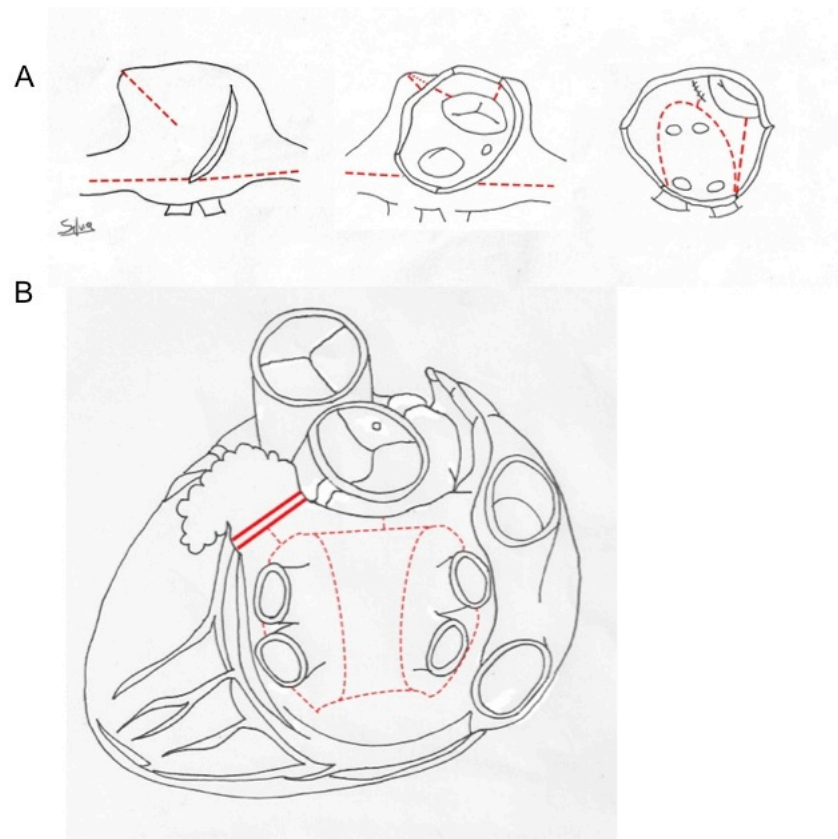
### 2025 **11.3.6. Follow-up after catheter ablation**

2026 Patients and physicians involved in the follow-up after catheter ablation should know the signs and symptoms of  
 2027 late complications to allow swift referral for treatment. Patient should also be aware that symptomatic and  
 2028 asymptomatic AF recurrences are frequent after catheter ablation.<sup>119, 781, 782</sup> In line with the primary goal of  
 2029 rhythm control therapy, asymptomatic episodes should generally not trigger further rhythm control therapy.  
 2030 Patients should be seen at least once by a rhythm specialist in the first 12 months after ablation. Further rhythm  
 2031 control options should be considered in patients with symptomatic recurrences, including discussion in a Heart  
 2032 Team (*Figure 17*).

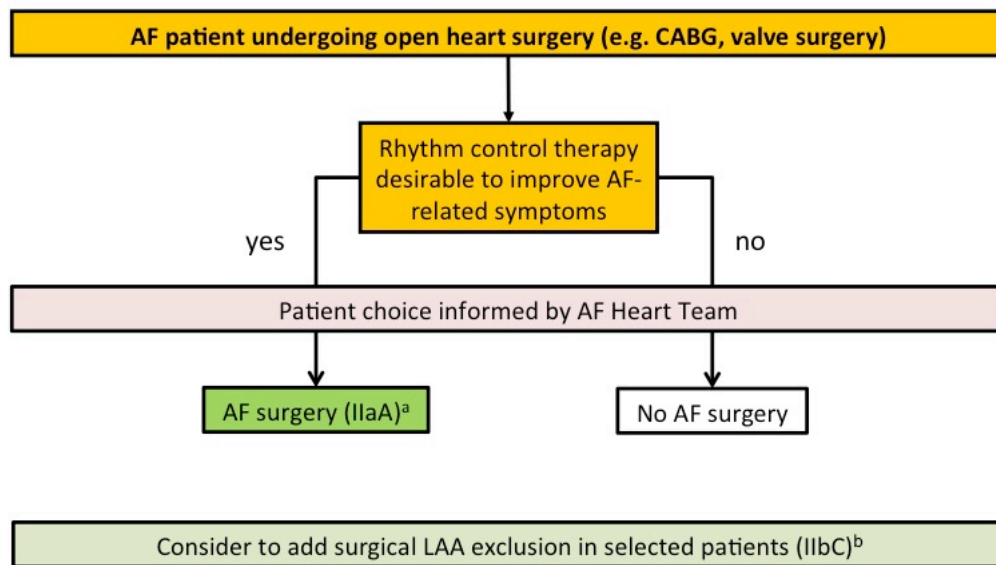
## 2034 **11.4. Atrial fibrillation surgery**

### 2035 **11.4.1. Concomitant atrial fibrillation surgery**

2036 The Cox maze procedure was first performed 30 years ago as a ‘cut-and-sew’ technique, including isolation of  
 2037 the posterior left atrium, a connection to the posterior mitral annulus, a cavotricuspid connection, a cavocaval  
 2038 connection, and exclusion of the LAA (*Figure 18*).<sup>783</sup> Thereby, the Cox maze procedure creates an electrical  
 2039 labyrinth (maze) of passages through which the sinoatrial node impulse finds a route to the atrioventricular node  
 2040 while preventing fibrillatory conduction. The Cox maze procedure and other, often simpler, forms of AF surgery  
 2041 have mainly been used in patients undergoing other open heart surgical procedures.<sup>461, 466, 784-798</sup> In a systematic  
 2042 review commissioned for these guidelines, concomitant AF surgery resulted in greater freedom from AF, atrial  
 2043 flutter, and atrial tachycardia (RR 1.94, 95% CI 1.51–2.49;  $n = 554$  from seven RCTs) (*Web Addenda Figure*  
 2044 *3*).<sup>1040</sup> Patients undergoing the Cox maze procedure required pacemaker implantation more often (RR 1.69, 95%  
 2045 CI 1.12–2.54;  $n = 1631$  from 17 RCTs), without a detectable difference in other outcomes or complications.  
 2046 These findings are underpinned by an analysis of Society of Thoracic Surgeons database comprising 67,389  
 2047 patients in AF: mortality or major morbidity was not affected by concomitant AF surgery (adjusted OR 1.00;  
 2048 95% CI 0.83–1.20), but pacemaker implantation was more frequent (adjusted OR 1.26; 95% CI 1.07–1.49).<sup>799</sup>  
 2049 Predictors of AF recurrence after surgery include left atrial dilatation, older age, > 10-year history of AF, and  
 2050 non-paroxysmal AF.<sup>800-804</sup> Regarding AF type, surgical PVI seems effective in paroxysmal AF.<sup>805</sup> Batrial lesion  
 2051 patterns may be more effective in persistent and long-standing persistent AF.<sup>797, 803, 806</sup> The suggested  
 2052 management of patients with AF-related symptoms undergoing cardiac surgery is displayed in *Figure 19*, with  
 2053 an important contribution of the AF Heart Team to advise and inform patient choice.



2054  
2055 **Figure 18** A. Surgical lesion sets for the biatrial Cox maze procedure. Left and middle panel: right atrial lesions.  
2056 Right panel: left atrial lesions.  
2057 B: Left atrial lesions in a thoracoscopic minimally invasive surgical procedure (dashed lines), including left  
2058 appendage exclusion (double line).



2059

2060 **Figure 19** Surgical rhythm control in patients undergoing cardiac surgery.2061 AF = atrial fibrillation; CABG = coronary artery bypass graft; LAA = left atrial appendage; PVI = pulmonary  
2062 vein isolation.2063 <sup>a</sup>AF surgery may be PVI in paroxysmal AF and biatrial maze in persistent or long-standing persistent AF.2064 <sup>b</sup>Oral anticoagulation should be continued in patients at risk of stroke irrespective of AF surgery or LAA  
2065 exclusion.

2066

2067

2068

**11.4.2. Stand-alone rhythm control surgery**2069 Current technology (e.g. bipolar radiofrequency or cryotherapy) renders the procedure easier and more  
2070 reproducible and feasible via a mini-thoracotomy.<sup>786, 807, 808</sup> Thoracoscopic PVI with bipolar radiofrequency2071 prevents recurrence of paroxysmal AF (69–91% freedom from arrhythmias at 1 year, see *Figure 18B* for lesion  
2072 set),<sup>468, 809, 810</sup> and seems effective in patients refractory to catheter ablation.<sup>811</sup> The average length of hospital2073 stay for thoracoscopic ablation varies from 3.6 to 6.0 days.<sup>468, 812, 813</sup> The FAST (Atrial Fibrillation Catheter2074 Ablation vs Surgical Ablation Treatment) trial,<sup>468</sup> and another smaller trial,<sup>814</sup> suggested that thoracoscopic AF2075 surgery could be more effective than catheter ablation for the maintenance of sinus rhythm,<sup>468, 814</sup> while also2076 causing more complications (*Table 19*).<sup>815</sup> To improve results,<sup>468, 816-818</sup> more extensive lesion sets have been2077 performed, connecting lines between the PVI encircling and towards the mitral annulus.<sup>812, 819-822</sup> To improve the2078 generation of transmural lesions,<sup>716</sup> endo-epicardial ablation strategies have recently been proposed.<sup>812, 823-825</sup>2079 Although preliminary experience with hybrid simultaneous ablation shows promise, procedural time and rates of  
2080 bleeding complications are higher.<sup>812, 823</sup>

2081

2082

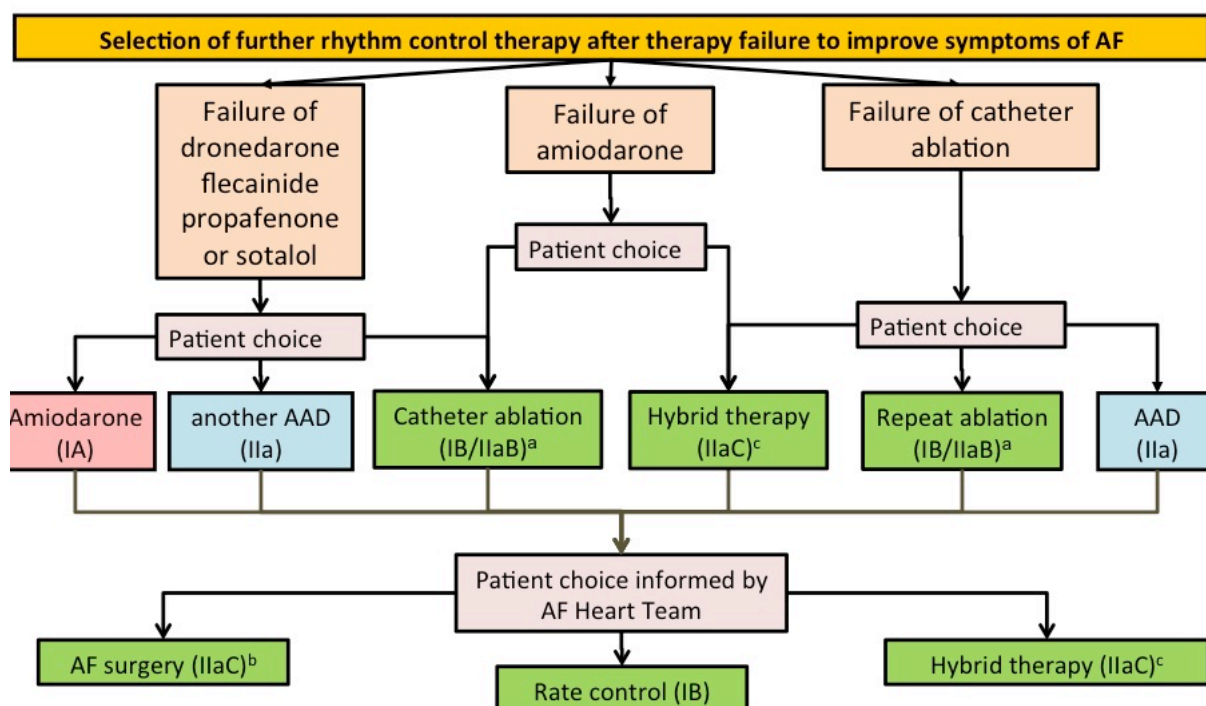
**Table 19** Complications of thoracoscopic AF surgery

Complication	Rate <sup>468, 815, 822, 826</sup>
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 <sup>a</sup>	0–3.0%

2083 AF = atrial fibrillation.  
 2084 <sup>a</sup>The rate of asymptomatic cerebral embolism is unknown  
 2085

### 2086 11.5. Choice of rhythm control following treatment failure

2087 There is insufficient evidence on which to base clear recommendations on how to treat patients with recurrent  
 2088 AF after catheter ablation. Early recurrences of AF or atrial tachycardias after ablation (occurring within 8  
 2089 weeks) may be treated with cardioversion. Many of the published series of patients undergoing AF ablation  
 2090 included those who failed antiarrhythmic drug therapy. Thus, considering ablation therapy in patients who have  
 2091 symptomatic recurrences on antiarrhythmic drug therapy is often reasonable. Alternatively, trialling another  
 2092 antiarrhythmic drug can be considered. Combining antiarrhythmic drug with ablation ('hybrid therapy', see  
 2093 Section 11) should be considered based on the different and possibly synergistic effects of these drugs with AF  
 2094 ablation, possibly benefitting patients in whom either treatment alone was previously ineffective. Rate control  
 2095 without rhythm control, surgical ablation, or repeat catheter ablation should be considered as well as third-line  
 2096 options (Figure 20). Patient preferences and local access to therapy are important considerations to inform the  
 2097 therapy choice in patients who are in need of further rhythm control therapy after an initial therapy failure.



2098  
 2099 **Figure 20** Choice of rhythm control approaches following treatment failure.  
 2100 AAD = antiarrhythmic drug; AF = atrial fibrillation; PVI = pulmonary vein isolation.  
 2101 <sup>a</sup> catheter ablation should target PVI. Class I level B for paroxysmal AF and Class IIa level B for persistent AF.  
 2102 <sup>b</sup> AF surgery may be PVI (e.g. in paroxysmal AF) or maze surgery (e.g. in therapy-refractory or long-standing  
 2103 persistent AF).  
 2104 <sup>c</sup> Hybrid therapy involves combination of antiarrhythmic drugs, catheter ablation, and/or AF surgery.  
 2105

### 2106 11.6. The atrial fibrillation Heart Team

2107 In view of the complexity of the different treatment options in patients with failed rhythm control therapy but  
 2108 who still require or demand further rhythm control therapy, this Task Force proposes that decisions involving  
 2109 AF surgery or extensive AF ablation should be based on advice from an AF Heart Team. This will also apply to  
 2110 reversal to a rate control strategy in patients with severe (EHRA III or IV) AF symptoms. An AF Heart Team  
 2111 should consist of a cardiologist with expertise in antiarrhythmic drug therapy, an interventional  
 2112 electrophysiologist, and a cardiac surgeon with expertise in appropriate patient selection, techniques, and

2113 technologies for interventional or surgical AF ablation. Such AF Heart Teams – and a collaborative  
 2114 infrastructure supporting a continued interaction between physicians delivering continued care, AF  
 2115 cardiologists, interventional electrophysiologists, and AF surgeons – should be established to provide optimal  
 2116 advice and ultimately to improve rhythm outcomes for patients in need of advanced and complex rhythm control  
 2117 interventions.

2118

2119 **Recommendations for catheter ablation of AF and AF surgery**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
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 cryotherapy 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

2120 AF = atrial fibrillation; NOAC = non-vitamin K antagonist oral anticoagulant; VKA = vitamin K antagonist.

2121 <sup>a</sup>Class of recommendation.

2122 <sup>b</sup>Level of evidence.

2123 <sup>c</sup>Reference(s) supporting recommendations.

2124

## 2125 **12 Hybrid rhythm control therapy**

2126 AF has many different drivers, which are only partially targeted by antiarrhythmic drug or catheter ablation.<sup>96</sup>

2127 Hence, combination or 'hybrid' rhythm control therapy seems reasonable, although there is little evidence  
2128 supporting its use.

2129

### 2130 **12.1. Combining antiarrhythmic drugs and catheter ablation**

2131 Antiarrhythmic drug therapy is commonly given for 8–12 weeks after ablation to reduce early recurrences of AF  
2132 after catheter ablation, supported by a recent controlled trial where amiodarone halved early AF recurrences  
2133 compared with placebo.<sup>650</sup> Prospective studies have not been done, but a meta-analysis of the available (weak)  
2134 evidence suggests slightly better prevention of recurrent AF in patients treated with antiarrhythmic drugs after  
2135 catheter ablation.<sup>713</sup> Many patients are treated with antiarrhythmic drug therapy after catheter ablation (most  
2136 often amiodarone or flecainide),<sup>587</sup> and this seems a reasonable option in patients with recurrent AF after  
2137 ablation. It seems common sense to consider antiarrhythmic drug therapy in patients who are in need of further  
2138 rhythm control therapy after catheter ablation, but controlled trials to confirm this are desirable.

2139 Combining cavotricuspid isthmus ablation and antiarrhythmic drugs may lead to improved rhythm  
2140 control without the need for left atrial ablation in patients who develop 'drug-induced atrial flutter' on therapy  
2141 with flecainide, propafenone, or amiodarone,<sup>834-836</sup> although recurrent AF is a concern in the long term.<sup>837, 838</sup>

2142

### 2143 **12.2. Combining antiarrhythmic drugs and pacemakers**

2144 In selected patients with sick sinus syndrome and fast ventricular response during AF paroxysms requiring rate  
2145 control therapy, the addition of a pacemaker not only optimizes rate control but may also help to control  
2146 rhythm.<sup>711, 712</sup> Moreover, when antiarrhythmic drug treatment leads to sinus node dysfunction and bradycardia,  
2147 pacing may permit up titration of the antiarrhythmic drug dose. Such strategies have never been prospectively  
2148 investigated and the existing populations studied are highly selected.<sup>839, 840</sup> Some patients with AF-induced  
2149 bradycardia may benefit from catheter ablation of AF, obviating the need for antiarrhythmic drugs and  
2150 pacemaker implantation.<sup>829, 830</sup>

2151

## 2152 **13 Specific situations**

### 2153 **13.1. Frail and 'elderly' patients**

2154 Many AF patients present at an older age (e.g. > 75 or > 80 years). There are no studies suggesting that  
2155 cardiovascular risk reduction is less effective in these 'elderly' AF patients than in younger patients. Rather, age  
2156 is one of the strongest predictors/risk factors for ischaemic stroke in AF (*Table 11*).<sup>382</sup> Good data are available to  
2157 support the use of anticoagulants in older patients from BAFTA (Birmingham Atrial Fibrillation Treatment of  
2158 the Aged Study),<sup>362</sup> the NOAC trials,<sup>39</sup> and from analyses in elderly Americans (Medicare).<sup>396</sup> Elderly AF  
2159 patients are at higher risk of stroke and thus are more likely to benefit from OAC than younger patients,<sup>841</sup> and  
2160 yet OAC is still underutilized in the elderly.<sup>220, 842</sup> Although the evidence base is smaller for other treatment  
2161 options in AF, the available data support the use of available rate and rhythm control interventions, including  
2162 pacemakers and catheter ablation, without justification to discriminate by age group. Individual patients at older  
2163 age may present with multiple comorbidities including dementia, a tendency to falls, CKD, anaemia,  
2164 hypertension, diabetes, and cognitive dysfunction. Such conditions may limit quality of life more than AF-  
2165 related symptoms. Impairment of renal and hepatic function and multiple simultaneous medications make drug  
2166 interactions and adverse drug reactions more likely. Integrated AF management and careful adaptation of drug  
2167 dosing seem reasonable to reduce complications of AF therapy in such patients.<sup>843</sup>

2168

### 2169 **13.2. Inherited cardiomyopathies, channelopathies, and accessory pathways**

2170 Several inherited cardiac conditions are associated with early-onset AF (*Table 20*). Treatment of the underlying  
 2171 cardiac condition is an important contribution to AF management in these young patients (see also ESC  
 2172 guidelines on the sudden cardiac death<sup>844</sup> and hypertrophic cardiomyopathy<sup>845</sup>).

2173

2174 **Table 20** Inherited cardiomyopathies, channelopathies, and pathways associated with AF

2175

Syndrome	Gene	Functional alteration	AF prevalence	References
Long QT syndrome	KCNQ1 KCNH2 SCN5A ANK2 others	IKs <input type="checkbox"/> IKr <input type="checkbox"/> INa <input type="checkbox"/> INa,K <input type="checkbox"/> Various effects	5–10%	846-850
Brugada syndrome	SCN5A GPDIL SCN1B CACNA1C CACNB2b others	INa <input type="checkbox"/> INa <input type="checkbox"/> INa <input type="checkbox"/> ICa <input type="checkbox"/> ICa <input type="checkbox"/> others	10–20%	851-855
Short QT syndrome	KCNH2 KCNQ1 KCNJ2 CACNA1C CACNB2b	IKr <input type="checkbox"/> IKs <input type="checkbox"/> IK1 <input type="checkbox"/> ICa <input type="checkbox"/> ICa <input type="checkbox"/>	Up to 70%	853, 856-858
Catecholaminergic ventricular tachycardia	RYR2 CASQ2	Abnormal Ca <sup>2+</sup> 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

2176 AF = atrial fibrillation.

2177

#### 2178 **13.2.1. Wolff–Parkinson–White syndrome**

2179 Patients with pre-excitation and AF are at risk of rapid conduction across the accessory pathway, resulting in a  
 2180 fast ventricular rate, possibly ventricular fibrillation, and sudden death. In AF patients with evidence of an  
 2181 antegrade accessory pathway, catheter ablation of the pathway is recommended.<sup>869, 870</sup> This procedure is safe and  
 2182 effective and may be considered as a prophylactic treatment strategy.<sup>871, 872</sup> In AF patients surviving a sudden  
 2183 death event with evidence of an accessory pathway, urgent catheter ablation of the pathway is recommended.<sup>869</sup>

2184 A documented short pre-excited RR interval (< 250 ms) during spontaneous or induced AF is one of the risk  
 2185 markers for sudden death in Wolff–Parkinson–White syndrome (WPW) syndrome, in addition to a history of  
 2186 symptomatic tachycardia, the presence of multiple accessory pathways, and Ebstein’s anomaly. Intravenous  
 2187 procainamide, propafenone, or ajmaline can be used to acutely slow ventricular rate,<sup>873, 874</sup> whereas digoxin,  
 2188 verapamil, and diltiazem are contraindicated.<sup>875</sup> Intravenous amiodarone should be used with caution, as there  
 2189 are case reports of accelerated ventricular rhythms and ventricular fibrillation in patients with pre-excited AF  
 2190 receiving intravenous amiodarone infusion.<sup>876</sup>

2191

#### 2192 **13.2.2. Hypertrophic cardiomyopathy**

2193 AF is the most common arrhythmia in patients with hypertrophic cardiomyopathy, affecting approximately one-  
 2194 quarter of this population.<sup>877</sup> Observational data highlight a high stroke risk in hypertrophic cardiomyopathy

2195 patients with AF, confirming the need for OAC.<sup>878</sup> While there is more experience with VKAs, there are no data  
 2196 to suggest that NOACs cannot be used in these patients.<sup>845</sup> Studies of rate or rhythm control medications in  
 2197 patients with hypertrophic cardiomyopathy are relatively scarce. Beta-blockers and diltiazem or verapamil seem  
 2198 reasonable treatment options for rate control in these patients. In the absence of significant LV outflow tract  
 2199 obstruction, digoxin can be used alone or in combination with beta-blockers.<sup>845</sup> Amiodarone seems a safe  
 2200 antiarrhythmic drug in AF patients with hypertrophic cardiomyopathy,<sup>879</sup> and expert opinion suggests that  
 2201 disopyramide may be beneficial in those with outflow tract obstruction. AF ablation is effective to suppress  
 2202 symptomatic AF recurrences.<sup>880-884</sup> Surgical treatment of AF may be appropriate in patients with hypertrophic  
 2203 cardiomyopathy undergoing surgery (e.g. for LV outflow tract obstruction or mitral valve surgery), but  
 2204 experience is limited.

### 2205 2206 **13.2.3. Channelopathies and arrhythmogenic right ventricular cardiomyopathy**

2207 Many channelopathies and inherited cardiomyopathies are associated with AF. AF prevalence ranges from 5%  
 2208 to 20% in patients with long QT syndrome or Brugada syndrome, and is up to 70% in short QT syndrome  
 2209 (Table 20).<sup>853, 856-858</sup> Penetrance of disease phenotype including AF is variable.<sup>61, 852, 885, 886</sup> Both shortening as  
 2210 well as prolongation of the atrial action potential have been demonstrated as likely mechanisms underlying AF  
 2211 in these diseases. It seems reasonable to consider antiarrhythmic drugs that reverse the suspected channel defect  
 2212 in AF patients with inherited cardiomyopathies (e.g. a sodium channel blocker in LQT3<sup>852</sup> and quinidine in  
 2213 Brugada syndrome<sup>887</sup>). More importantly, new-onset AF in young, otherwise healthy individuals should trigger  
 2214 a careful search for such inherited conditions, including clinical history, family history, ECG phenotype, and  
 2215 echocardiography and/or other cardiac imaging.

2216 Monogenic defects only account for 3–5% of all patients with AF, even in younger populations.<sup>846, 848,</sup>  
 2217 <sup>888-890</sup> Furthermore, there is no clear link between detected mutations and specific outcomes or therapeutic needs.  
 2218 For these reasons, genetic testing is not recommended in the general AF population.<sup>77</sup> Other guidelines have  
 2219 described the indications for genetic testing in patients with inherited arrhythmogenic diseases.<sup>844, 891</sup>

### 2220 2221 **Recommendations for inherited cardiomyopathies**

2222 <b>Recommendations</b>	<b>Class<sup>a</sup></b>	<b>Level<sup>b</sup></b>	<b>Refs<sup>c</sup></b>
<b>WPW syndrome</b>			
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
<b>Hypertrophic cardiomyopathy</b>			
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
<b>Inherited cardiomyopathies and channelopathies</b>			
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

2223 AF = atrial fibrillation; LV = left ventricular; WPW = Wolff–Parkinson–White syndrome.

2224 <sup>a</sup>Class of recommendation.

2225 <sup>b</sup>Level of evidence.

2226 <sup>c</sup>Reference(s) supporting recommendations.

2227

2228 **13.3. Sports and atrial fibrillation**

2229 Physical activity improves cardiovascular health, which translates into a lower risk of AF.<sup>898</sup> Therefore, physical  
 2230 activity is a cornerstone of preventing AF. Intensive sports practice, especially endurance sports (> 1500 h of  
 2231 endurance sports practice),<sup>899</sup> increases the risk of AF later in life,<sup>900-902</sup> probably mediated by altered autonomic  
 2232 tone, volume load during exercise, atrial hypertrophy, and dilatation.<sup>903,904</sup> This results in a U-shaped  
 2233 relationship of physical activity and incident AF.<sup>214,898,902,905,906</sup> Detraining can reduce AF in models<sup>904</sup> and  
 2234 reduces ventricular arrhythmias in athletes,<sup>907</sup> but the role of detraining for AF in human athletes is unknown.  
 2235 The management of athletes with AF is similar to general AF management, but requires a few special  
 2236 considerations. Clinical risk factors will determine the need for anticoagulation. Sports with direct bodily  
 2237 contact or prone to trauma should be avoided in patients on OAC. Beta-blockers are not well tolerated and at  
 2238 times prohibited, and digoxin, verapamil, and diltiazem are often not potent enough to slow heart rate during  
 2239 exertional AF. Catheter ablation for AF probably has similar outcomes in athletes as in non-athletes,<sup>908,909</sup> but  
 2240 further data are needed. Pill-in-the-pocket therapy has been used as well.<sup>620</sup> After ingestion of flecainide or  
 2241 propafenone as pill-in-the-pocket, patients should refrain from sports as long as AF persists and until two half-  
 2242 lives of the antiarrhythmic drug have elapsed. Prophylactic ablation of the flutter circuit may be considered in  
 2243 athletes treated with sodium channel blockers.<sup>910</sup>

2244

2245 **Recommendations for physical activity in patients with AF**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
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

2246 AF = atrial fibrillation.

2247 <sup>a</sup>Class of recommendation.2248 <sup>b</sup>Level of evidence.2249 <sup>c</sup>Reference(s) supporting recommendations.

2250

2251 **13.4. Pregnancy**

2252 AF in pregnant women is rare and is usually associated with pre-existing heart disease. AF is associated with  
 2253 increased complications for the mother and foetus.<sup>911,912</sup> Better treatment of congenital heart diseases will  
 2254 probably increase the incidence of AF during pregnancy in the future.<sup>913</sup> Pregnant women with AF should be  
 2255 managed as high-risk pregnancies in close collaboration with cardiologists, obstetricians, and neonatologists.

2256

2257 **13.4.1. Rate control**

2258 Owing to a lack of specific data, beta-blockers, verapamil, diltiazem, and digoxin all carry a US Food and Drug  
 2259 Administration pregnancy safety category of C (benefits may outweigh risk), except for atenolol (category D:  
 2260 positive evidence of risk). Their use should be at the lowest dose and for the shortest time required. None of the  
 2261 agents are teratogenic, but they readily cross the placenta.<sup>914</sup> Beta-blockers are commonly used in clinical  
 2262 practice (e.g. for management of gestational hypertension and pre-eclampsia), but may be associated with  
 2263 intrauterine growth retardation,<sup>915</sup> and hence growth scans after 20 weeks gestation are recommended. Digoxin  
 2264 is considered safe for maternal and foetal arrhythmias.<sup>916</sup> There are insufficient data to comment on verapamil or  
 2265 diltiazem, hence rate control using beta-blockers and/or digoxin is recommended.<sup>917</sup> With regards to  
 2266 breastfeeding, all rate control agents are present in breast milk, although levels of beta-blockers, digoxin, and  
 2267 verapamil are too low to be considered harmful. Diltiazem will be present at high levels and should be  
 2268 considered second-line treatment.<sup>918</sup>

2269

2270 **13.4.2. Rhythm control**

2271 Rhythm control therapy in pregnant patients with AF has only been reported in case studies. Amiodarone is  
 2272 associated with severe adverse foetal side-effects and should only be considered for emergency situations.<sup>919</sup>  
 2273 Flecainide and sotalol can both be used for conversion of foetal arrhythmias without major adverse effects,<sup>920</sup>  
 2274 and thus are likely to be safe to treat maternal symptomatic AF. Electrical cardioversion can be effective for  
 2275 restoration of sinus rhythm when tachyarrhythmia is causing haemodynamic instability, with low rates of  
 2276 adverse outcomes for both mother and foetus.<sup>921</sup> However, in view of the risk of foetal distress, electrical  
 2277 cardioversion should only be carried out where facilities are available for foetal monitoring and emergency  
 2278 caesarean section. As with other emergencies during pregnancy, patients should receive 100% oxygen,  
 2279 intravenous access should be established early, and the mother should be positioned in the left lateral position to  
 2280 improve venous return.<sup>922</sup>

2281

### 2282 13.4.3. Anticoagulation

2283 VKAs should be avoided in the first trimester because of teratogenic effects, and in the 2–4 weeks preceding  
 2284 delivery to avoid foetal bleeding. Low-molecular-weight heparins are a safe substitute, as they do not cross the  
 2285 placenta.<sup>923</sup> In the third trimester, frequent laboratory checks for adequate anticoagulation (e.g. every 10–14  
 2286 days) and corresponding dose adjustments are advised, given that in some women high doses of both VKA and  
 2287 heparin may be needed to maintain adequate anticoagulation. Pregnant patients with AF and mechanical  
 2288 prosthetic valves who elect to stop VKA treatment in consultation with their specialist team between 6 and 12  
 2289 weeks of gestation, should receive continuous, dose-adjusted unfractionated heparin or dose-adjusted  
 2290 subcutaneous low-molecular-weight heparin. As only limited data are available about teratogenesis for NOACs,  
 2291 these drugs should be avoided during pregnancy.

2292

### 2293 Recommendations during pregnancy

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
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	

2294 NOAC = non-vitamin K antagonist oral anticoagulants

2295 <sup>a</sup>Class of recommendation.

2296 <sup>b</sup>Level of evidence.

2297 <sup>c</sup>Reference(s) supporting recommendations.

2298

### 2299 13.5. Postoperative atrial fibrillation

2300 AF is common after cardiac surgery (occurring in 15–45% of patients),<sup>924-926</sup> and is associated with increased  
 2301 length of hospital stay and higher rates of complications and mortality.<sup>927</sup> Postoperative AF is also not  
 2302 uncommon after other major surgery, especially in elderly patients. The treatment of postoperative AF is mainly  
 2303 based on studies of patients undergoing cardiac surgery, with much less evidence in the non-cardiac surgery  
 2304 setting.

2305

#### 2306 13.5.1. Prevention of postoperative atrial fibrillation

2307 Beta-blockers reduce postoperative AF and supraventricular tachycardias, albeit with high heterogeneity and  
 2308 moderate risk of bias in a systematic review of published studies (the most commonly studied drug was  
 2309 propranolol, with AF in 16.3% of the treatment group vs. 31.7% in the control group).<sup>925</sup> In the majority of these  
 2310 studies, beta-blockers were administered postoperatively, a regimen supported in a recent meta-analysis.<sup>928</sup>  
 2311 Amiodarone reduced the incidence of postoperative AF compared to a beta-blocker regimen in several meta-  
 2312 analyses, also reducing hospital stay.<sup>925, 929-931</sup>

2313 Despite initial reports from meta-analyses,<sup>689, 932, 933</sup> preoperative treatment with statins did not prevent  
 2314 postoperative AF in a prospective controlled trial.<sup>934</sup> Other therapies have also been studied in small, hypothesis-  
 2315 generating trials, but have not demonstrated clear beneficial effects. These include magnesium,<sup>925, 935, 936</sup> n-3  
 2316 polyunsaturated fatty acids,<sup>937-945</sup> colchicine,<sup>946</sup> corticosteroids,<sup>947, 948</sup> and posterior pericardectomy.<sup>949</sup>  
 2317 Postoperative overdrive biatrial pacing has not gained widespread use despite some suggestion of prophylactic  
 2318 effects.<sup>925, 950</sup>  
 2319

### 2320 13.5.2. Anticoagulation

2321 Postoperative AF is associated with an increased early stroke risk, increased morbidity, and 30-day mortality.<sup>927,</sup>  
 2322 <sup>951, 952</sup> In the long term, patients with an episode of postoperative AF have a twofold increase in cardiovascular  
 2323 mortality and a substantially increased risk of future AF and ischaemic stroke compared with patients that  
 2324 remain in sinus rhythm after surgery.<sup>952-958</sup> OAC at discharge has been associated with a reduced long-term  
 2325 mortality in patients with postoperative AF,<sup>959</sup> without evidence from controlled trials. Good quality data are  
 2326 needed to determine whether long-term anticoagulation can prevent strokes in patients with postoperative AF at  
 2327 high stroke risk,<sup>368, 386</sup> and to assess whether short episodes of postoperative AF (e.g. < 48 h) carry a similar risk  
 2328 as longer episodes.<sup>960</sup> The indication and timing of OAC in postoperative AF patients should take into  
 2329 consideration the risk of postoperative bleeding.  
 2330

### 2331 13.5.3. Rhythm control therapy in postoperative atrial fibrillation

2332 In haemodynamically unstable patients, cardioversion and consideration of antiarrhythmic drugs is  
 2333 recommended. Amiodarone or vernakalant have been efficient in converting postoperative AF to sinus  
 2334 rhythm.<sup>603, 950, 961</sup> A recent medium-sized trial randomizing patients with postoperative AF to either rhythm  
 2335 control therapy with amiodarone or to rate control did not find a difference in hospital admissions during a 60-  
 2336 day follow-up,<sup>962</sup> underpinning that the aim of rhythm control therapy should be to improve AF-related  
 2337 symptoms in postoperative AF. In asymptomatic patients and in those with acceptable symptoms, rate control or  
 2338 deferred cardioversion preceded by anticoagulation is a reasonable approach.  
 2339

### 2340 Recommendations for preventing postoperative AF

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
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

2341 AF = atrial fibrillation.

2342 <sup>a</sup>Class of recommendation.

2343 <sup>b</sup>Level of evidence.

2344 <sup>c</sup>Reference(s) supporting recommendations.

2345

### 2346 13.6. Atrial arrhythmias in grown-up patients with congenital heart disease

2347 Atrial arrhythmias (AF, atrial flutter, atrial tachycardias) often occur late after surgical repair of congenital heart  
 2348 defects, occurring in 15–40% of grown-up patients with congenital heart disease (GUCH). They are associated  
 2349 with heart failure, syncope, thromboembolic events, and sudden death.<sup>963-967</sup> The pathophysiological substrate is  
 2350 complex, associated with hypertrophy, fibrosis, hypoxaemia, chronic haemodynamic overload, and surgical  
 2351 scars and patches. Additionally, related primary anomalies in the conduction pathways can lead to reentrant  
 2352 atrial and ventricular tachycardia, heart block, and sinus node dysfunction.<sup>963</sup> Macro-reentrant atrial tachycardia  
 2353 or atypical atrial flutter may be seen after nearly any surgical procedure involving atriotomy or atrial patches.  
 2354

### 2355 **13.6.1. General management of atrial arrhythmias in grown-up patients with** 2356 **congenital heart disease**

2357 The conventional stroke risk factors should be used to inform decisions on long-term anticoagulation in GUCH  
 2358 patients with AF. In addition, anticoagulation should be considered in GUCH patients with atrial arrhythmias  
 2359 when they present with intracardial repair, cyanosis, Fontan palliation, or systemic right ventricle, in addition to  
 2360 those with conventional stroke risk factors.<sup>968</sup> Beta-blockers, verapamil, diltiazem, and digitalis can be used.  
 2361 Care should be taken to avoid bradycardia and hypotension.

2362 Sodium channel blockers suppress approximately half of atrial arrhythmias in Fontan patients.<sup>969</sup>  
 2363 Amiodarone is more effective, but long-term treatment with an antiarrhythmic drugs carries a high risk of  
 2364 extracardiac side-effects in this relatively young population. Intracardiac thrombi are common in GUCH  
 2365 patients undergoing cardioversion for AF, but also in patients with atrial tachycardias or atrial flutter.<sup>970</sup>  
 2366 Therefore, both a TOE and anticoagulation for a few weeks before the planned cardioversion should be  
 2367 considered.<sup>964</sup> Radiofrequency ablation may be a good option for symptomatic GUCH patients with atrial  
 2368 arrhythmias, especially in those with atrial flutter and other macro-reentrant tachycardias. Interventions should  
 2369 be performed in adequately qualified centres by specialized teams.  
 2370

### 2371 **13.6.2. Atrial tachyarrhythmias and atrial septal defects**

2372 Atrial flutter and fibrillation occur in 14–22% of adults with unoperated atrial septal defects, especially in older  
 2373 patients,<sup>971</sup> and can lead to heart failure.<sup>972</sup> Early repair can reduce but not eliminate the risk of AF.<sup>973</sup> Biatrial  
 2374 volume overload,<sup>974</sup> pulmonary hypertension,<sup>975</sup> and possibly the arrhythmogenic effect of atrial patches can  
 2375 contribute to these arrhythmias.<sup>976</sup> Anticoagulation should be decided based on stroke risk factors. In patients  
 2376 with a history of paroxysmal or persistent AF, AF surgery could be considered at the time of surgical closure, or  
 2377 catheter ablation in patients undergoing interventional atrial septal defect closure. Catheter ablation of late atrial  
 2378 arrhythmias has shown to be effective in 46 consecutive patients after surgical atrial septal defect.<sup>977</sup>  
 2379

### 2380 **13.6.3. Atrial tachyarrhythmias after Fontan operation**

2381 Atrial arrhythmias occur in up to 40% of patients with a Fontan circulation, and can manifest as atrial flutter,  
 2382 primary atrial tachycardia, AF, and accelerated junctional rhythm or junctional tachycardia<sup>978</sup> with or without  
 2383 sinoatrial node dysfunction.<sup>979</sup> Patients with atriopulmonary anastomoses (possibly due to higher atrial volume  
 2384 and pressure load) and those with early postoperative atrial arrhythmias are more likely to develop long-term  
 2385 atrial arrhythmias.<sup>980</sup> Atrial arrhythmias can also be the first manifestation of obstruction of the atriopulmonary  
 2386 anastomosis, a complication that must be identified. Right atrial thrombus formation is common in Fontan  
 2387 patients with atrial arrhythmias and requires oral anticoagulation.<sup>981</sup> Operative conversion to total  
 2388 cavopulmonary artery connection with concomitant arrhythmia surgery can in some patients improve heart  
 2389 failure symptoms and reduce recurrent arrhythmias,<sup>969, 982</sup> with low recurrence rates of clinically apparent atrial  
 2390 arrhythmias in the first few years after repeat surgery.<sup>983-985</sup> Catheter ablation of atrial arrhythmia in Fontan  
 2391 patients has been successful in selected patients.<sup>986</sup>  
 2392

### 2393 **13.6.4. Atrial tachyarrhythmias after tetralogy of Fallot correction**

2394 Approximately one-third of patients after repair of tetralogy of Fallot develop atrial arrhythmias, including intra-  
 2395 atrial reentrant tachycardia, focal atrial tachycardia, and AF.<sup>987</sup> Circuits involving the cavotricuspid isthmus and  
 2396 areas of presumed surgical right atrial scarring have been described as responsible for atrial arrhythmias.  
 2397

### 2398 **Recommendations in patients with GUCH**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
Atrial septal defect closure should be considered before the fourth decade of life to diminish the chance of atrial flutter and fibrillation	Ila	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 anticoagulation 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 <sub>2</sub> DS <sub>2</sub> -VAS <sub>C</sub> score is $\geq 1$	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

2399 AF = atrial fibrillation; CHA<sub>2</sub>DS<sub>2</sub>-VASc = Congestive Heart failure, hypertension, Age  $\geq 75$  (doubled),  
 2400 Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female); GUCH = grown-up patients with  
 2401 congenital heart disease; OAC = oral anticoagulation; TOE = transoesophageal echocardiography.

2402 <sup>a</sup>Class of recommendation.

2403 <sup>b</sup>Level of evidence.

2404 <sup>c</sup>Reference(s) supporting recommendations.

2405

### 2406 13.7. Management of atrial flutter

2407 The goals for the management of atrial flutter are similar to those for AF.<sup>992</sup> Based on the available evidence, the  
 2408 stroke risk in patients with atrial flutter is not much different from that in AF.<sup>827</sup> Furthermore, many patients  
 2409 diagnosed with atrial flutter develop AF.<sup>993-995</sup> Thus, anticoagulation should be used in patients with atrial flutter  
 2410 similar to that in patients with AF. Rate control in atrial flutter is achieved with the same medications as in AF,  
 2411 but is often more difficult to achieve. Flecainide, propafenone, dofetilide, and intravenous ibutilide are useful for  
 2412 cardioversion of atrial flutter. They should be combined with a rate-controlling agent to avoid 1:1 conduction of  
 2413 slowing flutter waves to the ventricles. Ibutilide is more effective for conversion of atrial flutter than AF,  
 2414 whereas vernakalant is less effective in converting typical atrial flutter.<sup>996, 997</sup> Electrical cardioversion of atrial  
 2415 flutter can be performed using lower energies (50–100 J) than for AF.<sup>998, 999</sup> Atrial overdrive pacing through  
 2416 pacemaker leads or endocardial or transesophageal catheters can convert atrial flutter to sinus rhythm.<sup>1000, 1001</sup>  
 2417 Anticoagulation and transoesophageal echocardiography around cardioversion or overdrive pacing should be  
 2418 used similar to that in AF.

2419 Ablation of the cavotricuspid isthmus for isthmus-dependent right atrial flutter (either the common  
 2420 counter-clockwise atrial flutter or the less-common clockwise atrial flutter) restores and maintains sinus rhythm  
 2421 with a success rate of 90–95%.<sup>1002</sup> It may also reduce AF recurrences in selected patients,<sup>1003, 1004</sup> and help to  
 2422 prevent hospitalizations.<sup>1004, 1005</sup> Isthmus ablation is comparably safe and more effective than antiarrhythmic  
 2423 drug therapy, and is recommended for recurrent atrial flutter.<sup>585-587, 713</sup> Catheter ablation of left atrial macro-  
 2424 reentrant tachycardia is more complex, with lower success rates and higher recurrence rates.<sup>1006, 1007</sup>

2425

### 2426 Recommendations for management of atrial flutter

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
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	

2427 AF = atrial fibrillation.

2428 <sup>a</sup>Class of recommendation.

2429 <sup>b</sup>Level of evidence.

2430 <sup>c</sup>Reference(s) supporting recommendations.

2431

## 2432 **14 Patient involvement, education and self-management**

2433 A fundamental aspect of a structured AF management programme is the focus on patient-centred care.

2434

### 2435 **14.1. Patient-centred care**

2436 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.<sup>328</sup> Shared decision-making<sup>747</sup> 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).<sup>326, 1008, 1009</sup> 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.<sup>1010</sup>

2441

2442

2443

### 2444 **14.2. Integrated patient education**

2445 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,<sup>32, 1011, 1012</sup> indicating the need to further develop structured patient education. Several patient-information tools have been developed, largely focusing on oral anticoagulation.<sup>1013-1016</sup> Understanding patients' perceptions and attitudes towards AF and its management can improve AF management and related outcomes.<sup>1017</sup> This includes tailored patient education focusing on the disease, symptom recognition, therapy, modifiable risk factors for AF, and self-management activities.<sup>1018, 1019</sup>

2451

2452

### 2453 **14.3. Self-management and shared decision-making**

2454 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).<sup>1020</sup> It requires understanding of the treatment modalities and goals.<sup>350</sup> Within a multidisciplinary team, allied health professionals can guide this interactive process in which communication, trust, and reciprocal respect foster patient engagement.<sup>1021</sup> Shared decision-making should be considered as a routine part of the decision-making process,<sup>747</sup> supported by decision aids where applicable.<sup>1022</sup> Models of care that integrate education, engagement, and shared decision making are now available,<sup>1023</sup> and may be of particular value in the management of AF.

2461

2462

2463

#### **Recommendations for patient involvement, education, and self-management**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
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

2464 AF = atrial fibrillation.

2465 <sup>a</sup>Class of recommendation.

2466 <sup>b</sup>Level of evidence.

2467 <sup>c</sup>Reference(s) supporting recommendations.

2468

## 2469 **15 Gaps in evidence**

2470 There are some areas of AF management that are supported by excellent evidence from multiple, adequately  
2471 powered randomized trials (e.g. oral anticoagulation. Other areas, such as rhythm control therapy, integrated AF  
2472 management, and lifestyle modifications are clearly developing the required evidence, while areas such as rate  
2473 control are in dire need of better studies to underpin future guidelines. Here we identify areas in need of further  
2474 research.

2475

### 2476 **15.1. Major health modifiers causing atrial fibrillation**

2477 Atrial fibrillation has different causes in different patients. More research is needed into the major causes (and  
2478 electrophysiological mechanisms) of AF in different patient groups.<sup>176, 1024</sup> Such research should consider the  
2479 major comorbidities associated with AF, and characterize the response to AF therapy in patients with different,  
2480 pathophysiologically distinct types of AF.

2481

### 2482 **15.2. How much atrial fibrillation constitutes a mandate for therapy?**

2483 Technological advances allow screening for an irregular pulse using patient-operated ECG devices,  
2484 smartphones, and a variety of other technologies. These may be very useful to detect silent, undiagnosed AF.<sup>157</sup>  
2485 Adequately powered studies evaluating the diagnostic accuracy of such technologies, the diagnostic yield in  
2486 different populations, the shortest duration of atrial arrhythmias conveying a stroke risk, and ideally the effect of  
2487 ECG screening on outcomes are needed.

2488

### 2489 **15.3. Atrial high-rate episodes and need for anticoagulation**

2490 All of the information on the benefit of OAC has been in patients with AF diagnosed by ECG. Technological  
2491 advances allow ready detection of AHRE in patients with implanted devices and an atrial lead. Such patients are  
2492 at increased stroke risk, but it is unclear whether they benefit from OAC. Controlled trials evaluating OAC in  
2493 AHRE patients are ongoing and will provide evidence on the best antithrombotic therapy in these patients.

2494

### 2495 **15.4. Stroke risk in specific populations**

2496 Several specific AF groups should be studied to better characterize their risk for AF, stroke, and other AF-  
2497 related complications (e.g. patients with one stroke risk factor, and non-Caucasian patients). Confounding  
2498 factors (e.g. different therapy of concomitant cardiovascular diseases) may help to explain the variability in the  
2499 reported rates of incident AF, prevalent AF, and AF complications. This also applies to the effect of gender in  
2500 AF patients.<sup>47</sup>

2501

### 2502 **15.5. Anticoagulation in patients with severe chronic kidney disease**

2503 The use of NOACs has not been tested in patients with creatinine clearance < 30 mL/min, and there is very little  
2504 evidence on the effects of OAC in patients on haemodialysis or on other forms of renal-replacement therapy.  
2505 Studies evaluating OAC in patients with severe chronic kidney disease are needed to inform the best  
2506 management in this patient group at high risk for stroke and bleeding.

2507

### 2508 **15.6. Left atrial appendage occlusion for stroke prevention**

2509 The most common justification for LAA occlusion devices in clinical practice is a perceived high bleeding risk  
2510 and, less often, contraindications for OAC.<sup>459</sup> Unfortunately, LAA occluders have not been tested in such  
2511 populations. Furthermore, LAA occluders have not been compared with NOAC therapy in patients at risk for  
2512 bleeding, or with thoracoscopic LAA clipping. There is a clear need to conduct adequately designed and  
2513 powered trials to define the clinical role of LAA occluders compared with NOAC therapy in patients with  
2514 relative or absolute contraindications for anticoagulation, and/or in those suffering from an ischaemic stroke on  
2515 anticoagulant therapy.

2516

### 2517 **15.7. Anticoagulation in atrial fibrillation patients after a bleeding or stroke event**

2518 At least 2% of anticoagulated patients with AF will experience a serious bleeding event per year. Observational  
2519 data suggest that OAC can be reinitiated even after an intracerebral bleeding event.<sup>460, 484</sup> Controlled studies  
2520 evaluating different anticoagulation and stroke prevention interventions are urgently needed to provide evidence  
2521 on the best management of patients who have suffered a bleeding event that would usually lead to withholding

2522 OAC. Some studies (e.g. APACHE II<sup>1025</sup>) are ongoing, but adequately powered trials are needed. Similarly,  
2523 prospectively collected data are needed on the efficacy and bleeding risk following (re-)initiation of OAC after  
2524 stroke or intracranial bleeding.  
2525

### 2526 **15.8. Anticoagulation and optimal timing of non-acute cardioversion**

2527 Based on retrospective data, previous recommendations on the safe time-window in which a cardioversion can  
2528 be performed in new-onset AF used  $\leq 48$  hours as the ‘gold standard’ for non-protected cardioversion. However,  
2529 new evidence has emerged that initiating precardioversion anticoagulation in patients with AF episodes of < 24  
2530 hours or even < 12 hours would provide even better safety.<sup>642, 647, 1026-1028</sup> Further research is needed to establish  
2531 a clear safety margin in this clinical situation.  
2532

### 2533 **15.9. Competing causes of stroke or transient ischaemic attack in atrial fibrillation** 2534 **patients**

2535 Prospective RCTs have demonstrated the superiority of carotid endarterectomy compared to stenting in patients  
2536 with symptomatic high-degree stenosis of the internal carotid artery.<sup>1029</sup> As endarterectomy minimizes the need  
2537 for combination therapy with OAC and antiplatelets,<sup>1030</sup> this approach has appeal in patients with AF to reduce  
2538 bleeding risk. However, few of these studies included patients with AF. In a large observational study, the  
2539 composite of in-hospital mortality, post-procedural stroke, and cardiac complications was higher in AF patients  
2540 undergoing carotid stenting (457/7668; 6.0%) compared with endarterectomy (4438/51320; 8.6%;  $P <$   
2541 0.0001).<sup>1031</sup> Despite adjustment for baseline risk, this may just reflect the type of patients referred for each  
2542 procedure, and further randomized studies are needed to confirm the optimal treatment strategy in AF patients  
2543 with carotid disease.  
2544

### 2545 **15.10. Anticoagulation in patients with biological heart valves (including transcatheter** 2546 **aortic valve implantation) and non-rheumatic valve disease**

2547 The optimal antithrombotic therapy in the first months after biological valve replacement (including after  
2548 catheter-based valve replacement) is not known. VKAs remain the mainstay during the initial postoperative  
2549 period; NOACs probably deliver the same protection. In patients without AF, many centres use platelet  
2550 inhibitors only. NOACs appear to be equally effective as VKAs in patients with moderate aortic stenosis, based  
2551 on a subanalysis from the ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared  
2552 with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial<sup>1032</sup> as well  
2553 as the Loire Valley AF project.<sup>1033</sup> Further data would be helpful to confirm these observations.<sup>1034</sup> The safety  
2554 and efficacy of NOACs in patients with rheumatic mitral valve disease has not been evaluated and should be  
2555 studied.  
2556

### 2557 **15.11. Anticoagulation after ‘successful’ catheter ablation**

2558 In view of the long-term recurrence rates of AF, this Task Force recommends to continue OAC in AF patients  
2559 after ‘successful’ catheter ablation. Nonetheless, observational data suggest that the stroke risk may be lower  
2560 after catheter ablation of AF compared with other AF patients. The ongoing EAST (Early treatment of Atrial  
2561 fibrillation for Stroke prevention Trial) trial will inform in a more general way whether rhythm control therapy  
2562 can reduce stroke rates in anticoagulated AF patients. If confirmed, there may be a place for a controlled trial  
2563 evaluating the termination of OAC therapy at an interval after ‘successful’ catheter ablation.  
2564

### 2565 **15.12. Comparison of rate control agents**

2566 Although the use of rate control therapy is very common in AF patients, robust data comparing rate control  
2567 therapies are scant, with the majority of studies being small uncontrolled trials over short periods of follow-up.  
2568 Some studies are funded (e.g. RATE-AF [Rate Control Therapy Evaluation in Permanent Atrial Fibrillation]<sup>559</sup>)  
2569 and will investigate the potential benefits of different rate controlling agents, characteristics, or biomarkers that  
2570 can help to personalize the use of rate control, and the adverse-event profile of specific drugs in defined groups  
2571 of patients (e.g. AF with HFrEF).  
2572

### 2573 **15.13. Catheter ablation in persistent and long-standing persistent AF**

2574 While a few recent randomized studies support the use of catheter or surgical ablation in patients with persistent  
2575 AF and long-standing persistent AF, there is a clear need for more data evaluating this intervention in  
2576 adequately powered randomized trials.

2577

**2578 15.14. Optimal technique for repeat catheter ablation**

2579 PVI emerges as the most important target for catheter ablation of AF. Although a plethora of different additional  
2580 ablation techniques have been published, their added value is questionable in patients undergoing a first catheter  
2581 ablation, including those with persistent AF.<sup>735</sup> Many patients are in need of multiple catheter-ablation  
2582 procedures, and such interventions often follow local or operator-specific protocols without clear evidence to  
2583 support the choice of ablation target or intervention. There is a clear clinical need to define the best approach in  
2584 patients who are in need of a second ablation procedure.  
2585

**2586 15.15. Combination therapy for maintenance of sinus rhythm**

2587 In the follow-up after initially successful catheter ablation, even when done in experienced centres, many  
2588 patients will experience symptomatic recurrences of AF. These patients are often managed with antiarrhythmic  
2589 drugs. There is a surprising paucity of data evaluating different rhythm control interventions in patients with  
2590 recurrent AF after catheter ablation. Such studies seem reasonable and feasible.  
2591

**2592 15.16. Can rhythm control therapy convey a prognostic benefit in atrial fibrillation patients?**

2593 The progress in rhythm control therapy (catheter ablation, new antiarrhythmic drugs) and observational long-  
2594 term analyses suggest that rhythm control therapy may have a prognostic benefit. Ongoing trials such as  
2595 CABANA and EAST – AFNET 4 will provide initial answers to this important question, but more data are  
2596 needed, in addition to trials of surgical ablation techniques.  
2597  
2598

**2599 15.17. Thoracoscopic ‘stand-alone’ atrial fibrillation surgery**

2600 Minimally invasive epicardial ablation surgery for the treatment of stand-alone AF was reported a decade  
2601 ago.<sup>1035</sup> The procedure has since evolved towards a totally thoracoscopic procedure,<sup>1036</sup> and lesion sets were  
2602 extended to a complete left atrial maze.<sup>822</sup> With such rapid development and the coexistence of different  
2603 techniques and lesion sets, scientific evidence on long-term results is still limited. Randomized trials using a  
2604 standardized procedure are urgently needed to clearly define the benefits and risks of thoracoscopic AF ablation,  
2605 and to further support decisions of the AF Heart Team.  
2606

**2607 15.18. Surgical exclusion of the left atrial appendage**

2608 Exclusion of the LAA has been performed by cardiothoracic surgeons for decades, but prospective randomized  
2609 studies comparing the rate of ischaemic stroke with or without left appendage exclusion are presently lacking.  
2610 The LAAOS (Left Atrial Appendage Occlusion Study) III is currently randomizing cardiac surgery patients with  
2611 AF to undergo concomitant occlusion or no occlusion of the appendage.<sup>467</sup> More data are also needed to confirm  
2612 the safety and efficacy of thoracoscopic exclusion, following early positive observational data.<sup>1037</sup>  
2613

**2614 15.19. Concomitant atrial fibrillation surgery**

2615 Adequately powered randomized trials are needed, employing systematic follow-up, uniform lesion sets and  
2616 energy sources to evaluate the benefits and risks of concomitant AF surgery in symptomatic AF patients. An  
2617 RCT on non-uniform lesion sets with long-term follow-up is due to publish shortly.<sup>1038</sup> These will assist the AF  
2618 Heart Team to decide on optimal therapy for individual patients, including the full repertoire of medical and  
2619 surgical options for the treatment of AF.  
2620

2621 **16 To do and not to do messages from the Guidelines**

2622

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 <sub>2</sub> DS <sub>2</sub> -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 <sub>2</sub> DS <sub>2</sub> -VASc score of 2 or more	I	A
Oral anticoagulation therapy to prevent thromboembolism is recommended in all female AF patients with a CHA <sub>2</sub> DS <sub>2</sub> -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
<b>Recommendations for rate control of AF</b>	<b>Class</b>	<b>Level</b>
Beta-blocker, digoxin, diltiazem, or verapamil is recommended to control heart rate in AF patients with LVEF $\geq$ 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
<b>Recommendations for rhythm control of AF</b>	<b>Class</b>	<b>Level</b>
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

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2624  
2625

**2626 17 A short summary of the management of AF patients**

2627

2628 Here, we provide 17 simple rules to guide diagnosis and management of AF patients according to the 2016  
2629 ESC/EACTS/ESO Guidelines for the management of atrial fibrillation

2630

2631 1. Use ECG screening in at risk populations for atrial fibrillation, especially stroke survivors and the  
2632 Elderly.

2633

2. Document AF by ECG before starting treatment.

2634

2635 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.

2636

2637 4. Provide tailored information and education to AF patients to empower them to support AF  
management.

2638

5. Propose life style changes to all suitable AF patients to make their management more effective.

2639

2640 6. Treat underlying cardiovascular conditions adequately, e.g. valve repair or replacement in AF patients  
2641 with significant valvular heart disease, treatment of heart failure, or management of hypertension,  
among others.

2642

2643 7. Use oral anticoagulation in all AF patients unless they are at low risk for stroke based on the  
CHA<sub>2</sub>DS<sub>2</sub>VASc score or have true contraindications for anticoagulant therapy.

2644

2645 8. Anticoagulate patients with atrial flutter similar to atrial fibrillation. Offer isthmus ablation to  
symptomatic flutter patients.

2646

2647 9. Reduce all modifiable bleeding risk factors in all AF patients on oral anticoagulation, e.g. by treating  
2648 hypertension, minimising the duration and intensity of concomitant antiplatelet and NSAID therapy ,  
2649 treating anaemia and eliminating causes for blood loss, maintaining stable INR values in patients on  
vitamin K antagonists, and moderating alcohol intake

2650

2651 10. Check ventricular rate in all AF patients and use rate control medications to achieve lenient rate  
control.

2652

2653 11. Evaluate AF-related symptoms in all AF patients using the modified EHRA score. Whenever patients  
2654 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.

2655

2656 12. Select antiarrhythmic drugs based on their safety profile and consider catheter or surgical ablation  
when antiarrhythmic drugs fail.

2657

2658 13. Do not offer routine genetic testing in AF patients unless there is a suspicion for an inherited cardiac  
condition.

2659

14. Do not use antiplatelet therapy for stroke prevention in AF.

2660

2661 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.

2662

2663 16. Do neither use rhythm control therapy in asymptomatic AF patients, nor in patients with permanent  
AF.

2664

2665 17. Do not perform cardioversion or catheter ablation without anticoagulation unless an atrial thrombus has  
been ruled out by transesophageal echocardiogram.

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**2669 18 Web Addenda**

2670 All Web figures and Web tables are available in the Web addenda, available at European Heart Journal online  
2671 and also via the ESC Website (www.escardio.org/guidelines).

2672

**2673 19 Appendix**

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2682

2683 **ESC National Cardiac Societies** actively involved in the review process of the 2016 ESC Guidelines for the  
2684 management of atrial fibrillation developed in collaboration with EACTS

2685

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2719 **20 References**

2720

2721

- 2722 1. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, Gillum RF, Kim  
2723 YH, McAnulty JH, Jr., Zheng ZJ, Forouzanfar MH, Naghavi M, Mensah GA, Ezzati M, Murray CJ.  
2724 Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation*  
2725 2014;**129**:837-847.
- 2726 2. Colilla S, Crow A, Petkun W, Singer DE, Simon T, Liu X. Estimates of current and future  
2727 incidence and prevalence of atrial fibrillation in the U.S. adult population. *Am J Cardiol*  
2728 2013;**112**:1142-1147.
- 2729 3. Heeringa J, van der Kuip DA, Hofman A, Kors JA, van Herpen G, Stricker BH, Stijnen T, Lip  
2730 GY, Witteman JC. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur*  
2731 *Heart J* 2006;**27**:949-953.
- 2732 4. Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, D'Agostino RB, Massaro  
2733 JM, Beiser A, Wolf PA, Benjamin EJ. Lifetime risk for development of atrial fibrillation: the  
2734 Framingham Heart Study. *Circulation* 2004;**110**:1042-1046.
- 2735 5. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. Prevalence of  
2736 diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke  
2737 prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA*  
2738 2001;**285**:2370-2375.
- 2739 6. Krijthe BP, Kunst A, Benjamin EJ, Lip GY, Franco OH, Hofman A, Witteman JC, Stricker BH,  
2740 Heeringa J. Projections on the number of individuals with atrial fibrillation in the European Union, from  
2741 2000 to 2060. *Eur Heart J* 2013;**34**:2746-2751.
- 2742 7. Zoni-Berisso M, Lercari F, Carazza T, Domenicucci S. Epidemiology of atrial fibrillation:  
2743 European perspective. *Clin Epidemiol* 2014;**6**:213-220.
- 2744 8. Bjorck S, Palaszewski B, Friberg L, Bergfeldt L. Atrial fibrillation, stroke risk, and warfarin  
2745 therapy revisited: a population-based study. *Stroke* 2013;**44**:3103-3108.
- 2746 9. Haim M, Hoshen M, Reges O, Rabi Y, Balicer R, Leibowitz M. Prospective national study of  
2747 the prevalence, incidence, management and outcome of a large contemporary cohort of patients with  
2748 incident non-valvular atrial fibrillation. *J Am Heart Assoc* 2015;**4**:e001486.
- 2749 10. McManus DD, Rienstra M, Benjamin EJ. An update on the prognosis of patients with atrial  
2750 fibrillation. *Circulation* 2012;**126**:e143-146.
- 2751 11. Ball J, Carrington MJ, McMurray JJ, Stewart S. Atrial fibrillation: profile and burden of an  
2752 evolving epidemic in the 21st century. *Int J Cardiol* 2013;**167**:1807-1824.
- 2753 12. Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and  
2754 predisposing conditions for atrial fibrillation: population-based estimates. *Am J Cardiol* 1998;**82**:2N-  
2755 9N.
- 2756 13. Nguyen TN, Hilmer SN, Cumming RG. Review of epidemiology and management of atrial  
2757 fibrillation in developing countries. *Int J Cardiol* 2013;**167**:2412-2420.
- 2758 14. Oldgren J, Healey JS, Ezekowitz M, Commerford P, Avezum A, Pais P, Zhu J, Jansky P,  
2759 Sigamani A, Morillo CA, Liu L, Damasceno A, Grinvalds A, Nakamya J, Reilly PA, Keltai K, Van  
2760 Gelder IC, Yusufali AH, Watanabe E, Wallentin L, Connolly SJ, Yusuf S, RE-LY Atrial Fibrillation  
2761 Registry Investigators. Variations in cause and management of atrial fibrillation in a prospective  
2762 registry of 15,400 emergency department patients in 46 countries: the RE-LY Atrial Fibrillation  
2763 Registry. *Circulation* 2014;**129**:1568-1576.
- 2764 15. Chiang CE, Naditch-Brule L, Murin J, Goethals M, Inoue H, O'Neill J, Silva-Cardoso J,  
2765 Zharinov O, Gamra H, Alam S, Ponikowski P, Lewalter T, Rosenqvist M, Steg PG. Distribution and  
2766 risk profile of paroxysmal, persistent, and permanent atrial fibrillation in routine clinical practice: insight  
2767 from the real-life global survey evaluating patients with atrial fibrillation international registry. *Circ*  
2768 *Arrhythm Electrophysiol* 2012;**5**:632-639.
- 2769 16. Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, D'Agostino RB, Murabito JM,  
2770 Kannel WB, Benjamin EJ. Temporal relations of atrial fibrillation and congestive heart failure and their  
2771 joint influence on mortality: the Framingham Heart Study. *Circulation* 2003;**107**:2920-2925.
- 2772 17. Kishore A, Vail A, Majid A, Dawson J, Lees KR, Tyrrell PJ, Smith CJ. Detection of atrial  
2773 fibrillation after ischemic stroke or transient ischemic attack: a systematic review and meta-analysis.  
2774 *Stroke* 2014;**45**:520-526.
- 2775 18. Sanna T, Diener HC, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA, Rymer MM, Thijs  
2776 V, Rogers T, Beckers F, Lindborg K, Brachmann J, CRYSTAL AF Investigators. Cryptogenic stroke  
2777 and underlying atrial fibrillation. *N Engl J Med* 2014;**370**:2478-2486.

- 2778 19. Schnabel RB, Yin X, Gona P, Larson MG, Beiser AS, McManus DD, Newton-Cheh C, Lubitz  
2779 SA, Magnani JW, Ellinor PT, Seshadri S, Wolf PA, Vasan RS, Benjamin EJ, Levy D. 50 year trends in  
2780 atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a  
2781 cohort study. *Lancet* 2015;**386**:154-162.
- 2782 20. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial  
2783 fibrillation on the risk of death: the Framingham Heart Study. *Circulation* 1998;**98**:946-952.
- 2784 21. Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks  
2785 associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med*  
2786 2002;**113**:359-364.
- 2787 22. Andersson T, Magnuson A, Bryngelsson IL, Frobert O, Henriksson KM, Edvardsson N, Poci  
2788 D. All-cause mortality in 272,186 patients hospitalized with incident atrial fibrillation 1995-2008: a  
2789 Swedish nationwide long-term case-control study. *Eur Heart J* 2013;**34**:1061-1067.
- 2790 23. Kotecha D, Holmes J, Krum H, Altman DG, Manzano L, Cleland JG, Lip GY, Coats AJ,  
2791 Andersson B, Kirchhof P, von Lueder TG, Wedel H, Rosano G, Shibata MC, Rigby A, Flather MD,  
2792 Beta-Blockers in Heart Failure Collaborative Group. Efficacy of beta blockers in patients with heart  
2793 failure plus atrial fibrillation: an individual-patient data meta-analysis. *Lancet* 2014;**384**:2235-2243.
- 2794 24. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the  
2795 Framingham Study. *Stroke* 1991;**22**:983-988.
- 2796 25. Krahn AD, Manfreda J, Tate RB, Mathewson FA, Cuddy TE. The natural history of atrial  
2797 fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. *Am J Med*  
2798 1995;**98**:476-484.
- 2799 26. Henriksson KM, Farahmand B, Asberg S, Edvardsson N, Terent A. Comparison of  
2800 cardiovascular risk factors and survival in patients with ischemic or hemorrhagic stroke. *Int J Stroke*  
2801 2012;**7**:276-281.
- 2802 27. Grond M, Jauss M, Hamann G, Stark E, Veltkamp R, Nabavi D, Horn M, Weimar C,  
2803 Kohrmann M, Wachter R, Rosin L, Kirchhof P. Improved detection of silent atrial fibrillation using 72-  
2804 hour Holter ECG in patients with ischemic stroke: a prospective multicenter cohort study. *Stroke*  
2805 2013;**44**:3357-3364.
- 2806 28. Ott A, Breteler MM, de Bruyne MC, van Harskamp F, Grobbee DE, Hofman A. Atrial  
2807 fibrillation and dementia in a population-based study. The Rotterdam Study. *Stroke* 1997;**28**:316-321.
- 2808 29. Knecht S, Oelschlagel C, Duning T, Lohmann H, Albers J, Stehling C, Heindel W, Breithardt  
2809 G, Berger K, Ringelstein EB, Kirchhof P, Wersching H. Atrial fibrillation in stroke-free patients is  
2810 associated with memory impairment and hippocampal atrophy. *Eur Heart J* 2008;**29**:2125-2132.
- 2811 30. Ball J, Carrington MJ, Stewart S, SAFETY investigators. Mild cognitive impairment in high-risk  
2812 patients with chronic atrial fibrillation: a forgotten component of clinical management? *Heart*  
2813 2013;**99**:542-547.
- 2814 31. Marzona I, O'Donnell M, Teo K, Gao P, Anderson C, Bosch J, Yusuf S. Increased risk of  
2815 cognitive and functional decline in patients with atrial fibrillation: results of the ONTARGET and  
2816 TRANSCEND studies. *CMAJ* 2012;**184**:E329-336.
- 2817 32. Thrall G, Lane D, Carroll D, Lip GY. Quality of life in patients with atrial fibrillation: a  
2818 systematic review. *Am J Med* 2006;**119**:448 e441-419.
- 2819 33. von Eisenhart Rothe A, Hutt F, Baumert J, Breithardt G, Goette A, Kirchhof P, Ladwig KH.  
2820 Depressed mood amplifies heart-related symptoms in persistent and paroxysmal atrial fibrillation  
2821 patients: a longitudinal analysis - data from the German Competence Network on Atrial Fibrillation.  
2822 *Europace* 2015;**17**:1354-1362.
- 2823 34. Steinberg BA, Kim S, Fonarow GC, Thomas L, Ansell J, Kowey PR, Mahaffey KW, Gersh BJ,  
2824 Hylek E, Naccarelli G, Go AS, Reiffel J, Chang P, Peterson ED, Piccini JP. Drivers of hospitalization  
2825 for patients with atrial fibrillation: Results from the Outcomes Registry for Better Informed Treatment of  
2826 Atrial Fibrillation (ORBIT-AF). *Am Heart J* 2014;**167**:735-742 e732.
- 2827 35. Kirchhof P, Schmalowsky J, Pittrow D, Rosin L, Kirch W, Wegscheider K, Meinertz T.  
2828 Management of patients with atrial fibrillation by primary care physicians in Germany: 1-year results of  
2829 the ATRIUM registry. *Clin Cardiol* 2014;**37**:277-284.
- 2830 36. Stewart S, Murphy N, Walker A, McGuire A, McMurray JJV. Cost of an emerging epidemic:  
2831 an economic analysis of atrial fibrillation in the UK. *Heart* 2004;**90**:286-292.
- 2832 37. Kim MH, Johnston SS, Chu BC, Dalal MR, Schulman KL. Estimation of total incremental  
2833 health care costs in patients with atrial fibrillation in the United States. *Circ Cardiovasc Qual*  
2834 *Outcomes* 2011;**4**:313-320.
- 2835 38. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in  
2836 patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;**146**:857-867.

- 2837 39. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm  
2838 AJ, Weitz JI, Lewis BS, Parkhomenko A, Yamashita T, Antman EM. Comparison of the efficacy and  
2839 safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of  
2840 randomised trials. *Lancet* 2014;**383**:955-962.
- 2841 40. Kirchhof P, Breithardt G, Camm AJ, Crijns HJ, Kuck KH, Vardas P, Wegscheider K. Improving  
2842 outcomes in patients with atrial fibrillation: rationale and design of the Early treatment of Atrial  
2843 fibrillation for Stroke prevention Trial. *Am Heart J* 2013;**166**:442-448.
- 2844 41. Al-Khatib SM, Allen LaPointe NM, Chatterjee R, Crowley MJ, Dupre ME, Kong DF, Lopes RD,  
2845 Povsic TJ, Raju SS, Shah B, Kosinski AS, McBroom AJ, Sanders GD. Rate- and rhythm-control  
2846 therapies in patients with atrial fibrillation: a systematic review. *Ann Intern Med* 2014;**160**:760-773.
- 2847 42. Lip GY, Laroche C, Ioachim PM, Rasmussen LH, Vitali-Serdoz L, Petrescu L, Darabantiu D,  
2848 Crijns HJ, Kirchhof P, Vardas P, Tavazzi L, Maggioni AP, Boriani G. Prognosis and treatment of atrial  
2849 fibrillation patients by European cardiologists: one year follow-up of the EURObservational Research  
2850 Programme-Atrial Fibrillation General Registry Pilot Phase (EORP-AF Pilot registry). *Eur Heart J*  
2851 2014;**35**:3365-3376.
- 2852 43. Marijon E, Le Heuzey JY, Connolly S, Yang S, Pogue J, Brueckmann M, Eikelboom J,  
2853 Themeles E, Ezekowitz M, Wallentin L, Yusuf S, RE-LY Investigators. Causes of death and  
2854 influencing factors in patients with atrial fibrillation: a competing-risk analysis from the randomized  
2855 evaluation of long-term anticoagulant therapy study. *Circulation* 2013;**128**:2192-2201.
- 2856 44. Senoo K, Lip GY, Lane DA, Buller HR, Kotecha D. Residual risk of stroke and death in  
2857 anticoagulated patients according to the type of atrial fibrillation: AMADEUS Trial. *Stroke*  
2858 2015;**46**:2523-2528.
- 2859 45. Soliman EZ, Safford MM, Muntner P, Khodneva Y, Dawood FZ, Zakai NA, Thacker EL, Judd  
2860 S, Howard VJ, Howard G, Herrington DM, Cushman M. Atrial fibrillation and the risk of myocardial  
2861 infarction. *JAMA Intern Med* 2014;**174**:107-114.
- 2862 46. Emdin CA, Wong CX, Hsiao AJ, Altman DG, Peters SA, Woodward M, Odutayo AA. Atrial  
2863 fibrillation as risk factor for cardiovascular disease and death in women compared with men:  
2864 systematic review and meta-analysis of cohort studies. *BMJ* 2016;**532**:h7013.
- 2865 47. Ko D, Rahman F, Schnabel RB, Yin X, Benjamin EJ, Christophersen IE. Atrial fibrillation in  
2866 women: epidemiology, pathophysiology, presentation, and prognosis. *Nat Rev Cardiol* 2016:[Epub  
2867 ahead of print].
- 2868 48. Andersson T, Magnuson A, Bryngelsson IL, Frobert O, Henriksson KM, Edvardsson N, Poci  
2869 D. Gender-related differences in risk of cardiovascular morbidity and all-cause mortality in patients  
2870 hospitalized with incident atrial fibrillation without concomitant diseases: A nationwide cohort study of  
2871 9519 patients. *Int J Cardiol* 2014;**177**:91-99.
- 2872 49. Fang MC, Singer DE, Chang Y, Hylek EM, Henault LE, Jensvold NG, Go AS. Gender  
2873 differences in the risk of ischemic stroke and peripheral embolism in atrial fibrillation: the  
2874 AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) study. *Circulation* 2005;**112**:1687-1691.
- 2875 50. Panchoy SB, Sharma PS, Panchoy DS, Patel TM, Callans DJ, Marchlinski FE. Meta-analysis  
2876 of gender differences in residual stroke risk and major bleeding in patients with nonvalvular atrial  
2877 fibrillation treated with oral anticoagulants. *Am J Cardiol* 2014;**113**:485-490.
- 2878 51. Potpara TS, Marinkovic JM, Polovina MM, Stankovic GR, Seferovic PM, Ostojic MC, Lip GY.  
2879 Gender-related differences in presentation, treatment and long-term outcome in patients with first-  
2880 diagnosed atrial fibrillation and structurally normal heart: the Belgrade atrial fibrillation study. *Int J*  
2881 *Cardiol* 2012;**161**:39-44.
- 2882 52. Ball J, Carrington MJ, Wood KA, Stewart S, SAFETY Investigators. Women versus men with  
2883 chronic atrial fibrillation: insights from the Standard versus Atrial Fibrillation spEcific managemenT  
2884 studY (SAFETY). *PLoS One* 2013;**8**:e65795.
- 2885 53. Hughes M, Lip GY. Risk factors for anticoagulation-related bleeding complications in patients  
2886 with atrial fibrillation: a systematic review. *Qjm* 2007;**100**:599-607.
- 2887 54. Roten L, Rimoldi SF, Schwick N, Sakata T, Heimgartner C, Fuhrer J, Delacretaz E, Tanner H.  
2888 Gender differences in patients referred for atrial fibrillation management to a tertiary center. *Pacing*  
2889 *Clin Electrophysiol* 2009;**32**:622-626.
- 2890 55. Forleo GB, Tondo C, De Luca L, Dello Russo A, Casella M, De Sanctis V, Clementi F,  
2891 Fagundes RL, Leo R, Romeo F, Mantica M. Gender-related differences in catheter ablation of atrial  
2892 fibrillation. *Europace* 2007;**9**:613-620.
- 2893 56. Henry L, Hunt S, Holmes SD, Martin LM, Ad N. Are there gender differences in outcomes  
2894 after the Cox-Maze procedure for atrial fibrillation? *Innovations (Phila)* 2013;**8**:190-198.
- 2895 57. Michelena HI, Powell BD, Brady PA, Friedman PA, Ezekowitz MD. Gender in atrial fibrillation:  
2896 Ten years later. *Gen Med* 2010;**7**:206-217.

- 2897 58. Fox CS, Parise H, D'Agostino RB, Sr., Lloyd-Jones DM, Vasan RS, Wang TJ, Levy D, Wolf  
2898 PA, Benjamin EJ. Parental atrial fibrillation as a risk factor for atrial fibrillation in offspring. *JAMA*  
2899 2004;**291**:2851-2855.
- 2900 59. Oyen N, Ranthe MF, Carstensen L, Boyd HA, Olesen MS, Olesen SP, Wohlfahrt J, Melbye M.  
2901 Familial aggregation of lone atrial fibrillation in young persons. *J Am Coll Cardiol* 2012;**60**:917-921.
- 2902 60. Ellinor PT, Lunetta KL, Albert CM, Glazer NL, Ritchie MD, Smith AV, Arking DE, Muller-  
2903 Nurasyid M, Krijthe BP, Lubitz SA, Bis JC, Chung MK, Dorr M, Ozaki K, Roberts JD, Smith JG,  
2904 Pfeufer A, Sinner MF, Lohman K, Ding J, Smith NL, Smith JD, Rienstra M, Rice KM, Van Wagener  
2905 DR, Magnani JW, Wakili R, Clauss S, Rotter JI, Steinbeck G, Launer LJ, Davies RW, Borkovich M,  
2906 Harris TB, Lin H, Volker U, Volzke H, Milan DJ, Hofman A, Boerwinkle E, Chen LY, Soliman EZ,  
2907 Voight BF, Li G, Chakravarti A, Kubo M, Tedrow UB, Rose LM, Ridker PM, Conen D, Tsunoda T,  
2908 Furukawa T, Sotoodehnia N, Xu S, Kamatani N, Levy D, Nakamura Y, Parvez B, Mahida S, Furie KL,  
2909 Rosand J, Muhammad R, Psaty BM, Meitinger T, Perz S, Wichmann HE, Witteman JC, Kao WH,  
2910 Kathiresan S, Roden DM, Uitterlinden AG, Rivadeneira F, McKnight B, Sjogren M, Newman AB, Liu  
2911 Y, Gollob MH, Melander O, Tanaka T, Stricker BH, Felix SB, Alonso A, Darbar D, Barnard J,  
2912 Chasman DI, Heckbert SR, Benjamin EJ, Gudnason V, Kaab S. Meta-analysis identifies six new  
2913 susceptibility loci for atrial fibrillation. *Nat Genet* 2012;**44**:670-675.
- 2914 61. Olesen MS, Nielsen MW, Haunso S, Svendsen JH. Atrial fibrillation: the role of common and  
2915 rare genetic variants. *Eur J Hum Genet* 2014;**22**:297-306.
- 2916 62. Sinner MF, Tucker NR, Lunetta KL, Ozaki K, Smith JG, Trompet S, Bis JC, Lin H, Chung MK,  
2917 Nielsen JB, Lubitz SA, Krijthe BP, Magnani JW, Ye J, Gollob MH, Tsunoda T, Muller-Nurasyid M,  
2918 Lichtner P, Peters A, Dolmatova E, Kubo M, Smith JD, Psaty BM, Smith NL, Jukema JW, Chasman  
2919 DI, Albert CM, Ebana Y, Furukawa T, Macfarlane PW, Harris TB, Darbar D, Dorr M, Holst AG,  
2920 Svendsen JH, Hofman A, Uitterlinden AG, Gudnason V, Isobe M, Malik R, Dichgans M, Rosand J,  
2921 Van Wagener DR, METASTROKE Consortium, AFGen Consortium, Benjamin EJ, Milan DJ, Melander  
2922 O, Heckbert SR, Ford I, Liu Y, Barnard J, Olesen MS, Stricker BH, Tanaka T, Kaab S, Ellinor PT.  
2923 Integrating genetic, transcriptional, and functional analyses to identify 5 novel genes for atrial  
2924 fibrillation. *Circulation* 2014;**130**:1225-1235.
- 2925 63. Gudbjartsson DF, Arnar DO, Helgadóttir A, Gretarsdóttir S, Holm H, Sigurdsson A,  
2926 Jonasdóttir A, Baker A, Thorleifsson G, Kristjansson K, Pálsson A, Blondal T, Sulem P, Backman VM,  
2927 Hardarson GA, Palsdóttir E, Helgason A, Sigurjonsdóttir R, Sverrisson JT, Kostulas K, Ng MC, Baum  
2928 L, So WY, Wong KS, Chan JC, Furie KL, Greenberg SM, Sale M, Kelly P, MacRae CA, Smith EE,  
2929 Rosand J, Hillert J, Ma RC, Ellinor PT, Thorgeirsson G, Gulcher JR, Kong A, Thorsteinsdóttir U,  
2930 Stefansson K. Variants conferring risk of atrial fibrillation on chromosome 4q25. *Nature* 2007;**448**:353-  
2931 357.
- 2932 64. Lubitz SA, Lunetta KL, Lin H, Arking DE, Trompet S, Li G, Krijthe BP, Chasman DI, Barnard J,  
2933 Kleber ME, Dorr M, Ozaki K, Smith AV, Muller-Nurasyid M, Walter S, Agarwal SK, Bis JC, Brody JA,  
2934 Chen LY, Everett BM, Ford I, Franco OH, Harris TB, Hofman A, Kaab S, Mahida S, Kathiresan S,  
2935 Kubo M, Launer LJ, Macfarlane PW, Magnani JW, McKnight B, McManus DD, Peters A, Psaty BM,  
2936 Rose LM, Rotter JI, Silbernagel G, Smith JD, Sotoodehnia N, Stott DJ, Taylor KD, Tomaschitz A,  
2937 Tsunoda T, Uitterlinden AG, Van Wagener DR, Volker U, Volzke H, Murabito JM, Sinner MF,  
2938 Gudnason V, Felix SB, Marz W, Chung M, Albert CM, Stricker BH, Tanaka T, Heckbert SR, Jukema  
2939 JW, Alonso A, Benjamin EJ, Ellinor PT. Novel genetic markers associate with atrial fibrillation risk in  
2940 Europeans and Japanese. *J Am Coll Cardiol* 2014;**63**:1200-1210.
- 2941 65. Lemmens R, Buysschaert I, Geelen V, Fernandez-Cadenas I, Montaner J, Schmidt H,  
2942 Schmidt R, Attia J, Maguire J, Levi C, Jood K, Blomstrand C, Jern C, Wnuk M, Slowik A, Lambrechts  
2943 D, Thijs V, International Stroke Genetics Consortium. The association of the 4q25 susceptibility  
2944 variant for atrial fibrillation with stroke is limited to stroke of cardioembolic etiology. *Stroke*  
2945 2010;**41**:1850-1857.
- 2946 66. Tada H, Shiffman D, Smith JG, Sjogren M, Lubitz SA, Ellinor PT, Louie JZ, Catanese JJ,  
2947 Engstrom G, Devlin JJ, Kathiresan S, Melander O. Twelve-single nucleotide polymorphism genetic  
2948 risk score identifies individuals at increased risk for future atrial fibrillation and stroke. *Stroke*  
2949 2014;**45**:2856-2862.
- 2950 67. Wang J, Klysis E, Sood S, Johnson RL, Wehrens XH, Martin JF. Pitx2 prevents susceptibility  
2951 to atrial arrhythmias by inhibiting left-sided pacemaker specification. *Proc Natl Acad Sci U S A*  
2952 2010;**107**:9753-9758.
- 2953 68. Franco D, Chinchilla A, Daimi H, Dominguez JN, Aranega A. Modulation of conductive  
2954 elements by Pitx2 and their impact on atrial arrhythmogenesis. *Cardiovasc Res* 2011;**91**:223-231.
- 2955 69. Kirchhof P, Kahr PC, Kaese S, Piccini I, Vokshi I, Scheld HH, Rotering H, Fortmueller L,  
2956 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, Heidebuchel 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, Heidebuchel  
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. Venticlef 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-fibrokinases. *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.

- 3017 86. Spach MS, Josephson ME. Initiating reentry: the role of nonuniform anisotropy in small  
3018 circuits. *J Cardiovasc Electrophysiol* 1994;**5**:182-209.
- 3019 87. Shinagawa K, Shi YF, Tardif JC, Leung TK, Nattel S. Dynamic nature of atrial fibrillation  
3020 substrate during development and reversal of heart failure in dogs. *Circulation* 2002;**105**:2672-2678.
- 3021 88. Lim HS, Willoughby SR, Schultz C, Gan C, Alasady M, Lau DH, Leong DP, Brooks AG,  
3022 Young GD, Kistler PM, Kalman JM, Worthley MI, Sanders P. Effect of atrial fibrillation on atrial  
3023 thrombogenesis in humans: impact of rate and rhythm. *J Am Coll Cardiol* 2013;**61**:852-860.
- 3024 89. Hijazi Z, Oldgren J, Siegbahn A, Granger CB, Wallentin L. Biomarkers in atrial fibrillation: a  
3025 clinical review. *Eur Heart J* 2013;**34**:1475-1480.
- 3026 90. Xu J, Cui G, Esmailian F, Plunkett M, Marelli D, Ardehali A, Odim J, Laks H, Sen L. Atrial  
3027 extracellular matrix remodeling and the maintenance of atrial fibrillation. *Circulation* 2004;**109**:363-  
3028 368.
- 3029 91. Gramley F, Lorenzen J, Plisiene J, Rakauskas M, Benetis R, Schmid M, Autschbach R,  
3030 Knackstedt C, Schimpf T, Mischke K, Gressner A, Hanrath P, Kelm M, Schauerte P. Decreased  
3031 plasminogen activator inhibitor and tissue metalloproteinase inhibitor expression may promote  
3032 increased metalloproteinase activity with increasing duration of human atrial fibrillation. *J Cardiovasc*  
3033 *Electrophysiol* 2007;**18**:1076-1082.
- 3034 92. Hatem SN, Sanders P. Epicardial adipose tissue and atrial fibrillation. *Cardiovasc Res*  
3035 2014;**102**:205-213.
- 3036 93. Leone O, Boriani G, Chiappini B, Pacini D, Cenacchi G, Martin Suarez S, Rapezzi C, Bacchi  
3037 Reggiani ML, Marinelli G. Amyloid deposition as a cause of atrial remodelling in persistent valvular  
3038 atrial fibrillation. *Eur Heart J* 2004;**25**:1237-1241.
- 3039 94. Dobrev D, Friedrich A, Voigt N, Jost N, Wettwer E, Christ T, Knaut M, Ravens U. The G  
3040 protein-gated potassium current I(K,ACh) is constitutively active in patients with chronic atrial  
3041 fibrillation. *Circulation* 2005;**112**:3697-3706.
- 3042 95. Van Wagoner DR, Pond AL, Lamorgese M, Rossie SS, McCarthy PM, Nerbonne JM. Atrial L-  
3043 type Ca<sup>2+</sup> currents and human atrial fibrillation. *Circ Res* 1999;**85**:428-436.
- 3044 96. Schotten U, Verheule S, Kirchhof P, Goette A. Pathophysiological mechanisms of atrial  
3045 fibrillation: a translational appraisal. *Physiol Rev* 2011;**91**:265-325.
- 3046 97. Voigt N, Heijman J, Wang Q, Chiang DY, Li N, Karck M, Wehrens XH, Nattel S, Dobrev D.  
3047 Cellular and molecular mechanisms of atrial arrhythmogenesis in patients with paroxysmal atrial  
3048 fibrillation. *Circulation* 2014;**129**:145-156.
- 3049 98. Voigt N, Li N, Wang Q, Wang W, Trafford AW, Abu-Taha I, Sun Q, Wieland T, Ravens U,  
3050 Nattel S, Wehrens XH, Dobrev D. Enhanced sarcoplasmic reticulum Ca<sup>2+</sup> leak and increased Na<sup>+</sup>-  
3051 Ca<sup>2+</sup> exchanger function underlie delayed afterdepolarizations in patients with chronic atrial  
3052 fibrillation. *Circulation* 2012;**125**:2059-2070.
- 3053 99. Polontchouk L, Haefliger JA, Ebelt B, Schaefer T, Stuhlmann D, Mehlhorn U, Kuhn-Regnier F,  
3054 De Vivie ER, Dhein S. Effects of chronic atrial fibrillation on gap junction distribution in human and rat  
3055 atria. *J Am Coll Cardiol* 2001;**38**:883-891.
- 3056 100. Aime-Sempe C, Folliguet T, Rucker-Martin C, Krajewska M, Krajewska S, Heimburger M,  
3057 Aubier M, Mercadier JJ, Reed JC, Hatem SN. Myocardial cell death in fibrillating and dilated human  
3058 right atria. *J Am Coll Cardiol* 1999;**34**:1577-1586.
- 3059 101. Spach MS, Heidlage JF, Barr RC, Dolber PC. Cell size and communication: role in structural  
3060 and electrical development and remodeling of the heart. *Heart Rhythm* 2004;**1**:500-515.
- 3061 102. Skolidis EI, Hamilos MI, Karalis IK, Chlouverakis G, Kochiadakis GE, Vardas PE. Isolated  
3062 atrial microvascular dysfunction in patients with lone recurrent atrial fibrillation. *J Am Coll Cardiol*  
3063 2008;**51**:2053-2057.
- 3064 103. Barretto AC, Mady C, Nussbacher A, Ianni BM, Oliveira SA, Jatene A, Ramires JA. Atrial  
3065 fibrillation in endomyocardial fibrosis is a marker of worse prognosis. *Int J Cardiol* 1998;**67**:19-25.
- 3066 104. Levy S. Factors predisposing to the development of atrial fibrillation. *Pacing Clin*  
3067 *Electrophysiol* 1997;**20**:2670-2674.
- 3068 105. Chen PS, Chen LS, Fishbein MC, Lin SF, Nattel S. Role of the autonomic nervous system in  
3069 atrial fibrillation: pathophysiology and therapy. *Circ Res* 2014;**114**:1500-1515.
- 3070 106. Christ T, Rozmaritsa N, Engel A, Berk E, Knaut M, Metzner K, Canteras M, Ravens U,  
3071 Kaumann A. Arrhythmias, elicited by catecholamines and serotonin, vanish in human chronic atrial  
3072 fibrillation. *Proc Natl Acad Sci U S A* 2014;**111**:11193-11198.
- 3073 107. Greiser M, Kerfant BG, Williams GS, Voigt N, Harks E, Dibb KM, Giese A, Meszaros J,  
3074 Verheule S, Ravens U, Allessie MA, Gammie JS, van der Velden J, Lederer WJ, Dobrev D, Schotten  
3075 U. Tachycardia-induced silencing of subcellular Ca<sup>2+</sup> signaling in atrial myocytes. *J Clin Invest*  
3076 2014;**124**:4759-4772.

- 3077 108. Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le  
3078 Mouroux A, Le Metayer P, Clementy J. Spontaneous initiation of atrial fibrillation by ectopic beats  
3079 originating in the pulmonary veins. *N Engl J Med* 1998;**339**:659-666.
- 3080 109. Patterson E, Jackman WM, Beckman KJ, Lazzara R, Lockwood D, Scherlag BJ, Wu R, Po S.  
3081 Spontaneous pulmonary vein firing in man: relationship to tachycardia-pause early  
3082 afterdepolarizations and triggered arrhythmia in canine pulmonary veins in vitro. *J Cardiovasc*  
3083 *Electrophysiol* 2007;**18**:1067-1075.
- 3084 110. Ateniya F, Almendral J, Moreno J, Vaidyanathan R, Talkachou A, Kalifa J, Arenal A,  
3085 Villacastin JP, Torrecilla EG, Sanchez A, Ploutz-Snyder R, Jalife J, Berenfeld O. Activation of inward  
3086 rectifier potassium channels accelerates atrial fibrillation in humans: evidence for a reentrant  
3087 mechanism. *Circulation* 2006;**114**:2434-2442.
- 3088 111. Mandapati R, Skanes A, Chen J, Berenfeld O, Jalife J. Stable microreentrant sources as a  
3089 mechanism of atrial fibrillation in the isolated sheep heart. *Circulation* 2000;**101**:194-199.
- 3090 112. Sahadevan J, Ryu K, Peltz L, Khrestian CM, Stewart RW, Markowitz AH, Waldo AL.  
3091 Epicardial mapping of chronic atrial fibrillation in patients: preliminary observations. *Circulation*  
3092 2004;**110**:3293-3299.
- 3093 113. Sanders P, Nalliah CJ, Dubois R, Takahashi Y, Hocini M, Rotter M, Rostock T, Sacher F, Hsu  
3094 LF, Jonsson A, O'Neill MD, Jais P, Haissaguerre M. Frequency mapping of the pulmonary veins in  
3095 paroxysmal versus permanent atrial fibrillation. *J Cardiovasc Electrophysiol* 2006;**17**:965-972.
- 3096 114. Moe GK, Abildskov JA. Atrial fibrillation as a self-sustaining arrhythmia independent of focal  
3097 discharge. *Am Heart J* 1959;**58**:59-70.
- 3098 115. Cox JL, Canavan TE, Schuessler RB, Cain ME, Lindsay BD, Stone C, Smith PK, Corr PB,  
3099 Boineau JP. The surgical treatment of atrial fibrillation. II. Intraoperative electrophysiologic mapping  
3100 and description of the electrophysiologic basis of atrial flutter and atrial fibrillation. *J Thorac*  
3101 *Cardiovasc Surg* 1991;**101**:406-426.
- 3102 116. Narayan SM, Krummen DE, Shivkumar K, Clopton P, Rappel WJ, Miller JM. Treatment of  
3103 atrial fibrillation by the ablation of localized sources: CONFIRM (Conventional Ablation for Atrial  
3104 Fibrillation With or Without Focal Impulse and Rotor Modulation) trial. *J Am Coll Cardiol* 2012;**60**:628-  
3105 636.
- 3106 117. Haissaguerre M, Hocini M, Denis A, Shah AJ, Komatsu Y, Yamashita S, Daly M, Amraoui S,  
3107 Zellerhoff S, Picat MQ, Quotb A, Jesel L, Lim H, Ploux S, Bordachar P, Attuel G, Meillet V, Ritter P,  
3108 Derval N, Sacher F, Bernus O, Cochet H, Jais P, Dubois R. Driver domains in persistent atrial  
3109 fibrillation. *Circulation* 2014;**130**:530-538.
- 3110 118. Fetsch T, Bauer P, Engberding R, Koch HP, Luki J, Meinertz T, Oeff M, Seipel L, Trappe HJ,  
3111 Treese N, Breithardt G. Prevention of atrial fibrillation after cardioversion: results of the PAFAC trial.  
3112 *Eur Heart J* 2004;**25**:1385-1394.
- 3113 119. Hindricks G, Piorkowski C, Tanner H, Kobza R, Gerds-Li JH, Carbucicchio C, Kottkamp H.  
3114 Perception of atrial fibrillation before and after radiofrequency catheter ablation: relevance of  
3115 asymptomatic arrhythmia recurrence. *Circulation* 2005;**112**:307-313.
- 3116 120. Kirchhof P, Bax J, Blomstrom-Lundquist C, Calkins H, Camm AJ, Cappato R, Cosio F, Crijns  
3117 H, Diener HC, Goette A, Israel CW, Kuck KH, Lip GY, Nattel S, Page RL, Ravens U, Schotten U,  
3118 Steinbeck G, Vardas P, Waldo A, Wegscheider K, Willems S, Breithardt G. Early and comprehensive  
3119 management of atrial fibrillation: executive summary of the proceedings from the 2nd AFNET-EHRA  
3120 consensus conference 'research perspectives in AF'. *Eur Heart J* 2009;**30**:2969-2977c.
- 3121 121. Xiong Q, Proietti M, Senoo K, Lip GY. Asymptomatic versus symptomatic atrial fibrillation: A  
3122 systematic review of age/gender differences and cardiovascular outcomes. *Int J Cardiol*  
3123 2015;**191**:172-177.
- 3124 122. Savelieva I, Camm AJ. Clinical relevance of silent atrial fibrillation: prevalence, prognosis,  
3125 quality of life, and management. *J Interv Card Electrophysiol* 2000;**4**:369-382.
- 3126 123. Friberg L, Hammar N, Rosenqvist M. Stroke in paroxysmal atrial fibrillation: report from the  
3127 Stockholm Cohort of Atrial Fibrillation. *Eur Heart J* 2010;**31**:967-975.
- 3128 124. Vanassche T, Lauw MN, Eikelboom JW, Healey JS, Hart RG, Alings M, Avezum A, Diaz R,  
3129 Hohnloser SH, Lewis BS, Shestakovska O, Wang J, Connolly SJ. Risk of ischaemic stroke according  
3130 to pattern of atrial fibrillation: analysis of 6563 aspirin-treated patients in ACTIVE-A and AVERROES.  
3131 *Eur Heart J* 2015;**36**:281-287a.
- 3132 125. Steinberg BA, Hellkamp AS, Lokhnygina Y, Patel MR, Breithardt G, Hankey GJ, Becker RC,  
3133 Singer DE, Halperin JL, Hacke W, Nessel CC, Berkowitz SD, Mahaffey KW, Fox KA, Califf RM,  
3134 Piccini JP. Higher risk of death and stroke in patients with persistent vs. paroxysmal atrial fibrillation:  
3135 results from the ROCKET-AF Trial. *Eur Heart J* 2015;**36**:288-296.

- 3136 126. Fitzmaurice DA, Hobbs FD, Jowett S, Mant J, Murray ET, Holder R, Raftery JP, Bryan S,  
3137 Davies M, Lip GY, Allan TF. Screening versus routine practice in detection of atrial fibrillation in  
3138 patients aged 65 or over: cluster randomised controlled trial. *BMJ* 2007;**335**:383.
- 3139 127. Rizos T, Guntner J, Jenetzky E, Marquardt L, Reichardt C, Becker R, Reinhardt R, Hepp T,  
3140 Kirchhof P, Aleychnichenko E, Ringleb P, Hacke W, Veltkamp R. Continuous stroke unit  
3141 electrocardiographic monitoring versus 24-hour Holter electrocardiography for detection of  
3142 paroxysmal atrial fibrillation after stroke. *Stroke* 2012;**43**:2689-2694.
- 3143 128. Gladstone DJ, Spring M, Dorian P, Panzov V, Thorpe KE, Hall J, Vaid H, O'Donnell M,  
3144 Laupacis A, Cote R, Sharma M, Blakely JA, Shuaib A, Hachinski V, Coutts SB, Sahlas DJ, Teal P, Yip  
3145 S, Spence JD, Buck B, Verreault S, Casaubon LK, Penn A, Selchen D, Jin A, Howse D, Mehdiratna M,  
3146 Boyle K, Aviv R, Kapral MK, Mamdani M, EMBRACE Investigators and Coordinators. Atrial fibrillation  
3147 in patients with cryptogenic stroke. *N Engl J Med* 2014;**370**:2467-2477.
- 3148 129. Friberg L, Engdahl J, Frykman V, Svennberg E, Levin LA, Rosenqvist M. Population  
3149 screening of 75- and 76-year-old men and women for silent atrial fibrillation (STROKESTOP).  
3150 *Europace* 2013;**15**:135-140.
- 3151 130. Davis RC, Hobbs FD, Kenkre JE, Roalfe AK, Iles R, Lip GY, Davies MK. Prevalence of atrial  
3152 fibrillation in the general population and in high-risk groups: the ECHOES study. *Europace*  
3153 2012;**14**:1553-1559.
- 3154 131. Hobbs FD, Fitzmaurice DA, Mant J, Murray E, Jowett S, Bryan S, Raftery J, Davies M, Lip G.  
3155 A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total  
3156 population screening) versus routine practice for the detection of atrial fibrillation in people aged 65  
3157 and over. The SAFE study. *Health Technol Assess* 2005;**9**:iii-iv, ix-x, 1-74.
- 3158 132. Aronsson M, Svennberg E, Rosenqvist M, Engdahl J, Al-Khalili F, Friberg L, Frykman-Kull V,  
3159 Levin LA. Cost-effectiveness of mass screening for untreated atrial fibrillation using intermittent ECG  
3160 recording. *Europace* 2015;**17**:1023-1029.
- 3161 133. Levin LA, Husberg M, Sobocinski PD, Kull VF, Friberg L, Rosenqvist M, Davidson T. A cost-  
3162 effectiveness analysis of screening for silent atrial fibrillation after ischaemic stroke. *Europace*  
3163 2015;**17**:207-214.
- 3164 134. Lowres N, Neubeck L, Redfern J, Freedman SB. Screening to identify unknown atrial  
3165 fibrillation. A systematic review. *Thromb Haemost* 2013;**110**:213-222.
- 3166 135. Engdahl J, Andersson L, Mirskaya M, Rosenqvist M. Stepwise screening of atrial fibrillation in  
3167 a 75-year-old population: implications for stroke prevention. *Circulation* 2013;**127**:930-937.
- 3168 136. Kaleschke G, Hoffmann B, Drewitz I, Steinbeck G, Naebauer M, Goette A, Breithardt G,  
3169 Kirchhof P. Prospective, multicentre validation of a simple, patient-operated electrocardiographic  
3170 system for the detection of arrhythmias and electrocardiographic changes. *Europace* 2009;**11**:1362-  
3171 1368.
- 3172 137. Tieleman RG, Plantinga Y, Rinkes D, Bartels GL, Posma JL, Cator R, Hofman C, Houben RP.  
3173 Validation and clinical use of a novel diagnostic device for screening of atrial fibrillation. *Europace*  
3174 2014;**16**:1291-1295.
- 3175 138. Barrett PM, Komatireddy R, Haaser S, Topol S, Sheard J, Encinas J, Fought AJ, Topol EJ.  
3176 Comparison of 24-hour Holter monitoring with 14-day novel adhesive patch electrocardiographic  
3177 monitoring. *Am J Med* 2014;**127**:95 e11-97.
- 3178 139. Lowres N, Neubeck L, Salkeld G, Krass I, McLachlan AJ, Redfern J, Bennett AA, Briffa T,  
3179 Bauman A, Martinez C, Wallenhorst C, Lau JK, Brieger DB, Sy RW, Freedman SB. Feasibility and  
3180 cost-effectiveness of stroke prevention through community screening for atrial fibrillation using iPhone  
3181 ECG in pharmacies. The SEARCH-AF study. *Thromb Haemost* 2014;**111**:1167-1176.
- 3182 140. Quinn FR, Gladstone D. Screening for undiagnosed atrial fibrillation in the community. *Curr*  
3183 *Opin Cardiol* 2014;**29**:28-35.
- 3184 141. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, Lau CP, Fain E,  
3185 Yang S, Bailleul C, Morillo CA, Carlson M, Themeles E, Kaufman ES, Hohnloser SH, ASSERT  
3186 Investigators. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med* 2012;**366**:120-129.
- 3187 142. Hindricks G, Pokushalov E, Urban L, Taborisky M, Kuck KH, Lebedev D, Rieger G,  
3188 Purerfellner H. Performance of a new leadless implantable cardiac monitor in detecting and  
3189 quantifying atrial fibrillation - results of the XPECT trial. *Circ Arrhythm Electrophysiol* 2010;**3**:141-147.
- 3190 143. Brambatti M, Connolly SJ, Gold MR, Morillo CA, Capucci A, Muto C, Lau CP, Van Gelder IC,  
3191 Hohnloser SH, Carlson M, Fain E, Nakamya J, Mairesse GH, Halytska M, Deng WQ, Israel CW,  
3192 Healey JS, ASSERT Investigators. Temporal relationship between subclinical atrial fibrillation and  
3193 embolic events. *Circulation* 2014;**129**:2094-2099.
- 3194 144. Boriani G, Glotzer TV, Santini M, West TM, De Melis M, Sepsi M, Gasparini M, Lewalter T,  
3195 Camm JA, Singer DE. Device-detected atrial fibrillation and risk for stroke: an analysis of >10,000

- 3196 patients from the SOS AF project (Stroke preventiOn Strategies based on Atrial Fibrillation  
3197 information from implanted devices). *Eur Heart J* 2014;**35**:508-516.
- 3198 145. Santini M, Gasparini M, Landolina M, Lunati M, Proclemer A, Padeletti L, Catanzariti D, Molon  
3199 G, Botto GL, La Rocca L, Grammatico A, Boriani G. Device-detected atrial tachyarrhythmias predict  
3200 adverse outcome in real-world patients with implantable biventricular defibrillators. *J Am Coll Cardiol*  
3201 2011;**57**:167-172.
- 3202 146. Daoud EG, Glotzer TV, Wyse DG, Ezekowitz MD, Hilker C, Koehler J, Ziegler PD. Temporal  
3203 relationship of atrial tachyarrhythmias, cerebrovascular events, and systemic emboli based on stored  
3204 device data: a subgroup analysis of TRENDS. *Heart Rhythm* 2011;**8**:1416-1423.
- 3205 147. Glotzer TV, Daoud EG, Wyse DG, Singer DE, Ezekowitz MD, Hilker C, Miller C, Qi D, Ziegler  
3206 PD. The relationship between daily atrial tachyarrhythmia burden from implantable device diagnostics  
3207 and stroke risk: the TRENDS study. *Circ Arrhythm Electrophysiol* 2009;**2**:474-480.
- 3208 148. Lamas G. How much atrial fibrillation is too much atrial fibrillation? *N Engl J Med*  
3209 2012;**366**:178-180.
- 3210 149. Kirchhof P, Lip GY, Van Gelder IC, Bax J, Hylek E, Kaab S, Schotten U, Wegscheider K,  
3211 Boriani G, Brandes A, Ezekowitz M, Diener H, Haegeli L, Heidbuchel H, Lane D, Mont L, Willems S,  
3212 Dorian P, Aunes-Jansson M, Blomstrom-Lundqvist C, Borentain M, Breitenstein S, Brueckmann M,  
3213 Cater N, Clemens A, Dobrev D, Dubner S, Edvardsson NG, Friberg L, Goette A, Gulizia M, Hatala R,  
3214 Horwood J, Szumowski L, Kappenberger L, Kautzner J, Leute A, Lobban T, Meyer R, Millerhagen J,  
3215 Morgan J, Muenzel F, Nabauer M, Baertels C, Oeff M, Paar D, Polifka J, Ravens U, Rosin L, Stegink  
3216 W, Steinbeck G, Vardas P, Vincent A, Walter M, Breithardt G, Camm AJ. Comprehensive risk  
3217 reduction in patients with atrial fibrillation: emerging diagnostic and therapeutic options--a report from  
3218 the 3rd Atrial Fibrillation Competence NETwork/European Heart Rhythm Association consensus  
3219 conference. *Europace* 2012;**14**:8-27.
- 3220 150. Kirchhof P, Lip GY, Van Gelder IC, Bax J, Hylek E, Kaab S, Schotten U, Wegscheider K,  
3221 Boriani G, Ezekowitz M, Diener H, Heidbuchel H, Lane D, Mont L, Willems S, Dorian P, Vardas P,  
3222 Breithardt G, Camm AJ. Comprehensive risk reduction in patients with atrial fibrillation: Emerging  
3223 diagnostic and therapeutic options. Executive summary of the report from the 3rd AFNET/EHRA  
3224 consensus conference. *Thromb Haemost* 2011;**106**:1012-1019.
- 3225 151. Sposato LA, Cipriano LE, Saposnik G, Ruiz Vargas E, Riccio PM, Hachinski V. Diagnosis of  
3226 atrial fibrillation after stroke and transient ischaemic attack: a systematic review and meta-analysis.  
3227 *Lancet Neurol* 2015;**14**:377-387.
- 3228 152. Thijs VN, Brachmann J, Morillo CA, Passman RS, Sanna T, Bernstein RA, Diener HC, Di  
3229 Lazzaro V, Rymer MM, Hogge L, Rogers TB, Ziegler PD, Assar MD. Predictors for atrial fibrillation  
3230 detection after cryptogenic stroke: Results from CRYSTAL AF. *Neurology* 2016;**86**:261-269.
- 3231 153. Adams HP, Jr., Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE, 3rd.  
3232 Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial.  
3233 TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993;**24**:35-41.
- 3234 154. Hart RG, Diener HC, Coutts SB, Easton JD, Granger CB, O'Donnell MJ, Sacco RL, Connolly  
3235 SJ, Cryptogenic Stroke/ESUS International Working Group. Embolic strokes of undetermined source:  
3236 the case for a new clinical construct. *Lancet Neurol* 2014;**13**:429-438.
- 3237 155. Mant J, Fitzmaurice DA, Hobbs FD, Jowett S, Murray ET, Holder R, Davies M, Lip GY.  
3238 Accuracy of diagnosing atrial fibrillation on electrocardiogram by primary care practitioners and  
3239 interpretative diagnostic software: analysis of data from screening for atrial fibrillation in the elderly  
3240 (SAFE) trial. *BMJ* 2007;**335**:380.
- 3241 156. Israel CW, Gronefeld G, Ehrlich JR, Li YG, Hohnloser SH. Long-term risk of recurrent atrial  
3242 fibrillation as documented by an implantable monitoring device: implications for optimal patient care. *J*  
3243 *Am Coll Cardiol* 2004;**43**:47-52.
- 3244 157. Svennberg E, Engdahl J, Al-Khalili F, Friberg L, Frykman V, Rosenqvist M. Mass Screening  
3245 for Untreated Atrial Fibrillation: The STROKESTOP Study. *Circulation* 2015;**131**:2176-2184.
- 3246 158. Bun SS, Latcu DG, Marchlinski F, Saudi N. Atrial flutter: more than just one of a kind. *Eur*  
3247 *Heart J* 2015;**36**:2356-2363.
- 3248 159. Granada J, Uribe W, Chyou PH, Maassen K, Vierkant R, Smith PN, Hayes J, Eaker E,  
3249 Vidaillet H. Incidence and predictors of atrial flutter in the general population. *J Am Coll Cardiol*  
3250 2000;**36**:2242-2246.
- 3251 160. Halligan SC, Gersh BJ, Brown RD, Jr., Rosales AG, Munger TM, Shen WK, Hammill SC,  
3252 Friedman PA. The natural history of lone atrial flutter. *Ann Intern Med* 2004;**140**:265-268.
- 3253 161. Jahangir A, Lee V, Friedman PA, Trusty JM, Hodge DO, Kopecky SL, Packer DL, Hammill  
3254 SC, Shen WK, Gersh BJ. Long-term progression and outcomes with aging in patients with lone atrial  
3255 fibrillation: a 30-year follow-up study. *Circulation* 2007;**115**:3050-3056.

- 3256 162. Gillis AM, Rose MS. Temporal patterns of paroxysmal atrial fibrillation following DDDR  
3257 pacemaker implantation. *Am J Cardiol* 2000;**85**:1445-1450.
- 3258 163. Charitos EI, Purefellner H, Glotzer TV, Ziegler PD. Clinical classifications of atrial fibrillation  
3259 poorly reflect its temporal persistence: insights from 1,195 patients continuously monitored with  
3260 implantable devices. *J Am Coll Cardiol* 2014;**63**:2840-2848.
- 3261 164. Banerjee A, Taillandier S, Olesen JB, Lane DA, Lallemand B, Lip GY, Fauchier L. Pattern of  
3262 atrial fibrillation and risk of outcomes: the Loire Valley Atrial Fibrillation Project. *Int J Cardiol*  
3263 2013;**167**:2682-2687.
- 3264 165. Lee G, Sanders P, Kalman JM. Catheter ablation of atrial arrhythmias: state of the art. *Lancet*  
3265 2012;**380**:1509-1519.
- 3266 166. Wyse DG, Van Gelder IC, Ellinor PT, Go AS, Kalman JM, Narayan SM, Nattel S, Schotten U,  
3267 Rienstra M. Lone atrial fibrillation: does it exist? *J Am Coll Cardiol* 2014;**63**:1715-1723.
- 3268 167. Andrade J, Khairy P, Dobrev D, Nattel S. The clinical profile and pathophysiology of atrial  
3269 fibrillation: relationships among clinical features, epidemiology, and mechanisms. *Circ Res*  
3270 2014;**114**:1453-1468.
- 3271 168. Chao TF, Suenari K, Chang SL, Lin YJ, Lo LW, Hu YF, Tuan TC, Tai CT, Tsao HM, Li CH,  
3272 Ueng KC, Wu TJ, Chen SA. Atrial substrate properties and outcome of catheter ablation in patients  
3273 with paroxysmal atrial fibrillation associated with diabetes mellitus or impaired fasting glucose. *Am J*  
3274 *Cardiol* 2010;**106**:1615-1620.
- 3275 169. Albertsen IE, Rasmussen LH, Lane DA, Overvad TF, Skjoth F, Overvad K, Lip GY, Larsen  
3276 TB. The impact of smoking on thromboembolism and mortality in patients with incident atrial  
3277 fibrillation: insights from the Danish Diet, Cancer, and Health study. *Chest* 2014;**145**:559-566.
- 3278 170. Overvad TF, Rasmussen LH, Skjoth F, Overvad K, Albertsen IE, Lane DA, Lip GY, Larsen  
3279 TB. Alcohol intake and prognosis of atrial fibrillation. *Heart* 2013;**99**:1093-1099.
- 3280 171. Daccarett M, Badger TJ, Akoum N, Burgon NS, Mahnkopf C, Vergara G, Kholmovski E,  
3281 McGann CJ, Parker D, Brachmann J, Macleod RS, Marrouche NF. Association of left atrial fibrosis  
3282 detected by delayed-enhancement magnetic resonance imaging and the risk of stroke in patients with  
3283 atrial fibrillation. *J Am Coll Cardiol* 2011;**57**:831-838.
- 3284 172. Neilan TG, Shah RV, Abbasi SA, Farhad H, Groarke JD, Dodson JA, Coelho-Filho O,  
3285 McMullan CJ, Heydari B, Michaud GF, John RM, van der Geest R, Steigner ML, Blankstein R,  
3286 Jerosch-Herold M, Kwong RY. The incidence, pattern, and prognostic value of left ventricular  
3287 myocardial scar by late gadolinium enhancement in patients with atrial fibrillation. *J Am Coll Cardiol*  
3288 2013;**62**:2205-2214.
- 3289 173. Marrouche NF, Wilber D, Hindricks G, Jais P, Akoum N, Marchlinski F, Kholmovski E, Burgon  
3290 N, Hu N, Mont L, Deneke T, Duytschaever M, Neumann T, Mansour M, Mahnkopf C, Herweg B,  
3291 Daoud E, Wissner E, Bansmann P, Brachmann J. Association of atrial tissue fibrosis identified by  
3292 delayed enhancement MRI and atrial fibrillation catheter ablation: the DECAAF study. *JAMA*  
3293 2014;**311**:498-506.
- 3294 174. Bonizzi P, Zeemering S, Karel JM, Di Marco LY, Uldry L, Van Zaen J, Vesin JM, Schotten U.  
3295 Systematic comparison of non-invasive measures for the assessment of atrial fibrillation complexity: a  
3296 step forward towards standardization of atrial fibrillation electrogram analysis. *Europace* 2014.
- 3297 175. Kirchhof P, Breithardt G, Bax J, Benninger G, Blomstrom-Lundqvist C, Boriani G, Brandes A,  
3298 Brown H, Brueckmann M, Calkins H, Calvert M, Christoffels V, Crijns H, Dobrev D, Ellinor P, Fabritz  
3299 L, Fetsch T, Freedman SB, Gerth A, Goette A, Guasch E, Hack G, Haegeli L, Hatem S, Haeusler KG,  
3300 Heidbuchel H, Heinrich-Nols J, Hidden-Lucet F, Hindricks G, Juul-Moller S, Kaab S, Kappenberger L,  
3301 Kespohl S, Kotecha D, Lane DA, Leute A, Lewalter T, Meyer R, Mont L, Munzel F, Nabauer M,  
3302 Nielsen JC, Oeff M, Oldgren J, Oto A, Piccini JP, Pilmeyer A, Potpara T, Ravens U, Reinecke H,  
3303 Rostock T, Rustige J, Savelieva I, Schnabel R, Schotten U, Schwichtenberg L, Sinner MF, Steinbeck  
3304 G, Stoll M, Tavazzi L, Themistoclakis S, Tse HF, Van Gelder IC, Vardas PE, Varpula T, Vincent A,  
3305 Werring D, Willems S, Ziegler A, Lip GY, Camm AJ. A roadmap to improve the quality of atrial  
3306 fibrillation management: proceedings from the fifth Atrial Fibrillation Network/European Heart Rhythm  
3307 Association consensus conference. *Europace* 2016;**18**:37-50.
- 3308 176. Fabritz L, Guasch E, Antoniadou C, Bardinet I, Benninger G, Betts TR, Brand E, Breithardt G,  
3309 Bucklar-Suchankova G, Camm AJ, Cartlidge D, Casadei B, Chua WW, Crijns HJ, Deeks J, Hatem S,  
3310 Hidden-Lucet F, Kaab S, Maniadas N, Martin S, Mont L, Reinecke H, Sinner MF, Schotten U,  
3311 Southwood T, Stoll M, Vardas P, Wakili R, West A, Ziegler A, Kirchhof P. Expert consensus  
3312 document: Defining the major health modifiers causing atrial fibrillation: a roadmap to underpin  
3313 personalized prevention and treatment. *Nat Rev Cardiol* 2016;**13**:230-237.

- 3314 177. Dorian P, Jung W, Newman D, Paquette M, Wood K, Ayers GM, Camm J, Akhtar M, Luderitz  
3315 B. The impairment of health-related quality of life in patients with intermittent atrial fibrillation:  
3316 implications for the assessment of investigational therapy. *J Am Coll Cardiol* 2000;**36**:1303-1309.
- 3317 178. Sears SF, Serber ER, Alvarez LG, Schwartzman DS, Hoyt RH, Ujhelyi MR. Understanding  
3318 atrial symptom reports: objective versus subjective predictors. *Pacing Clin Electrophysiol*  
3319 2005;**28**:801-807.
- 3320 179. Peinado R, Arribas F, Ormaetxe JM, Badia X. Variation in quality of life with type of atrial  
3321 fibrillation. *Rev Esp Cardiol* 2010;**63**:1402-1409.
- 3322 180. Steg PG, Alam S, Chiang CE, Gamra H, Goethals M, Inoue H, Krapf L, Lewalter T, Merioua I,  
3323 Murin J, Naditch-Brule L, Ponikowski P, Rosenqvist M, Silva-Cardoso J, Zharinov O, Brette S, Neill  
3324 JO, RealiseAF investigators. Symptoms, functional status and quality of life in patients with controlled  
3325 and uncontrolled atrial fibrillation: data from the RealiseAF cross-sectional international registry. *Heart*  
3326 2012;**98**:195-201.
- 3327 181. Gronefeld GC, Lilienthal J, Kuck KH, Hohnloser SH, Pharmacological Intervention in Atrial  
3328 Fibrillation (PIAF) Study investigators. Impact of rate versus rhythm control on quality of life in patients  
3329 with persistent atrial fibrillation. Results from a prospective randomized study. *Eur Heart J*  
3330 2003;**24**:1430-1436.
- 3331 182. Pepine CJ. Effects of pharmacologic therapy on health-related quality of life in elderly patients  
3332 with atrial fibrillation: a systematic review of randomized and nonrandomized trials. *Clin Med Insights*  
3333 *Cardiol* 2013;**7**:1-20.
- 3334 183. Hagens VE, Ranchor AV, Van Sonderen E, Bosker HA, Kamp O, Tijssen JG, Kingma JH,  
3335 Crijns HJ, Van Gelder IC, RACE Study Group. Effect of rate or rhythm control on quality of life in  
3336 persistent atrial fibrillation. Results from the Rate Control Versus Electrical Cardioversion (RACE)  
3337 Study. *J Am Coll Cardiol* 2004;**43**:241-247.
- 3338 184. Weerasooriya R, Davis M, Powell A, Szili-Torok T, Shah C, Whalley D, Kanagaratnam L,  
3339 Heddle W, Leitch J, Perks A, Ferguson L, Bulsara M. The Australian intervention randomized control  
3340 of rate in atrial fibrillation trial (AIRCRAFT). *J Am Coll Cardiol* 2003;**41**:1697-1702.
- 3341 185. Jones DG, Haldar SK, Hussain W, Sharma R, Francis DP, Rahman-Haley SL, McDonagh TA,  
3342 Underwood SR, Markides V, Wong T. A randomized trial to assess catheter ablation versus rate  
3343 control in the management of persistent atrial fibrillation in heart failure. *J Am Coll Cardiol*  
3344 2013;**61**:1894-1903.
- 3345 186. Rienstra M, Lubitz SA, Mahida S, Magnani JW, Fontes JD, Sinner MF, Van Gelder IC, Ellinor  
3346 PT, Benjamin EJ. Symptoms and functional status of patients with atrial fibrillation: state of the art and  
3347 future research opportunities. *Circulation* 2012;**125**:2933-2943.
- 3348 187. Arribas F, Ormaetxe JM, Peinado R, Perulero N, Ramirez P, Badia X. Validation of the AF-  
3349 QoL, a disease-specific quality of life questionnaire for patients with atrial fibrillation. *Europace*  
3350 2010;**12**:364-370.
- 3351 188. Spertus J, Dorian P, Bubien R, Lewis S, Godejohn D, Reynolds MR, Lakkireddy DR, Wimmer  
3352 AP, Bhandari A, Burk C. Development and validation of the Atrial Fibrillation Effect on QualiTY-of-Life  
3353 (AFEQT) Questionnaire in patients with atrial fibrillation. *Circ Arrhythm Electrophysiol* 2011;**4**:15-25.
- 3354 189. Dorian P, Burk C, Mullin CM, Bubien R, Godejohn D, Reynolds MR, Lakkireddy DR, Wimmer  
3355 AP, Bhandari A, Spertus J. Interpreting changes in quality of life in atrial fibrillation: How much change  
3356 is meaningful? *Am Heart J* 2013;**166**:381-387.e388.
- 3357 190. Ware JE, Jr., Gandek B. Overview of the SF-36 Health Survey and the International Quality of  
3358 Life Assessment (IQOLA) Project. *J Clin Epidemiol* 1998;**51**:903-912.
- 3359 191. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, Bonnel G, Badia X.  
3360 Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life*  
3361 *Res* 2011;**20**:1727-1736.
- 3362 192. Kirchhof P, Auricchio A, Bax J, Crijns H, Camm J, Diener HC, Goette A, Hindricks G,  
3363 Hohnloser S, Kappenberger L, Kuck KH, Lip GY, Olsson B, Meinertz T, Priori S, Ravens U, Steinbeck  
3364 G, Svernhage E, Tijssen J, Vincent A, Breithardt G. Outcome parameters for trials in atrial fibrillation:  
3365 executive summary. *Eur Heart J* 2007;**28**:2803-2817.
- 3366 193. Dorian P, Cvitkovic SS, Kerr CR, Crystal E, Gillis AM, Guerra PG, Mitchell LB, Roy D, Skanes  
3367 AC, Wyse DG. A novel, simple scale for assessing the symptom severity of atrial fibrillation at the  
3368 bedside: the CCS-SAF scale. *Can J Cardiol* 2006;**22**:383-386.
- 3369 194. Kirchhof P, Ammentorp B, Darius H, De Caterina R, Le Heuzey JY, Schilling RJ, Schmitt J,  
3370 Zamorano JL. Management of atrial fibrillation in seven European countries after the publication of the  
3371 2010 ESC Guidelines on atrial fibrillation: primary results of the PREvention of thromboemolic  
3372 events--European Registry in Atrial Fibrillation (PREFER in AF). *Europace* 2014;**16**:6-14.

- 3373 195. Lip GY, Laroche C, Popescu MI, Rasmussen LH, Vitali-Serdoz L, Dan GA, Kalarus Z, Crijns  
3374 HJ, Oliveira MM, Tavazzi L, Maggioni AP, Boriani G. Improved outcomes with European Society of  
3375 Cardiology guideline-adherent antithrombotic treatment in high-risk patients with atrial fibrillation: a  
3376 report from the EORP-AF General Pilot Registry. *Europace* 2015;**17**:1777-1786.
- 3377 196. Freeman JV, Simon DN, Go AS, Spertus J, Fonarow GC, Gersh BJ, Hylek EM, Kowey PR,  
3378 Mahaffey KW, Thomas LE, Chang P, Peterson ED, Piccini JP, Outcomes Registry for Better Informed  
3379 Treatment of Atrial Fibrillation (ORBIT-AF) Investigators and Patients. Association Between Atrial  
3380 Fibrillation Symptoms, Quality of Life, and Patient Outcomes: Results From the Outcomes Registry for  
3381 Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *Circ Cardiovasc Qual Outcomes*  
3382 2015;**8**:393-402.
- 3383 197. Boriani G, Laroche C, Diemberger I, Fantecchi E, Popescu MI, Rasmussen LH, Sinagra G,  
3384 Petrescu L, Tavazzi L, Maggioni AP, Lip GY. Asymptomatic atrial fibrillation: clinical correlates,  
3385 management, and outcomes in the EORP-AF Pilot General Registry. *Am J Med* 2015;**128**:509-518  
3386 e502.
- 3387 198. Szymanski FM, Filipiak KJ, Karpinski G, Platek AE, Opolski G. Occurrence of poor sleep  
3388 quality in atrial fibrillation patients according to the EHRA score. *Acta Cardiol* 2014;**69**:291-296.
- 3389 199. Wynn GJ, Todd DM, Webber M, Bonnett L, McShane J, Kirchhof P, Gupta D. The European  
3390 Heart Rhythm Association symptom classification for atrial fibrillation: validation and improvement  
3391 through a simple modification. *Europace* 2014;**16**:965-972.
- 3392 200. Meinertz T, Kirch W, Rosin L, Pittrow D, Willich SN, Kirchhof P, ATRIUM investigators.  
3393 Management of atrial fibrillation by primary care physicians in Germany: baseline results of the  
3394 ATRIUM registry. *Clin Res Cardiol* 2011;**100**:897-905.
- 3395 201. Nabauer M, Gerth A, Limbourg T, Schneider S, Oeff M, Kirchhof P, Goette A, Lewalter T,  
3396 Ravens U, Meinertz T, Breithardt G, Steinbeck G. The Registry of the German Competence NETwork  
3397 on Atrial Fibrillation: Patient characteristics and initial management. *Europace* 2009;**11**:423-434.
- 3398 202. von Eisenhart Rothe AF, Goette A, Kirchhof P, Breithardt G, Limbourg T, Calvert M, Baumert  
3399 J, Ladwig KH. Depression in paroxysmal and persistent atrial fibrillation patients: a cross-sectional  
3400 comparison of patients enrolled in two large clinical trials. *Europace* 2014;**16**:812-819.
- 3401 203. Pathak RK, Middeldorp ME, Lau DH, Mehta AB, Mahajan R, Twomey D, Alasady M, Hanley  
3402 L, Antic NA, McEvoy RD, Kalman JM, Abhayaratna WP, Sanders P. Aggressive risk factor reduction  
3403 study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. *J*  
3404 *Am Coll Cardiol* 2014;**64**:2222-2231.
- 3405 204. Abed HS, Wittert GA, Leong DP, Shirazi MG, Bahrami B, Middeldorp ME, Lorimer MF, Lau  
3406 DH, Antic NA, Brooks AG, Abhayaratna WP, Kalman JM, Sanders P. Effect of weight reduction and  
3407 cardiometabolic risk factor management on symptom burden and severity in patients with atrial  
3408 fibrillation: a randomized clinical trial. *JAMA* 2013;**310**:2050-2060.
- 3409 205. Psaty BM, Manolio TA, Kuller LH, Kronmal RA, Cushman M, Fried LP, White R, Furberg CD,  
3410 Rautaharju PM. Incidence of and risk factors for atrial fibrillation in older adults. *Circulation*  
3411 1997;**96**:2455-2461.
- 3412 206. Selmer C, Olesen JB, Hansen ML, Lindhardsen J, Olsen AM, Madsen JC, Faber J, Hansen  
3413 PR, Pedersen OD, Torp-Pedersen C, Gislason GH. The spectrum of thyroid disease and risk of new  
3414 onset atrial fibrillation: a large population cohort study. *BMJ* 2012;**345**:e7895.
- 3415 207. Kim EJ, Lyass A, Wang N, Massaro JM, Fox CS, Benjamin EJ, Magnani JW. Relation of  
3416 hypothyroidism and incident atrial fibrillation (from the Framingham Heart Study). *Am Heart J*  
3417 2014;**167**:123-126.
- 3418 208. Vermond RA, Geelhoed B, Verweij N, Tieleman RG, Van der Harst P, Hillege HL, Van Gilst  
3419 WH, Van Gelder IC, Rienstra M. Incidence of atrial fibrillation and relationship with cardiovascular  
3420 events, heart failure, and mortality: A community-based study from the netherlands. *J Am Coll Cardiol*  
3421 2015;**66**:1000-1007.
- 3422 209. Buch P, Friberg J, Scharling H, Lange P, Prescott E. Reduced lung function and risk of atrial  
3423 fibrillation in the Copenhagen City Heart Study. *Eur Respir J* 2003;**21**:1012-1016.
- 3424 210. Gami AS, Hodge DO, Herges RM, Olson EJ, Nykodym J, Kara T, Somers VK. Obstructive  
3425 sleep apnea, obesity, and the risk of incident atrial fibrillation. *J Am Coll Cardiol* 2007;**49**:565-571.
- 3426 211. Baber U, Howard VJ, Halperin JL, Soliman EZ, Zhang X, McClellan W, Warnock DG, Muntner  
3427 P. Association of chronic kidney disease with atrial fibrillation among adults in the United States:  
3428 REasons for Geographic and Racial Differences in Stroke (REGARDS) Study. *Circ Arrhythm*  
3429 *Electrophysiol* 2011;**4**:26-32.
- 3430 212. Chamberlain AM, Agarwal SK, Folsom AR, Duval S, Soliman EZ, Ambrose M, Eberly LE,  
3431 Alonso A. Smoking and incidence of atrial fibrillation: results from the Atherosclerosis Risk in  
3432 Communities (ARIC) study. *Heart Rhythm* 2011;**8**:1160-1166.

- 3433 213. Larsson SC, Drca N, Wolk A. Alcohol consumption and risk of atrial fibrillation: a prospective  
3434 study and dose-response meta-analysis. *J Am Coll Cardiol* 2014;**64**:281-289.
- 3435 214. Aizer A, Gaziano JM, Cook NR, Manson JE, Buring JE, Albert CM. Relation of vigorous  
3436 exercise to risk of atrial fibrillation. *Am J Cardiol* 2009;**103**:1572-1577.
- 3437 215. Guha K, McDonagh T. Heart failure epidemiology: European perspective. *Curr Cardiol Rev*  
3438 2013;**9**:123-127.
- 3439 216. Braunschweig F, Cowie MR, Auricchio A. What are the costs of heart failure? *Europace*  
3440 2011;**13 Suppl 2**:ii13-17.
- 3441 217. Wodchis WP, Bhatia RS, Leblanc K, Meshkat N, Morra D. A review of the cost of atrial  
3442 fibrillation. *Value Health* 2012;**15**:240-248.
- 3443 218. Kotecha D, Piccini JP. Atrial fibrillation in heart failure: what should we do? *Eur Heart J*  
3444 2015;**36**:3250-3257.
- 3445 219. Olsson LG, Swedberg K, Ducharme A, Granger CB, Michelson EL, McMurray JJ, Puu M,  
3446 Yusuf S, Pfeffer MA. Atrial fibrillation and risk of clinical events in chronic heart failure with and without  
3447 left ventricular systolic dysfunction: results from the Candesartan in Heart failure-Assessment of  
3448 Reduction in Mortality and morbidity (CHARM) program. *J Am Coll Cardiol* 2006;**47**:1997-2004.
- 3449 220. Kotecha D, Chudasama R, Lane DA, Kirchhof P, Lip GY. Atrial fibrillation and heart failure  
3450 due to reduced versus preserved ejection fraction: A systematic review and meta-analysis of death  
3451 and adverse outcomes. *Int J Cardiol* 2016;**203**:660-666.
- 3452 221. Mamas MA, Caldwell JC, Chacko S, Garratt CJ, Fath-Ordoubadi F, Neyses L. A meta-  
3453 analysis of the prognostic significance of atrial fibrillation in chronic heart failure. *Eur J Heart Fail*  
3454 2009;**11**:676-683.
- 3455 222. AUTHORS TO BE ADDED, The Task Force for the diagnosis and treatment of acute and  
3456 chronic heart failure of the European Society of Cardiology (ESC). 2016 ESC Guidelines for the  
3457 diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2016.
- 3458 223. Lip GY, Heinzel FR, Gaita F, Juanatey JR, Le Heuzey JY, Potpara T, Svendsen JH, Vos MA,  
3459 Anker SD, Coats AJ, Haverkamp W, Manolis AS, Chung MK, Sanders P, Pieske B, Gorenek B, Lane  
3460 D, Boriani G, Linde C, Hindricks G, Tsutsui H, Homma S, Brownstein S, Nielsen JC, Lainscak M,  
3461 Crespo-Leiro M, Piepoli M, Seferovic P, Savelieva I. European Heart Rhythm Association/Heart  
3462 Failure Association joint consensus document on arrhythmias in heart failure, endorsed by the Heart  
3463 Rhythm Society and the Asia Pacific Heart Rhythm Society. *Europace* 2016;**18**:12-36.
- 3464 224. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC,  
3465 Solomon SD, Swedberg K, Zile MR, PARADIGM-HF Investigators and Committees. Angiotensin-  
3466 neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;**371**:993-1004.
- 3467 225. Ziff OJ, Lane DA, Samra M, Griffith M, Kirchhof P, Lip GY, Steeds RP, Townend J, Kotecha  
3468 D. Safety and efficacy of digoxin: systematic review and meta-analysis of observational and controlled  
3469 trial data. *BMJ* 2015;**351**:h4451.
- 3470 226. Anselmino M, Matta M, D'Ascenzo F, Bunch TJ, Schilling RJ, Hunter RJ, Pappone C,  
3471 Neumann T, Noelker G, Fiala M, Bertaglia E, Frontera A, Duncan E, Nalliah C, Jais P, Weerasooriya  
3472 R, Kalman JM, Gaita F. Catheter ablation of atrial fibrillation in patients with left ventricular systolic  
3473 dysfunction: a systematic review and meta-analysis. *Circ Arrhythm Electrophysiol* 2014;**7**:1011-1018.
- 3474 227. Ganesan AN, Nandal S, Luker J, Pathak RK, Mahajan R, Twomey D, Lau DH, Sanders P.  
3475 Catheter ablation of atrial fibrillation in patients with concomitant left ventricular impairment: a  
3476 systematic review of efficacy and effect on ejection fraction. *Heart Lung Circ* 2015;**24**:270-280.
- 3477 228. Khan MN, Jais P, Cummings J, Di Biase L, Sanders P, Martin DO, Kautzner J, Hao S,  
3478 Themistoclakis S, Fanelli R, Potenza D, Massaro R, Wazni O, Schweikert R, Saliba W, Wang P, Al-  
3479 Ahmad A, Beheiry S, Santarelli P, Starling RC, Dello Russo A, Pelargonio G, Brachmann J, Schibgilla  
3480 V, Bonso A, Casella M, Raviele A, Haissaguerre M, Natale A, PABA-CHF Investigators. Pulmonary-  
3481 vein isolation for atrial fibrillation in patients with heart failure. *N Engl J Med* 2008;**359**:1778-1785.
- 3482 229. Gupta S, Figueredo VM. Tachycardia mediated cardiomyopathy: pathophysiology,  
3483 mechanisms, clinical features and management. *Int J Cardiol* 2014;**172**:40-46.
- 3484 230. Kusunose K, Yamada H, Nishio S, Tomita N, Niki T, Yamaguchi K, Koshiha K, Yagi S,  
3485 Taketani Y, Iwase T, Soeki T, Wakatsuki T, Akaike M, Sata M. Clinical utility of single-beat E/e'  
3486 obtained by simultaneous recording of flow and tissue Doppler velocities in atrial fibrillation with  
3487 preserved systolic function. *JACC Cardiovasc Imaging* 2009;**2**:1147-1156.
- 3488 231. Li C, Zhang J, Zhou C, Huang L, Tang H, Rao L. Will simultaneous measurement of E/e'  
3489 index facilitate the non-invasive assessment of left ventricular filling pressure in patients with non-  
3490 valvular atrial fibrillation? *Eur J Echocardiogr* 2010;**11**:296-301.

- 3491 232. Senechal M, O'Connor K, Deblois J, Magne J, Dumesnil JG, Pibarot P, Bergeron S, Poirier P.  
3492 A simple Doppler echocardiography method to evaluate pulmonary capillary wedge pressure in  
3493 patients with atrial fibrillation. *Echocardiography* 2008;**25**:57-63.
- 3494 233. Sohn DW, Song JM, Zo JH, Chai IH, Kim HS, Chun HG, Kim HC. Mitral annulus velocity in  
3495 the evaluation of left ventricular diastolic function in atrial fibrillation. *J Am Soc Echocardiogr*  
3496 1999;**12**:927-931.
- 3497 234. Wada Y, Murata K, Tanaka T, Nose Y, Kihara C, Uchida K, Okuda S, Susa T, Kishida Y,  
3498 Matsuzaki M. Simultaneous Doppler tracing of transmitral inflow and mitral annular velocity as an  
3499 estimate of elevated left ventricular filling pressure in patients with atrial fibrillation. *Circ J*  
3500 2012;**76**:675-681.
- 3501 235. Kelly JP, Mentz RJ, Mebazaa A, Voors AA, Butler J, Roessig L, Fiuzat M, Zannad F, Pitt B,  
3502 O'Connor CM, Lam CS. Patient selection in heart failure with preserved ejection fraction clinical trials.  
3503 *J Am Coll Cardiol* 2015;**65**:1668-1682.
- 3504 236. Schneider MP, Hua TA, Bohm M, Wachtell K, Kjeldsen SE, Schmieder RE. Prevention of  
3505 atrial fibrillation by Renin-Angiotensin system inhibition a meta-analysis. *J Am Coll Cardiol*  
3506 2010;**55**:2299-2307.
- 3507 237. Healey JS, Baranchuk A, Crystal E, Morillo CA, Garfinkle M, Yusuf S, Connolly SJ.  
3508 Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor  
3509 blockers: a meta-analysis. *J Am Coll Cardiol* 2005;**45**:1832-1839.
- 3510 238. Jibrini MB, Molnar J, Arora RR. Prevention of atrial fibrillation by way of abrogation of the  
3511 renin-angiotensin system: a systematic review and meta-analysis. *Am J Ther* 2008;**15**:36-43.
- 3512 239. Ducharme A, Swedberg K, Pfeffer MA, Cohen-Solal A, Granger CB, Maggioni AP, Michelson  
3513 EL, McMurray JJ, Olsson L, Rouleau JL, Young JB, Olofsson B, Puum M, Yusuf S, CHARM  
3514 Investigators. Prevention of atrial fibrillation in patients with symptomatic chronic heart failure by  
3515 candesartan in the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity  
3516 (CHARM) program. *Am Heart J* 2006;**152**:86-92.
- 3517 240. GISSI-AF Investigators, Disertori M, Latini R, Barlera S, Franzosi MG, Staszewsky L,  
3518 Maggioni AP, Lucci D, Di Pasquale G, Tognoni G. Valsartan for prevention of recurrent atrial  
3519 fibrillation. *N Engl J Med* 2009;**360**:1606-1617.
- 3520 241. Goette A, Schon N, Kirchhof P, Breithardt G, Fetsch T, Hausler KG, Klein HU, Steinbeck G,  
3521 Wegscheider K, Meinertz T. Angiotensin II-antagonist in paroxysmal atrial fibrillation (ANTIPAF) trial.  
3522 *Circ Arrhythm Electrophysiol* 2012;**5**:43-51.
- 3523 242. Active I Investigators, Yusuf S, Healey JS, Pogue J, Chrolavicius S, Flather M, Hart RG,  
3524 Hohnloser SH, Joyner CD, Pfeffer MA, Connolly SJ. Irbesartan in patients with atrial fibrillation. *N*  
3525 *Engl J Med* 2011;**364**:928-938.
- 3526 243. Swedberg K, Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Shi H, Vincent J, Pitt B.  
3527 Eplerenone and atrial fibrillation in mild systolic heart failure: results from the EMPHASIS-HF  
3528 (Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure) study. *J Am Coll*  
3529 *Cardiol* 2012;**59**:1598-1603.
- 3530 244. Goette A, Staack T, Rocken C, Arndt M, Geller JC, Huth C, Ansoerge S, Klein HU, Lendeckel  
3531 U. Increased expression of extracellular signal-regulated kinase and angiotensin-converting enzyme  
3532 in human atria during atrial fibrillation. *J Am Coll Cardiol* 2000;**35**:1669-1677.
- 3533 245. Marott SC, Nielsen SF, Benn M, Nordestgaard BG. Antihypertensive treatment and risk of  
3534 atrial fibrillation: a nationwide study. *Eur Heart J* 2014;**35**:1205-1214.
- 3535 246. Wachtell K, Lehto M, Gerds E, Olsen MH, Hornestam B, Dahlöf B, Ibsen H, Julius S,  
3536 Kjeldsen SE, Lindholm LH, Nieminen MS, Devereux RB. Angiotensin II receptor blockade reduces  
3537 new-onset atrial fibrillation and subsequent stroke compared to atenolol: the Losartan Intervention For  
3538 End Point Reduction in Hypertension (LIFE) study. *J Am Coll Cardiol* 2005;**45**:712-719.
- 3539 247. Manolis AJ, Rosei EA, Coca A, Cifkova R, Erdine SE, Kjeldsen S, Lip GY, Narkiewicz K,  
3540 Parati G, Redon J, Schmieder R, Tsioufis C, Mancia G. Hypertension and atrial fibrillation: diagnostic  
3541 approach, prevention and treatment. Position paper of the Working Group 'Hypertension Arrhythmias  
3542 and Thrombosis' of the European Society of Hypertension. *J Hypertens* 2012;**30**:239-252.
- 3543 248. Madrid AH, Bueno MG, Rebollo JM, Marin I, Pena G, Bernal E, Rodriguez A, Cano L, Cano  
3544 JM, Cabeza P, Moro C. Use of irbesartan to maintain sinus rhythm in patients with long-lasting  
3545 persistent atrial fibrillation: a prospective and randomized study. *Circulation* 2002;**106**:331-336.
- 3546 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,  
3547 Chen S-A. Use of enalapril to facilitate sinus rhythm maintenance after external cardioversion of long-  
3548 standing persistent atrial fibrillation. Results of a prospective and controlled study. *Eur Heart J*  
3549 2003;**24**:2090-2098.

- 3550 250. Anand K, Mooss AN, Hee TT, Mohiuddin SM. Meta-analysis: inhibition of renin-angiotensin  
3551 system prevents new-onset atrial fibrillation. *Am Heart J* 2006;**152**:217-222.
- 3552 251. Tveit A, Seljeflot I, Grundvold I, Abdelnoor M, Smith P, Arnesen H. Effect of candesartan and  
3553 various inflammatory markers on maintenance of sinus rhythm after electrical cardioversion for atrial  
3554 fibrillation. *Am J Cardiol* 2007;**99**:1544-1548.
- 3555 252. Furberg CD, Psaty BM, Manolio TA, Gardin JM, Smith VE, Rautaharju PM. Prevalence of  
3556 atrial fibrillation in elderly subjects (the Cardiovascular Health Study). *Am J Cardiol* 1994;**74**:236-241.
- 3557 253. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, Borger  
3558 MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Jung B, Lancellotti P, Pierard L, Price S, Schafers  
3559 HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL,  
3560 Zembala M, Joint Task Force on the Management of Valvular Heart Disease of the European Society  
3561 of Cardiology (ESC), European Association for Cardio-Thoracic Surgery (EACTS). Guidelines on the  
3562 management of valvular heart disease (version 2012). *Eur Heart J* 2012;**33**:2451-2496.
- 3563 254. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Guyton RA, O'Gara PT,  
3564 Ruiz CE, Skubas NJ, Sorajja P, Sundt TM, 3rd, Thomas JD. 2014 AHA/ACC guideline for the  
3565 management of patients with valvular heart disease: executive summary: a report of the American  
3566 College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll*  
3567 *Cardiol* 2014;**63**:2438-2488.
- 3568 255. Nieuwlaat R, Capucci A, Camm AJ, Olsson SB, Andresen D, Davies DW, Cobbe S, Breithardt  
3569 G, Le Heuzey JY, Prins MH, Levy S, Crijns HJ. Atrial fibrillation management: a prospective survey in  
3570 ESC member countries: the Euro Heart Survey on Atrial Fibrillation. *Eur Heart J* 2005;**26**:2422-2434.
- 3571 256. Moretti M, Fabris E, Morosin M, Merlo M, Barbati G, Pinamonti B, Gatti G, Pappalardo A,  
3572 Sinagra G. Prognostic significance of atrial fibrillation and severity of symptoms of heart failure in  
3573 patients with low gradient aortic stenosis and preserved left ventricular ejection fraction. *Am J Cardiol*  
3574 2014;**114**:1722-1728.
- 3575 257. Ngaage DL, Schaff HV, Mullany CJ, Barnes S, Dearani JA, Daly RC, Orszulak TA, Sundt TM,  
3576 3rd. Influence of preoperative atrial fibrillation on late results of mitral repair: is concomitant ablation  
3577 justified? *Ann Thorac Surg* 2007;**84**:434-442; discussion 442-433.
- 3578 258. Ngaage DL, Schaff HV, Barnes SA, Sundt TM, 3rd, Mullany CJ, Dearani JA, Daly RC,  
3579 Orszulak TA. Prognostic implications of preoperative atrial fibrillation in patients undergoing aortic  
3580 valve replacement: is there an argument for concomitant arrhythmia surgery? *Ann Thorac Surg*  
3581 2006;**82**:1392-1399.
- 3582 259. Eguchi K, Ohtaki E, Matsumura T, Tanaka K, Tohbaru T, Iguchi N, Misu K, Asano R,  
3583 Nagayama M, Sumiyoshi T, Kasegawa H, Hosoda S. Pre-operative atrial fibrillation as the key  
3584 determinant of outcome of mitral valve repair for degenerative mitral regurgitation. *Eur Heart J*  
3585 2005;**26**:1866-1872.
- 3586 260. Lim E, Barlow CW, Hosseinpour AR, Wisbey C, Wilson K, Pidgeon W, Charman S, Barlow  
3587 JB, Wells FC. Influence of atrial fibrillation on outcome following mitral valve repair. *Circulation*  
3588 2001;**104**:159-63.
- 3589 261. Maan A, Heist EK, Passeri J, Inglessis I, Baker J, Ptaszek L, Vlahakes G, Ruskin JN,  
3590 Palacios I, Sundt T, Mansour M. Impact of atrial fibrillation on outcomes in patients who underwent  
3591 transcatheter aortic valve replacement. *Am J Cardiol* 2015;**115**:220-226.
- 3592 262. Barbash IM, Minha S, Ben-Dor I, Dvir D, Torguson R, Aly M, Bond E, Satler LF, Pichard AD,  
3593 Waksman R. Predictors and clinical implications of atrial fibrillation in patients with severe aortic  
3594 stenosis undergoing transcatheter aortic valve implantation. *Catheter Cardiovasc Interv* 2015;**85**:468-  
3595 477.
- 3596 263. Halperin JL, Hart RG. Atrial fibrillation and stroke: new ideas, persisting dilemmas. *Stroke*  
3597 1988;**19**:937-941.
- 3598 264. Messika-Zeitoun D, Bellamy M, Avierinos JF, Breen J, Eusemann C, Rossi A, Behrenbeck T,  
3599 Scott C, Tajik JA, Enriquez-Sarano M. Left atrial remodelling in mitral regurgitation--methodologic  
3600 approach, physiological determinants, and outcome implications: a prospective quantitative Doppler-  
3601 echocardiographic and electron beam-computed tomographic study. *Eur Heart J* 2007;**28**:1773-1781.
- 3602 265. Calvo N, Bisbal F, Guiu E, Ramos P, Nadal M, Tolosana JM, Arbelo E, Berruezo A, Sitges M,  
3603 Brugada J, Mont L. Impact of atrial fibrillation-induced tachycardiomyopathy in patients undergoing  
3604 pulmonary vein isolation. *Int J Cardiol* 2013;**168**:4093-4097.
- 3605 266. Edner M, Caidahl K, Bergfeldt L, Darpo B, Edvardsson N, Rosenqvist M. Prospective study of  
3606 left ventricular function after radiofrequency ablation of atrioventricular junction in patients with atrial  
3607 fibrillation. *Br Heart J* 1995;**74**:261-267.

- 3608 267. Gertz ZM, Raina A, Saghy L, Zado ES, Callans DJ, Marchlinski FE, Keane MG, Silvestry FE.  
3609 Evidence of atrial functional mitral regurgitation due to atrial fibrillation: reversal with arrhythmia  
3610 control. *J Am Coll Cardiol* 2011;**58**:1474-1481.
- 3611 268. Kihara T, Gillinov AM, Takasaki K, Fukuda S, Song JM, Shiota M, Shiota T. Mitral  
3612 regurgitation associated with mitral annular dilation in patients with lone atrial fibrillation: an  
3613 echocardiographic study. *Echocardiography* 2009;**26**:885-889.
- 3614 269. Zhou X, Otsuji Y, Yoshifuku S, Yuasa T, Zhang H, Takasaki K, Matsukida K, Kisanuki A,  
3615 Minagoe S, Tei C. Impact of atrial fibrillation on tricuspid and mitral annular dilatation and valvular  
3616 regurgitation. *Circ J* 2002;**66**:913-916.
- 3617 270. Ring L, Dutka DP, Wells FC, Fynn SP, Shapiro LM, Rana BS. Mechanisms of atrial mitral  
3618 regurgitation: insights using 3D transoesophageal echo. *Eur Heart J Cardiovasc Imaging*  
3619 2014;**15**:500-508.
- 3620 271. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, Borger  
3621 MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Lung B, Lancellotti P, Pierard L, Price S, Schafers  
3622 HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL,  
3623 Zembala M, ESC Committee for Practice Guidelines (CPG), Joint Task Force on the Management of  
3624 Valvular Heart Disease of the European Society of Cardiology (ESC), European Association for  
3625 Cardio-Thoracic Surgery (EACTS). Guidelines on the management of valvular heart disease (version  
3626 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of  
3627 Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur J*  
3628 *Cardiothorac Surg* 2012;**42**:S1-44.
- 3629 272. Molteni M, Polo Friz H, Primitz L, Marano G, Boracchi P, Cimminiello C. The definition of  
3630 valvular and non-valvular atrial fibrillation: results of a physicians' survey. *Europace* 2014;**16**:1720-  
3631 1725.
- 3632 273. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients  
3633 with atrial fibrillation. *Ann Thorac Surg* 1996;**61**:755-759.
- 3634 274. Szekely P. Systemic Embolism and Anticoagulant Prophylaxis in Rheumatic Heart Disease.  
3635 *Br Med J* 1964;**1**:1209-1212.
- 3636 275. De Caterina R, Camm AJ. What is 'valvular' atrial fibrillation? A reappraisal. *Eur Heart J*  
3637 2014;**35**:3328-3335.
- 3638 276. Goldstone AB, Patrick WL, Cohen JE, Aribena CN, Popat R, Woo YJ. Early surgical  
3639 intervention or watchful waiting for the management of asymptomatic mitral regurgitation: a  
3640 systematic review and meta-analysis. *Ann Cardiothorac Surg* 2015;**4**:220-229.
- 3641 277. Schoen T, Pradhan AD, Albert CM, Conen D. Type 2 diabetes mellitus and risk of incident  
3642 atrial fibrillation in women. *J Am Coll Cardiol* 2012;**60**:1421-1428.
- 3643 278. Du X, Ninomiya T, de Galan B, Abadir E, Chalmers J, Pillai A, Woodward M, Cooper M,  
3644 Harrap S, Hamet P, Poulter N, Lip GY, Patel A. Risks of cardiovascular events and effects of routine  
3645 blood pressure lowering among patients with type 2 diabetes and atrial fibrillation: results of the  
3646 ADVANCE study. *Eur Heart J* 2009;**30**:1128-1135.
- 3647 279. Rizzo MR, Sasso FC, Marfella R, Siniscalchi M, Paolisso P, Carbonara O, Capoluongo MC,  
3648 Lascar N, Pace C, Sardu C, Passavanti B, Barbieri M, Mauro C, Paolisso G. Autonomic dysfunction is  
3649 associated with brief episodes of atrial fibrillation in type 2 diabetes. *J Diabetes Complications*  
3650 2015;**29**:88-92.
- 3651 280. Olson TM, Terzic A. Human K(ATP) channelopathies: diseases of metabolic homeostasis.  
3652 *Pflugers Arch* 2010;**460**:295-306.
- 3653 281. Chung MK, Martin DO, Sprecher D, Wazni O, Kanderian A, Carnes CA, Bauer JA, Tchou PJ,  
3654 Niebauer MJ, Natale A, Van Wagoner DR. C-reactive protein elevation in patients with atrial  
3655 arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation. *Circulation*  
3656 2001;**104**:2886-2891.
- 3657 282. Donath MY, Shoelson SE. Type 2 diabetes as an inflammatory disease. *Nat Rev Immunol*  
3658 2011;**11**:98-107.
- 3659 283. Ziolo MT, Mohler PJ. Defining the role of oxidative stress in atrial fibrillation and diabetes. *J*  
3660 *Cardiovasc Electrophysiol* 2015;**26**:223-225.
- 3661 284. Fatemi O, Yuriditsky E, Tsioufis C, Tsachris D, Morgan T, Basile J, Bigger T, Cushman W,  
3662 Goff D, Soliman EZ, Thomas A, Papademetriou V. Impact of intensive glycemic control on the  
3663 incidence of atrial fibrillation and associated cardiovascular outcomes in patients with type 2 diabetes  
3664 mellitus (from the Action to Control Cardiovascular Risk in Diabetes Study). *Am J Cardiol*  
3665 2014;**114**:1217-1222.

- 3666 285. Overvad TF, Skjoth F, Lip GY, Lane DA, Albertsen IE, Rasmussen LH, Larsen TB. Duration  
3667 of Diabetes Mellitus and Risk of Thromboembolism and Bleeding in Atrial Fibrillation: Nationwide  
3668 Cohort Study. *Stroke* 2015;**46**:2168-2174.
- 3669 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,  
3670 See L-C. Association of metformin with lower atrial fibrillation risk among patients with type 2 diabetes  
3671 mellitus: a population-based dynamic cohort and in vitro studies. *Cardiovasc Diabetol* 2014;**13**:123.
- 3672 287. Lip GY, Clementy N, Pierre B, Boyer M, Fauchier L. The impact of associated diabetic  
3673 retinopathy on stroke and severe bleeding risk in diabetic patients with atrial fibrillation: the Loire  
3674 valley atrial fibrillation project. *Chest* 2015;**147**:1103-1110.
- 3675 288. Huxley RR, Misialek JR, Agarwal SK, Loehr LR, Soliman EZ, Chen LY, Alonso A. Physical  
3676 activity, obesity, weight change, and risk of atrial fibrillation: the Atherosclerosis Risk in Communities  
3677 study. *Circ Arrhythm Electrophysiol* 2014;**7**:620-625.
- 3678 289. Murphy NF, MacIntyre K, Stewart S, Hart CL, Hole D, McMurray JJ. Long-term cardiovascular  
3679 consequences of obesity: 20-year follow-up of more than 15 000 middle-aged men and women (the  
3680 Renfrew-Paisley study). *Eur Heart J* 2006;**27**:96-106.
- 3681 290. Wanahita N, Messerli FH, Bangalore S, Gami AS, Somers VK, Steinberg JS. Atrial fibrillation  
3682 and obesity--results of a meta-analysis. *Am Heart J* 2008;**155**:310-315.
- 3683 291. Wang TJ, Parise H, Levy D, D'Agostino RB, Sr., Wolf PA, Vasan RS, Benjamin EJ. Obesity  
3684 and the risk of new-onset atrial fibrillation. *JAMA* 2004;**292**:2471-2477.
- 3685 292. Overvad TF, Rasmussen LH, Skjoth F, Overvad K, Lip GY, Larsen TB. Body mass index and  
3686 adverse events in patients with incident atrial fibrillation. *Am J Med* 2013;**126**:640.e649-617.
- 3687 293. Karason K, Molgaard H, Wikstrand J, Sjoström L. Heart rate variability in obesity and the  
3688 effect of weight loss. *Am J Cardiol* 1999;**83**:1242-1247.
- 3689 294. Russo C, Jin Z, Homma S, Rundek T, Elkind MS, Sacco RL, Di Tullio MR. Effect of obesity  
3690 and overweight on left ventricular diastolic function: a community-based study in an elderly cohort. *J  
3691 Am Coll Cardiol* 2011;**57**:1368-1374.
- 3692 295. Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. Elevated C-reactive protein levels  
3693 in overweight and obese adults. *Jama* 1999;**282**:2131-2135.
- 3694 296. Pathak RK, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Wong CX, Twomey D, Elliott  
3695 AD, Kalman JM, Abhayaratna WP, Lau DH, Sanders P. Long-Term Effect of Goal-Directed Weight  
3696 Management in an Atrial Fibrillation Cohort: A Long-Term Follow-Up Study (LEGACY). *J Am Coll  
3697 Cardiol* 2015;**65**:2159-2169.
- 3698 297. Pathak RK, Elliott A, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Hendriks JM,  
3699 Twomey D, Kalman JM, Abhayaratna WP, Lau DH, Sanders P. Impact of CARDIOrespiratory FITness  
3700 on Arrhythmia Recurrence in Obese Individuals With Atrial Fibrillation: The CARDIO-FIT Study. *J Am  
3701 Coll Cardiol* 2015;**66**:985-996.
- 3702 298. Cha YM, Friedman PA, Asirvatham SJ, Shen WK, Munger TM, Rea RF, Brady PA, Jahangir  
3703 A, Monahan KH, Hodge DO, Meverden RA, Gersh BJ, Hammill SC, Packer DL. Catheter ablation for  
3704 atrial fibrillation in patients with obesity. *Circulation* 2008;**117**:2583-2590.
- 3705 299. Jongnarangsin K, Chugh A, Good E, Mukerji S, Dey S, Crawford T, Sarrazin JF, Kuhne M,  
3706 Chalfoun N, Wells D, Boonyapisit W, Pelosi F, Jr., Bogun F, Morady F, Oral H. Body mass index,  
3707 obstructive sleep apnea, and outcomes of catheter ablation of atrial fibrillation. *J Cardiovasc  
3708 Electrophysiol* 2008;**19**:668-672.
- 3709 300. Guijian L, Jinchuan Y, Rongzeng D, Jun Q, Jun W, Wenqing Z. Impact of body mass index on  
3710 atrial fibrillation recurrence: a meta-analysis of observational studies. *Pacing Clin Electrophysiol*  
3711 2013;**36**:748-756.
- 3712 301. Zhuang J, Lu Y, Tang K, Peng W, Xu Y. Influence of body mass index on recurrence and  
3713 quality of life in atrial fibrillation patients after catheter ablation: a meta-analysis and systematic  
3714 review. *Clin Cardiol* 2013;**36**:269-275.
- 3715 302. Ector J, Dragusin O, Adriaenssens B, Huybrechts W, Willems R, Ector H, Heidbuchel H.  
3716 Obesity is a major determinant of radiation dose in patients undergoing pulmonary vein isolation for  
3717 atrial fibrillation. *J Am Coll Cardiol* 2007;**50**:234-242.
- 3718 303. Shoemaker MB, Muhammad R, Farrell M, Parvez B, White BW, Streur M, Stubblefield T,  
3719 Rytlewski J, Parvathaneni S, Nagarakanti R, Roden DM, Saavedra P, Ellis C, Whalen SP, Darbar D.  
3720 Relation of morbid obesity and female gender to risk of procedural complications in patients  
3721 undergoing atrial fibrillation ablation. *Am J Cardiol* 2013;**111**:368-373.
- 3722 304. Vizzardì E, Sciatti E, Bonadei I, D'Aloia A, Curnis A, Metra M. Obstructive sleep apnoea-  
3723 hypopnoea and arrhythmias: new updates. *J Cardiovasc Med (Hagerstown)* 2014.
- 3724 305. Digby GC, Baranchuk A. Sleep apnea and atrial fibrillation; 2012 update. *Curr Cardiol Rev*  
3725 2012;**8**:265-272.

- 3726 306. Lin YK, Lai MS, Chen YC, Cheng CC, Huang JH, Chen SA, Chen YJ, Lin CI. Hypoxia and  
3727 reoxygenation modulate the arrhythmogenic activity of the pulmonary vein and atrium. *Clin Sci (Lond)*  
3728 2012;**122**:121-132.
- 3729 307. Linz D. Atrial fibrillation in obstructive sleep apnea: atrial arrhythmogenic substrate of a  
3730 different sort. *Am J Cardiol* 2012;**110**:1071.
- 3731 308. Patel D, Mohanty P, Di Biase L, Shaheen M, Lewis WR, Quan K, Cummings JE, Wang P, Al-  
3732 Ahmad A, Venkatraman P, Nashawati E, Lakkireddy D, Schweikert R, Horton R, Sanchez J,  
3733 Gallinghouse J, Hao S, Beheiry S, Cardinal DS, Zagrodzky J, Canby R, Bailey S, Burkhardt JD,  
3734 Natale A. Safety and efficacy of pulmonary vein antral isolation in patients with obstructive sleep  
3735 apnea: the impact of continuous positive airway pressure. *Circ Arrhythm Electrophysiol* 2010;**3**:445-  
3736 451.
- 3737 309. Fein AS, Shvilkin A, Shah D, Haffajee CI, Das S, Kumar K, Kramer DB, Zimetbaum PJ,  
3738 Buxton AE, Josephson ME, Anter E. Treatment of obstructive sleep apnea reduces the risk of atrial  
3739 fibrillation recurrence after catheter ablation. *J Am Coll Cardiol* 2013;**62**:300-305.
- 3740 310. Naruse Y, Tada H, Satoh M, Yanagihara M, Tsuneoka H, Hirata Y, Ito Y, Kuroki K, Machino  
3741 T, Yamasaki H, Igarashi M, Sekiguchi Y, Sato A, Aonuma K. Concomitant obstructive sleep apnea  
3742 increases the recurrence of atrial fibrillation following radiofrequency catheter ablation of atrial  
3743 fibrillation: clinical impact of continuous positive airway pressure therapy. *Heart Rhythm* 2013;**10**:331-  
3744 337.
- 3745 311. Neilan TG, Farhad H, Dodson JA, Shah RV, Abbasi SA, Bakker JP, Michaud GF, van der  
3746 Geest R, Blankstein R, Steigner M, John RM, Jerosch-Herold M, Malhotra A, Kwong RY. Effect of  
3747 sleep apnea and continuous positive airway pressure on cardiac structure and recurrence of atrial  
3748 fibrillation. *J Am Heart Assoc* 2013;**2**:e000421.
- 3749 312. Li L, Wang ZW, Li J, Ge X, Guo LZ, Wang Y, Guo WH, Jiang CX, Ma CS. Efficacy of catheter  
3750 ablation of atrial fibrillation in patients with obstructive sleep apnoea with and without continuous  
3751 positive airway pressure treatment: a meta-analysis of observational studies. *Europace*  
3752 2014;**16**:1309-1314.
- 3753 313. Cowie MR, Woehrle H, Wegscheider K, Angermann C, d'Ortho MP, Erdmann E, Levy P,  
3754 Simonds AK, Somers VK, Zannad F, Teschler H. Adaptive Servo-Ventilation for Central Sleep Apnea  
3755 in Systolic Heart Failure. *N Engl J Med* 2015;**373**:1095-1105.
- 3756 314. Bitter T, Nolker G, Vogt J, Prinz C, Horstkotte D, Oldenburg O. Predictors of recurrence in  
3757 patients undergoing cryoballoon ablation for treatment of atrial fibrillation: the independent role of  
3758 sleep-disordered breathing. *J Cardiovasc Electrophysiol* 2012;**23**:18-25.
- 3759 315. Ng CY, Liu T, Shehata M, Stevens S, Chugh SS, Wang X. Meta-analysis of obstructive sleep  
3760 apnea as predictor of atrial fibrillation recurrence after catheter ablation. *Am J Cardiol* 2011;**108**:47-  
3761 51.
- 3762 316. Hart RG, Eikelboom JW, Brimble KS, McMurry MS, Ingram AJ. Stroke prevention in atrial  
3763 fibrillation patients with chronic kidney disease. *Can J Cardiol* 2013;**29**:S71-78.
- 3764 317. Roldan V, Marin F, Fernandez H, Manzano-Fernandez S, Gallego P, Valdes M, Vicente V, Lip  
3765 GY. Renal impairment in a "real-life" cohort of anticoagulated patients with atrial fibrillation  
3766 (implications for thromboembolism and bleeding). *Am J Cardiol* 2013;**111**:1159-1164.
- 3767 318. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA,  
3768 Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC,  
3769 Joyner CD, Wallentin L, RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in  
3770 patients with atrial fibrillation. *N Engl J Med* 2009;**361**:1139-1151.
- 3771 319. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR,  
3772 Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D,  
3773 Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P,  
3774 Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L,  
3775 ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation.  
3776 *N Engl J Med* 2011;**365**:981-992.
- 3777 320. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL,  
3778 Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM,  
3779 ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*  
3780 2011;**365**:883-891.
- 3781 321. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL,  
3782 Ezekowitz MD, Weitz JI, Spinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel  
3783 SP, Patel I, Hanyok JJ, Mercuri M, Antman EM, Investigators EA-T. Edoxaban versus warfarin in  
3784 patients with atrial fibrillation. *N Engl J Med* 2013;**369**:2093-2104.

- 3785 322. Page K, Marwick TH, Lee R, Grenfell R, Abhayaratna WP, Aggarwal A, Briffa TG, Cameron J,  
3786 Davidson PM, Driscoll A, Garton-Smith J, Gascard DJ, Hickey A, Korczyk D, Mitchell JA, Sanders R,  
3787 Spicer D, Stewart S, Wade V. A systematic approach to chronic heart failure care: a consensus  
3788 statement. *Med J Aust* 2014;**201**:146-150.
- 3789 323. Stock S, Pitcavage JM, Simic D, Altin S, Graf C, Feng W, Graf TR. Chronic care model  
3790 strategies in the United States and Germany deliver patient-centered, high-quality diabetes care.  
3791 *Health Aff (Millwood)* 2014;**33**:1540-1548.
- 3792 324. Lundstrom H, Siersma V, Nielsen AB, Brodersen J, Reventlow S, Andersen PK, de Fine  
3793 Olivarius N. The effectiveness of structured personal care of type 2 diabetes on recurrent outcomes: a  
3794 19 year follow-up of the study Diabetes Care in General Practice (DCGP). *Diabetologia*  
3795 2014;**57**:1119-1123.
- 3796 325. Berti D, Hendriks JM, Brandes A, Deaton C, Crijns HJ, Camm AJ, Hindricks G, Moons P,  
3797 Heidebuchel H. A proposal for interdisciplinary, nurse-coordinated atrial fibrillation expert programmes  
3798 as a way to structure daily practice. *Eur Heart J* 2013;**34**:2725-2730.
- 3799 326. Wagner EH, Austin BT, Von Korff M. Organizing care for patients with chronic illness. *Milbank*  
3800 *Q* 1996;**74**:511-544.
- 3801 327. Nieuwlaat R, Olsson SB, Lip GY, Camm AJ, Breithardt G, Capucci A, Meeder JG, Prins MH,  
3802 Levy S, Crijns HJ, Euro Heart Survey Investigators. Guideline-adherent antithrombotic treatment is  
3803 associated with improved outcomes compared with undertreatment in high-risk patients with atrial  
3804 fibrillation. The Euro Heart Survey on Atrial Fibrillation. *Am Heart J* 2007;**153**:1006-1012.
- 3805 328. Nuno R, Coleman K, Bengoa R, Sauto R. Integrated care for chronic conditions: the  
3806 contribution of the ICCF Framework. *Health Policy* 2012;**105**:55-64.
- 3807 329. Kirchhof P, Nabauer M, Gerth A, Limbourg T, Lewalter T, Goette A, Wegscheider K, Treszl A,  
3808 Meinertz T, Oeff M, Ravens U, Breithardt G, Steinbeck G. Impact of the type of centre on  
3809 management of AF patients: surprising evidence for differences in antithrombotic therapy decisions.  
3810 *Thromb Haemost* 2011;**105**:1010-1023.
- 3811 330. Hendriks JM, de Wit R, Crijns HJ, Vrijhoef HJ, Prins MH, Pisters R, Pison LA, Blaauw Y,  
3812 Tieleman RG. Nurse-led care vs. usual care for patients with atrial fibrillation: results of a randomized  
3813 trial of integrated chronic care vs. routine clinical care in ambulatory patients with atrial fibrillation. *Eur*  
3814 *Heart J* 2012;**33**:2692-2699.
- 3815 331. Hendriks J, Tomini F, van Asselt T, Crijns H, Vrijhoef H. Cost-effectiveness of a specialized  
3816 atrial fibrillation clinic vs. usual care in patients with atrial fibrillation. *Europace* 2013;**15**:1128-1135.
- 3817 332. Stewart S, Ball J, Horowitz JD, Marwick TH, Mahadevan G, Wong C, Abhayaratna WP, Chan  
3818 YK, Esterman A, Thompson DR, Scuffham PA, Carrington MJ. Standard versus atrial fibrillation-  
3819 specific management strategy (SAFETY) to reduce recurrent admission and prolong survival:  
3820 pragmatic, multicentre, randomised controlled trial. *Lancet* 2015;**385**:775-784.
- 3821 333. Tran HN, Tafreshi J, Hernandez EA, Pai SM, Torres VI, Pai RG. A multidisciplinary atrial  
3822 fibrillation clinic. *Curr Cardiol Rev* 2013;**9**:55-62.
- 3823 334. Conti A, Canuti E, Mariannini Y, Viviani G, Poggioni C, Boni V, Pini R, Vanni S, Padeletti L,  
3824 Gensini GF. Clinical management of atrial fibrillation: early interventions, observation, and structured  
3825 follow-up reduce hospitalizations. *Am J Emerg Med* 2012;**30**:1962-1969.
- 3826 335. Carter L, Gardner M, Magee K, Fearon A, Morgulis I, Doucette S, Sapp JL, Gray C,  
3827 Abdelwahab A, Parkash R. An Integrated Management Approach to Atrial Fibrillation. *J Am Heart*  
3828 *Assoc* 2016;**5**:e002950.
- 3829 336. Peterson ED, Ho PM, Barton M, Beam C, Burgess LH, Casey DE, Jr., Drozda JP, Jr.,  
3830 Fonarow GC, Goff D, Jr., Grady KL, King DE, King ML, Masoudi FA, Nielsen DR, Stanko S.  
3831 ACC/AHA/AACVPR/AAFP/ANA Concepts for Clinician-Patient Shared Accountability in Performance  
3832 Measures: A Report of the American College of Cardiology/American Heart Association Task Force  
3833 on Performance Measures. *Circulation* 2014.
- 3834 337. Lane DA, Aguinaga L, Blomstrom-Lundqvist C, Boriani G, Dan GA, Hills MT, Hylek EM,  
3835 LaHaye SA, Lip GY, Lobban T, Mandrola J, McCabe PJ, Pedersen SS, Pisters R, Stewart S, Wood K,  
3836 Potpara TS, Gorenek B, Conti JB, Keegan R, Power S, Hendriks J, Ritter P, Calkins H, Violi F,  
3837 Hurwitz J. Cardiac tachyarrhythmias and patient values and preferences for their management: the  
3838 European Heart Rhythm Association (EHRA) consensus document endorsed by the Heart Rhythm  
3839 Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), and Sociedad Latinoamericana de  
3840 Estimulacion Cardiaca y Electrofisiologia (SOLEACE). *Europace* 2015;**17**:1747-1769.
- 3841 338. Hendriks JM, de Wit R, Vrijhoef HJ, Tieleman RG, Crijns HJ. An integrated chronic care  
3842 program for patients with atrial fibrillation: study protocol and methodology for an ongoing prospective  
3843 randomised controlled trial. *Int J Nurs Stud* 2010;**47**:1310-1316.

- 3844 339. Donal E, Lip GY, Galderisi M, Goette A, Shah D, Marwan M, Lederlin M, Mondillo S,  
3845 Edvardsen T, Sitges M, Grapsa J, Garbi M, Senior R, Gimelli A, Potpara TS, Van Gelder IC, Gorenek  
3846 B, Mabo P, Lancellotti P, Kuck KH, Popescu BA, Hindricks G, Habib G, Cosyns B, Delgado V,  
3847 Haugaa KH, Muraru D, Nieman K, Cohen A. EACVI/EHRA Expert Consensus Document on the role  
3848 of multi-modality imaging for the evaluation of patients with atrial fibrillation. *Eur Heart J Cardiovasc*  
3849 *Imaging* 2016;**17**:355-383.
- 3850 340. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster  
3851 E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L,  
3852 Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by  
3853 echocardiography in adults: an update from the american society of echocardiography and the  
3854 European association of cardiovascular imaging. *Eur Heart J Cardiovasc Imaging* 2015;**16**:233-271.
- 3855 341. Filion KB, Agarwal SK, Ballantyne CM, Eberg M, Hoogeveen RC, Huxley RR, Loehr LR,  
3856 Nambi V, Soliman EZ, Alonso A. High-sensitivity cardiac troponin T and the risk of incident atrial  
3857 fibrillation: The Atherosclerosis Risk in Communities (ARIC) study. *Am Heart J* 2015;**169**:31-38
- 3858 342. Aviles RJ, Martin DO, Apperson-Hansen C, Houghtaling PL, Rautaharju P, Kronmal RA,  
3859 Tracy RP, Van Wagener DR, Psaty BM, Lauer MS, Chung MK. Inflammation as a risk factor for atrial  
3860 fibrillation. *Circulation* 2003;**108**:3006-3010.
- 3861 343. Patton KK, Ellinor PT, Heckbert SR, Christenson RH, DeFilippi C, Gottdiener JS, Kronmal  
3862 RA. N-terminal pro-B-type natriuretic peptide is a major predictor of the development of atrial  
3863 fibrillation: the Cardiovascular Health Study. *Circulation* 2009;**120**:1768-1774.
- 3864 344. Bartel T, Erbel R, Acute Trial Investigators. Transoesophageal echocardiography for  
3865 immediate and safe cardioversion in patients with atrial fibrillation. *Eur Heart J* 2001;**22**:2041-2044.
- 3866 345. Mahnkopf C, Mitlacher M, Brachmann J. [Relevance of magnetic resonance imaging for  
3867 catheter ablation of atrial fibrillation]. *Herzschrittmacherther Elektrophysiol* 2014;**25**:252-257.
- 3868 346. Haemers P, Claus P, Willems R. The use of cardiac magnetic resonance imaging in the  
3869 diagnostic workup and treatment of atrial fibrillation. *Cardiol Res Pract* 2012;**2012**:658937.
- 3870 347. Ling LH, Kistler PM, Ellims AH, Iles LM, Lee G, Hughes GL, Kalman JM, Kaye DM, Taylor AJ.  
3871 Diffuse ventricular fibrosis in atrial fibrillation: noninvasive evaluation and relationships with aging and  
3872 systolic dysfunction. *J Am Coll Cardiol* 2012;**60**:2402-2408.
- 3873 348. Lewalter T, Ibrahim R, Albers B, Camm AJ. An update and current expert opinions on  
3874 percutaneous left atrial appendage occlusion for stroke prevention in atrial fibrillation. *Europace*  
3875 2013;**15**:652-656.
- 3876 349. Kirchhof P, Auricchio A, Bax J, Crijns H, Camm J, Diener HC, Goette A, Hindricks G,  
3877 Hohnloser S, Kappenberger L, Kuck KH, Lip GY, Olsson B, Meinertz T, Priori S, Ravens U, Steinbeck  
3878 G, Svernhage E, Tijssen J, Vincent A, Breithardt G. Outcome parameters for trials in atrial fibrillation:  
3879 executive summary: Recommendations from a consensus conference organized by the German Atrial  
3880 Fibrillation Competence Network (AFNET) and the European Heart Rhythm Association (EHRA). *Eur*  
3881 *Heart J* 2007;**28**:2803-2817.
- 3882 350. Alonso-Coello P, Montori VM, Sola I, Schunemann HJ, Devereaux P, Charles C, Roura M,  
3883 Diaz MG, Souto JC, Alonso R, Oliver S, Ruiz R, Coll-Vinent B, Diez AI, Gich I, Guyatt G. Values and  
3884 preferences in oral anticoagulation in patients with atrial fibrillation, physicians' and patients'  
3885 perspectives: protocol for a two-phase study. *BMC Health Serv Res* 2008;**8**:221.
- 3886 351. Lip GY, Al-Khatib SM, Cosio FG, Banerjee A, Savelieva I, Ruskin J, Blendea D, Nattel S, De  
3887 Bono J, Conroy JM, Hess PL, Guasch E, Halperin JL, Kirchhof P, MD GC, Camm AJ. Contemporary  
3888 management of atrial fibrillation: what can clinical registries tell us about stroke prevention and current  
3889 therapeutic approaches? *J Am Heart Assoc* 2014;**3**.
- 3890 352. Gorst-Rasmussen A, Skjoth F, Larsen TB, Rasmussen LH, Lip GY, Lane DA. Dabigatran  
3891 adherence in atrial fibrillation patients during the first year after diagnosis: a nationwide cohort study. *J*  
3892 *Thromb Haemost* 2015;**13**:495-504.
- 3893 353. Hart RG, Pearce LA, Aguilar MI. Adjusted-dose warfarin versus aspirin for preventing stroke  
3894 in patients with atrial fibrillation. *Ann Intern Med* 2007;**147**:590-592.
- 3895 354. Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, Flaker G, Avezum A,  
3896 Hohnloser SH, Diaz R, Talajic M, Zhu J, Pais P, Budaj A, Parkhomenko A, Jansky P, Commerford P,  
3897 Tan RS, Sim KH, Lewis BS, Van Mieghem W, Lip GY, Kim JH, Lanus-Zanetti F, Gonzalez-Hermosillo  
3898 A, Dans AL, Munawar M, O'Donnell M, Lawrence J, Lewis G, Afzal R, Yusuf S, AVERROES Steering  
3899 Committee Investigators. Apixaban in patients with atrial fibrillation. *N Engl J Med* 2011;**364**:806-817.
- 3900 355. Frankel DS, Parker SE, Rosenfeld LE, Gorelick PB. HRS/NSA 2014 Survey of Atrial  
3901 Fibrillation and Stroke: Gaps in Knowledge and Perspective, Opportunities for Improvement. *Heart*  
3902 *Rhythm* 2015.

- 3903 356. Le Heuzey JY, Ammentorp B, Darius H, De Caterina R, Schilling RJ, Schmitt J, Zamorano JL,  
3904 Kirchhof P. Differences among western European countries in anticoagulation management of atrial  
3905 fibrillation. Data from the PREFER IN AF registry. *Thromb Haemost* 2014;**111**:833-841.
- 3906 357. O'Brien EC, Holmes DN, Ansell JE, Allen LA, Hylek E, Kowey PR, Gersh BJ, Fonarow GC,  
3907 Koller CR, Ezekowitz MD, Mahaffey KW, Chang P, Peterson ED, Piccini JP, Singer DE. Physician  
3908 practices regarding contraindications to oral anticoagulation in atrial fibrillation: findings from the  
3909 Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry. *Am Heart*  
3910 *J* 2014;**167**:601-609 e601.
- 3911 358. Fang MC, Go AS, Chang Y, Borowsky LH, Pomernacki NK, Udaltsova N, Singer DE. Warfarin  
3912 discontinuation after starting warfarin for atrial fibrillation. *Circ Cardiovasc Qual Outcomes*  
3913 2010;**3**:624-631.
- 3914 359. Zalesak M, Siu K, Francis K, Yu C, Alvrtsyan H, Rao Y, Walker D, Sander S, Miyasato G,  
3915 Matchar D, Sanchez H. Higher persistence in newly diagnosed nonvalvular atrial fibrillation patients  
3916 treated with dabigatran versus warfarin. *Circ Cardiovasc Qual Outcomes* 2013;**6**:567-574.
- 3917 360. Donze J, Clair C, Hug B, Rodondi N, Waeber G, Cornuz J, Aujesky D. Risk of falls and major  
3918 bleeds in patients on oral anticoagulation therapy. *Am J Med* 2012;**125**:773-778.
- 3919 361. Man-Son-Hing M, Nichol G, Lau A, Laupacis A. Choosing antithrombotic therapy for elderly  
3920 patients with atrial fibrillation who are at risk for falls. *Arch Intern Med* 1999;**159**:677-685.
- 3921 362. Mant J, Hobbs FD, Fletcher K, Roalfe A, Fitzmaurice D, Lip GY, Murray E, BAFTA  
3922 investigators, Midland Research Practices Network (MidReC). Warfarin versus aspirin for stroke  
3923 prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation  
3924 Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet* 2007;**370**:493-503.
- 3925 363. Diener HC, Eikelboom J, Connolly SJ, Joyner CD, Hart RG, Lip GY, O'Donnell M, Hohnloser  
3926 SH, Hankey GJ, Shestakovska O, Yusuf S, AVERROES Steering Committee and Investigators.  
3927 Apixaban versus aspirin in patients with atrial fibrillation and previous stroke or transient ischaemic  
3928 attack: a predefined subgroup analysis from AVERROES, a randomised trial. *Lancet Neurol*  
3929 2012;**11**:225-231.
- 3930 364. The SPAF III Writing Committee for the Stroke Prevention in Atrial Fibrillation Investigators.  
3931 Patients with nonvalvular atrial fibrillation at low risk of stroke during treatment with aspirin: Stroke  
3932 Prevention in Atrial Fibrillation III Study. *JAMA* 1998;**279**:1273-1277.
- 3933 365. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of  
3934 clinical classification schemes for predicting stroke: results from the National Registry of Atrial  
3935 Fibrillation. *JAMA* 2001;**285**:2864-2870.
- 3936 366. van Walraven C, Hart RG, Wells GA, Petersen P, Koudstaal PJ, Gullov AL, Hellemons BS,  
3937 Koefed BG, Laupacis A. A clinical prediction rule to identify patients with atrial fibrillation and a low  
3938 risk for stroke while taking aspirin. *Arch Intern Med* 2003;**163**:936-943.
- 3939 367. Wang TJ, Massaro JM, Levy D, Vasani RS, Wolf PA, D'Agostino RB, Larson MG, Kannel WB,  
3940 Benjamin EJ. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation  
3941 in the community: the Framingham Heart Study. *JAMA* 2003;**290**:1049-1056.
- 3942 368. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for  
3943 predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach:  
3944 the euro heart survey on atrial fibrillation. *Chest* 2010;**137**:263-272.
- 3945 369. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N,  
3946 Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R,  
3947 De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P,  
3948 Rutten FH, ESC Committee for Practice Guidelines, European Heart Rhythm Association, European  
3949 Association for Cardio-Thoracic Surgery. Guidelines for the management of atrial fibrillation: the Task  
3950 Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC).  
3951 *Europace* 2010;**12**:1360-1420.
- 3952 370. Kirchhof P, Curtis AB, Skanes AC, Gillis AM, Samuel Wann L, Camm AJ. Atrial fibrillation  
3953 guidelines across the Atlantic: a comparison of the current recommendations of the European Society  
3954 of Cardiology/European Heart Rhythm Association/European Association of Cardiothoracic Surgeons,  
3955 the American College of Cardiology Foundation/American Heart Association/Heart Rhythm Society,  
3956 and the Canadian Cardiovascular Society. *Eur Heart J* 2013;**34**:1471-1474.
- 3957 371. Olesen JB, Lip GY, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, Selmer C, Ahlehoff  
3958 O, Olsen AM, Gislason GH, Torp-Pedersen C. Validation of risk stratification schemes for predicting  
3959 stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. *BMJ*  
3960 2011;**342**:d124.

- 3961 372. Chao TF, Liu CJ, Wang KL, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Chen TJ, Lip GY,  
3962 Chen SA. Should atrial fibrillation patients with 1 additional risk factor of the CHA2DS2-VASc score  
3963 (beyond sex) receive oral anticoagulation? *J Am Coll Cardiol* 2015;**65**:635-642.
- 3964 373. Lip GY, Skjoth F, Rasmussen LH, Larsen TB. Oral anticoagulation, aspirin, or no therapy in  
3965 patients with nonvalvular AF with 0 or 1 stroke risk factor based on the CHA2DS2-VASc score. *J Am*  
3966 *Coll Cardiol* 2015;**65**:1385-1394.
- 3967 374. Fauchier L, Lecoq C, Clementy N, Bernard A, Angoulvant D, Ivanes F, Babuty D, Lip GY. Oral  
3968 Anticoagulation and the Risk of Stroke or Death in Patients With Atrial Fibrillation and One Additional  
3969 Stroke Risk Factor: The Loire Valley Atrial Fibrillation Project. *Chest* 2016;**149**:960-968.
- 3970 375. Joundi RA, Cipriano LE, Sposato LA, Saposnik G, Stroke Outcomes Research Working  
3971 Group. Ischemic Stroke Risk in Patients With Atrial Fibrillation and CHA2DS2-VASc Score of 1:  
3972 Systematic Review and Meta-Analysis. *Stroke* 2016;**47**:1364-1367.
- 3973 376. Friberg L, Skeppholm M, Terent A. Benefit of anticoagulation unlikely in patients with atrial  
3974 fibrillation and a CHA2DS2-VASc score of 1. *J Am Coll Cardiol* 2015;**65**:225-232.
- 3975 377. Lip GY, Skjoth F, Nielsen PB, Larsen TB. Non-valvular atrial fibrillation patients with none or  
3976 one additional risk factor of the CHA2DS2-VASc score. A comprehensive net clinical benefit analysis  
3977 for warfarin, aspirin, or no therapy. *Thromb Haemost* 2015;**114**:826-834.
- 3978 378. Mikkelsen AP, Lindhardsen J, Lip GY, Gislason GH, Torp-Pedersen C, Olesen JB. Female  
3979 sex as a risk factor for stroke in atrial fibrillation: a nationwide cohort study. *J Thromb Haemost*  
3980 2012;**10**:1745-1751.
- 3981 379. Wagstaff AJ, Overvad TF, Lip GY, Lane DA. Is female sex a risk factor for stroke and  
3982 thromboembolism in patients with atrial fibrillation? A systematic review and meta-analysis. *Qjm*  
3983 2014;**107**:955-967.
- 3984 380. Hijazi Z, Oldgren J, Andersson U, Connolly SJ, Ezekowitz MD, Hohnloser SH, Reilly PA,  
3985 Vinereanu D, Siegbahn A, Yusuf S, Wallentin L. Cardiac biomarkers are associated with an increased  
3986 risk of stroke and death in patients with atrial fibrillation: a Randomized Evaluation of Long-term  
3987 Anticoagulation Therapy (RE-LY) substudy. *Circulation* 2012;**125**:1605-1616.
- 3988 381. Hijazi Z, Wallentin L, Siegbahn A, Andersson U, Christersson C, Ezekowitz J, Gersh BJ,  
3989 Hanna M, Hohnloser S, Horowitz J, Huber K, Hylek EM, Lopes RD, McMurray JJ, Granger CB. N-  
3990 terminal pro-B-type natriuretic peptide for risk assessment in patients with atrial fibrillation: insights  
3991 from the ARISTOTLE Trial (Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation).  
3992 *J Am Coll Cardiol* 2013;**61**:2274-2284.
- 3993 382. Hijazi Z, Lindback J, Alexander JH, Hanna M, Held C, Hylek EM, Lopes RD, Oldgren J,  
3994 Siegbahn A, Stewart RA, White HD, Granger CB, Wallentin L, ARISTOTLE and STABILITY  
3995 Investigators. The ABC (age, biomarkers, clinical history) stroke risk score: a biomarker-based risk  
3996 score for predicting stroke in atrial fibrillation. *Eur Heart J* 2016:[Epub ahead of print].
- 3997 383. Gage BF, Yan Y, Milligan PE, Waterman AD, Culverhouse R, Rich MW, Radford MJ. Clinical  
3998 classification schemes for predicting hemorrhage: results from the National Registry of Atrial  
3999 Fibrillation (NRAF). *Am Heart J* 2006;**151**:713-719.
- 4000 384. Pisters R, Lane DA, Nieuwlaet R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score  
4001 (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart  
4002 Survey. *Chest* 2010;**138**:1093-1100.
- 4003 385. Fang MC, Go AS, Chang Y, Borowsky LH, Pomernacki NK, Udaltsova N, Singer DE. A new  
4004 risk scheme to predict warfarin-associated hemorrhage: The ATRIA (Anticoagulation and Risk Factors  
4005 in Atrial Fibrillation) Study. *J Am Coll Cardiol* 2011;**58**:395-401.
- 4006 386. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke  
4007 and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. *Eur*  
4008 *Heart J* 2012;**33**:1500-1510.
- 4009 387. Hijazi Z, Oldgren J, Lindback J, Alexander JH, Connolly SJ, Eikelboom JW, Ezekowitz MD,  
4010 Held C, Hylek EM, Lopes RD, Siegbahn A, Yusuf S, Granger CB, Wallentin L, ARISTOTLE and RE-  
4011 LY Investigators. The novel biomarker-based ABC (age, biomarkers, clinical history)-bleeding risk  
4012 score for patients with atrial fibrillation: a derivation and validation study. *Lancet* 2016:[Epub ahead of  
4013 print].
- 4014 388. O'Brien EC, Simon DN, Thomas LE, Hylek EM, Gersh BJ, Ansell JE, Kowey PR, Mahaffey  
4015 KW, Chang P, Fonarow GC, Pencina MJ, Piccini JP, Peterson ED. The ORBIT bleeding score: a  
4016 simple bedside score to assess bleeding risk in atrial fibrillation. *Eur Heart J* 2015;**36**:3258-3264.
- 4017 389. Loewen P, Dahri K. Risk of bleeding with oral anticoagulants: an updated systematic review  
4018 and performance analysis of clinical prediction rules. *Ann Hematol* 2011;**90**:1191-1200.
- 4019 390. Olesen JB, Lip GY, Hansen PR, Lindhardsen J, Ahlehoff O, Andersson C, Weeke P, Hansen  
4020 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, Lobbmeyer 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.

- 4080 406. Beyer-Westendorf J, Forster K, Pannach S, Ebertz F, Gelbricht V, Thieme C, Michalski F,  
4081 Kohler C, Werth S, Sahin K, Tittl L, Hansel U, Weiss N. Rates, management, and outcome of  
4082 rivaroxaban bleeding in daily care: results from the Dresden NOAC registry. *Blood* 2014;**124**:955-962.
- 4083 407. Camm AJ, Amarenco P, Haas S, Hess S, Kirchhof P, Kuhls S, van Eickels M, Turpie AG,  
4084 XANTUS Investigators. XANTUS: a real-world, prospective, observational study of patients treated  
4085 with rivaroxaban for stroke prevention in atrial fibrillation. *Eur Heart J* 2016;**37**:1145-1153.
- 4086 408. Wallentin L, Yusuf S, Ezekowitz MD, Alings M, Flather M, Franzosi MG, Pais P, Dans A,  
4087 Eikelboom J, Oldgren J, Pogue J, Reilly PA, Yang S, Connolly SJ, RE-LY investigators. Efficacy and  
4088 safety of dabigatran compared with warfarin at different levels of international normalised ratio control  
4089 for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. *Lancet* 2010;**376**:975-983.
- 4090 409. Piccini JP, Hellkamp AS, Lokhnygina Y, Patel MR, Harrell FE, Singer DE, Becker RC,  
4091 Breithardt G, Halperin JL, Hankey GJ, Berkowitz SD, Nessel CC, Mahaffey KW, Fox KA, Califf RM,  
4092 ROCKET AF Investigators. Relationship between time in therapeutic range and comparative  
4093 treatment effect of rivaroxaban and warfarin: results from the ROCKET AF trial. *J Am Heart Assoc*  
4094 2014;**3**:e000521.
- 4095 410. Olesen JB, Lip GY, Kamper AL, Hommel K, Kober L, Lane DA, Lindhardsen J, Gislason GH,  
4096 Torp-Pedersen C. Stroke and bleeding in atrial fibrillation with chronic kidney disease. *N Engl J Med*  
4097 2012;**367**:625-635.
- 4098 411. Albertsen IE, Rasmussen LH, Overvad TF, Graungaard T, Larsen TB, Lip GY. Risk of stroke  
4099 or systemic embolism in atrial fibrillation patients treated with warfarin: A systematic review and meta-  
4100 analysis. *Stroke* 2013;**44**:1329-1336.
- 4101 412. Hart RG, Pearce LA, Asinger RW, Herzog CA. Warfarin in atrial fibrillation patients with  
4102 moderate chronic kidney disease. *Clin J Am Soc Nephrol* 2011;**6**:2599-2604.
- 4103 413. Friberg L, Benson L, Lip GY. Balancing stroke and bleeding risks in patients with atrial  
4104 fibrillation and renal failure: the Swedish Atrial Fibrillation Cohort study. *Eur Heart J* 2014.
- 4105 414. Jun M, James MT, Manns BJ, Quinn RR, Ravani P, Tonelli M, Perkovic V, Winkelmayr WC,  
4106 Ma Z, Hemmelgarn BR. The association between kidney function and major bleeding in older adults  
4107 with atrial fibrillation starting warfarin treatment: population based observational study. *BMJ*  
4108 2015;**350**:h246.
- 4109 415. Del-Carpio Munoz F, Gharacholou SM, Munger TM, Friedman PA, Asirvatham SJ, Packer  
4110 DL, Noseworthy PA. Meta-Analysis of Renal Function on the Safety and Efficacy of Novel Oral  
4111 Anticoagulants for Atrial Fibrillation. *Am J Cardiol* 2016;**117**:69-75.
- 4112 416. Heidbuchel H, Verhamme P, Alings M, Antz M, Diener HC, Hacke W, Oldgren J, Sinnaeve P,  
4113 Camm AJ, Kirchhof P. Updated European Heart Rhythm Association Practical Guide on the use of  
4114 non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. *Europace*  
4115 2015;**17**:1467-1507.
- 4116 417. Zimmerman D, Sood MM, Rigatto C, Holden RM, Hiremath S, Clase CM. Systematic review  
4117 and meta-analysis of incidence, prevalence and outcomes of atrial fibrillation in patients on dialysis.  
4118 *Nephrol Dial Transplant* 2012;**27**:3816-3822.
- 4119 418. Marinigh R, Lane DA, Lip GY. Severe renal impairment and stroke prevention in atrial  
4120 fibrillation: implications for thromboprophylaxis and bleeding risk. *J Am Coll Cardiol* 2011;**57**:1339-  
4121 1348.
- 4122 419. Wizemann V, Tong L, Satayathum S, Disney A, Akiba T, Fissell RB, Kerr PG, Young EW,  
4123 Robinson BM. Atrial fibrillation in hemodialysis patients: clinical features and associations with  
4124 anticoagulant therapy. *Kidney Int* 2010;**77**:1098-1106.
- 4125 420. Chan KE, Lazarus JM, Thadhani R, Hakim RM. Warfarin use associates with increased risk  
4126 for stroke in hemodialysis patients with atrial fibrillation. *J Am Soc Nephrol* 2009;**20**:2223-2233.
- 4127 421. Winkelmayr WC, Liu J, Setoguchi S, Choudhry NK. Effectiveness and safety of warfarin  
4128 initiation in older hemodialysis patients with incident atrial fibrillation. *Clin J Am Soc Nephrol*  
4129 2011;**6**:2662-2668.
- 4130 422. Shah M, Avgil Tsadok M, Jackevicius CA, Essebag V, Eisenberg MJ, Rahme E, Humphries  
4131 KH, Tu JV, Behloul H, Guo H, Pilote L. Warfarin use and the risk for stroke and bleeding in patients  
4132 with atrial fibrillation undergoing dialysis. *Circulation* 2014;**129**:1196-1203.
- 4133 423. Bonde AN, Lip GY, Kamper AL, Hansen PR, Lamberts M, Hommel K, Hansen ML, Gislason  
4134 GH, Torp-Pedersen C, Olesen JB. Net clinical benefit of antithrombotic therapy in patients with atrial  
4135 fibrillation and chronic kidney disease: a nationwide observational cohort study. *J Am Coll Cardiol*  
4136 2014;**64**:2471-2482.
- 4137 424. Chan KE, Edelman ER, Wenger JB, Thadhani RI, Maddux FW. Dabigatran and rivaroxaban  
4138 use in atrial fibrillation patients on hemodialysis. *Circulation* 2015;**131**:972-979.

- 4139 425. Hijazi Z, Hohnloser SH, Oldgren J, Andersson U, Connolly SJ, Eikelboom JW, Ezekowitz MD,  
4140 Reilly PA, Siegbahn A, Yusuf S, Wallentin L. Efficacy and safety of dabigatran compared with warfarin  
4141 in relation to baseline renal function in patients with atrial fibrillation: a RE-LY (Randomized Evaluation  
4142 of Long-term Anticoagulation Therapy) trial analysis. *Circulation* 2014;**129**:961-970.
- 4143 426. Fox KA, Piccini JP, Wojdyla D, Becker RC, Halperin JL, Nessel CC, Paolini JF, Hankey GJ,  
4144 Mahaffey KW, Patel MR, Singer DE, Califf RM. Prevention of stroke and systemic embolism with  
4145 rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal  
4146 impairment. *Eur Heart J* 2011;**32**:2387-2394.
- 4147 427. Hohnloser SH, Hijazi Z, Thomas L, Alexander JH, Amerena J, Hanna M, Keltai M, Lanas F,  
4148 Lopes RD, Lopez-Sendon J, Granger CB, Wallentin L. Efficacy of apixaban when compared with  
4149 warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE  
4150 trial. *Eur Heart J* 2012;**33**:2821-2830.
- 4151 428. Stroke Prevention in Atrial Fibrillation Investigators. Stroke Prevention in Atrial Fibrillation  
4152 Study. Final results. *Circulation* 1991;**84**:527-539.
- 4153 429. Olesen JB, Lip GY, Lindhardsen J, Lane DA, Ahlehoff O, Hansen ML, Raunso J, Tolstrup JS,  
4154 Hansen PR, Gislason GH, Torp-Pedersen C. Risks of thromboembolism and bleeding with  
4155 thromboprophylaxis in patients with atrial fibrillation: A net clinical benefit analysis using a 'real world'  
4156 nationwide cohort study. *Thromb Haemost* 2011;**106**:739-749.
- 4157 430. Sjalander S, Sjalander A, Svensson PJ, Friberg L. Atrial fibrillation patients do not benefit  
4158 from acetylsalicylic acid. *Europace* 2014;**16**:631-638.
- 4159 431. ACTIVE Writing Group of the ACTIVE Investigators, Connolly S, Pogue J, Hart R, Pfeffer M,  
4160 Hohnloser S, Chrolavicius S, Pfeffer M, Hohnloser S, Yusuf S. Clopidogrel plus aspirin versus oral  
4161 anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for  
4162 prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet* 2006;**367**:1903-  
4163 1912.
- 4164 432. Connolly SJ, Pogue J, Eikelboom J, Flaker G, Commerford P, Franzosi MG, Healey JS, Yusuf  
4165 S, ACTIVE W Investigators. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation  
4166 depends on the quality of international normalized ratio control achieved by centers and countries as  
4167 measured by time in therapeutic range. *Circulation* 2008;**118**:2029-2037.
- 4168 433. Connolly SJ, Pogue J, Hart RG, Hohnloser SH, Pfeffer M, Chrolavicius S, Yusuf S, ACTIVE  
4169 Investigators. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med*  
4170 2009;**360**:2066-2078.
- 4171 434. van Walraven C, Hart RG, Connolly S, Austin PC, Mant J, Hobbs FD, Koudstaal PJ, Petersen  
4172 P, Perez-Gomez F, Knottnerus JA, Boode B, Ezekowitz MD, Singer DE. Effect of age on stroke  
4173 prevention therapy in patients with atrial fibrillation: the atrial fibrillation investigators. *Stroke*  
4174 2009;**40**:1410-1416.
- 4175 435. Olesen KH. The natural history of 271 patients with mitral stenosis under medical treatment.  
4176 *Br Heart J* 1962;**24**:349-357.
- 4177 436. Perez-Gomez F, Alegria E, Berjon J, Iriarte JA, Zumalde J, Salvador A, Mataix L, NASPEAF  
4178 Investigators. Comparative effects of antiplatelet, anticoagulant, or combined therapy in patients with  
4179 valvular and nonvalvular atrial fibrillation: a randomized multicenter study. *J Am Coll Cardiol*  
4180 2004;**44**:1557-1566.
- 4181 437. Rowe JC, Bland EF, Sprague HB, White PD. The course of mitral stenosis without surgery:  
4182 ten- and twenty-year perspectives. *Ann Intern Med* 1960;**52**:741-749.
- 4183 438. Wilson JK, Greenwood WF. The natural history of mitral stenosis. *Can Med Assoc J*  
4184 1954;**71**:323-331.
- 4185 439. Cannegieter SC, van der Meer FJ, Briet E, Rosendaal FR. Warfarin and aspirin after heart-  
4186 valve replacement. *N Engl J Med* 1994;**330**:507-508; author reply 508-509.
- 4187 440. Chiang CW, Lo SK, Ko YS, Cheng NJ, Lin PJ, Chang CH. Predictors of systemic embolism in  
4188 patients with mitral stenosis. A prospective study. *Ann Intern Med* 1998;**128**:885-889.
- 4189 441. Wan Y, Heneghan C, Perera R, Roberts N, Hollowell J, Glasziou P, Bankhead C, Xu Y.  
4190 Anticoagulation control and prediction of adverse events in patients with atrial fibrillation: a systematic  
4191 review. *Circ Cardiovasc Qual Outcomes* 2008;**1**:84-91.
- 4192 442. Morgan CL, McEwan P, Tukiendorf A, Robinson PA, Clemens A, Plumb JM. Warfarin  
4193 treatment in patients with atrial fibrillation: observing outcomes associated with varying levels of INR  
4194 control. *Thromb Res* 2009;**124**:37-41.
- 4195 443. Gallagher AM, Setakis E, Plumb JM, Clemens A, van Staa TP. Risks of stroke and mortality  
4196 associated with suboptimal anticoagulation in atrial fibrillation patients. *Thromb Haemost*  
4197 2011;**106**:968-977.

- 4198 444. De Caterina R, Husted S, Wallentin L, Andreotti F, Arnesen H, Bachmann F, Baigent C,  
4199 Huber K, Jespersen J, Kristensen SD, Lip GY, Morais J, Rasmussen LH, Siegbahn A, Verheugt FW,  
4200 Weitz JI. Vitamin K antagonists in heart disease: current status and perspectives (Section III). Position  
4201 paper of the ESC Working Group on Thrombosis--Task Force on Anticoagulants in Heart Disease.  
4202 *Thromb Haemost* 2013;**110**:1087-1107.
- 4203 445. Dans AL, Connolly SJ, Wallentin L, Yang S, Nakamya J, Brueckmann M, Ezekowitz M,  
4204 Oldgren J, Eikelboom JW, Reilly PA, Yusuf S. Concomitant use of antiplatelet therapy with dabigatran  
4205 or warfarin in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial.  
4206 *Circulation* 2013;**127**:634-640.
- 4207 446. Bajaj NS, Parashar A, Agarwal S, Sodhi N, Poddar KL, Garg A, Tuzcu EM, Kapadia SR.  
4208 Percutaneous left atrial appendage occlusion for stroke prophylaxis in nonvalvular atrial fibrillation: a  
4209 systematic review and analysis of observational studies. *JACC Cardiovasc Interv* 2014;**7**:296-304.
- 4210 447. Lewalter T, Kanagaratnam P, Schmidt B, Rosenqvist M, Nielsen-Kudsk JE, Ibrahim R, Albers  
4211 BA, Camm AJ. Ischaemic stroke prevention in patients with atrial fibrillation and high bleeding risk:  
4212 opportunities and challenges for percutaneous left atrial appendage occlusion. *Europace*  
4213 2014;**16**:626-630.
- 4214 448. Meier B, Blaauw Y, Khattab AA, Lewalter T, Sievert H, Tondo C, Glikson M. EHRA/EAPCI  
4215 expert consensus statement on catheter-based left atrial appendage occlusion. *Europace*  
4216 2014;**16**:1397-1416.
- 4217 449. Holmes DR, Jr., Kar S, Price MJ, Whisenant B, Sievert H, Doshi SK, Huber K, Reddy VY.  
4218 Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients  
4219 with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. *J Am Coll Cardiol*  
4220 2014;**64**:1-12.
- 4221 450. Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, Mullin CM, Sick P.  
4222 Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in  
4223 patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet* 2009;**374**:534-542.
- 4224 451. Reddy VY, Doshi SK, Sievert H, Buchbinder M, Neuzil P, Huber K, Halperin JL, Holmes D.  
4225 Percutaneous left atrial appendage closure for stroke prophylaxis in patients with atrial fibrillation: 2.3-  
4226 Year Follow-up of the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection  
4227 in Patients with Atrial Fibrillation) Trial. *Circulation* 2013;**127**:720-729.
- 4228 452. Reddy VY, Sievert H, Halperin J, Doshi SK, Buchbinder M, Neuzil P, Huber K, Whisenant B,  
4229 Kar S, Swarup V, Gordon N, Holmes D, PROTECT AF Steering Committee and Investigators.  
4230 Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial.  
4231 *JAMA* 2014;**312**:1988-1998.
- 4232 453. Holmes DR, Jr., Doshi SK, Kar S, Price MJ, Sanchez JM, Sievert H, Valderrabano M, Reddy  
4233 VY. Left Atrial Appendage Closure as an Alternative to Warfarin for Stroke Prevention in Atrial  
4234 Fibrillation: A Patient-Level Meta-Analysis. *J Am Coll Cardiol* 2015;**65**:2614-2623.
- 4235 454. Reddy VY, Mobius-Winkler S, Miller MA, Neuzil P, Schuler G, Wiebe J, Sick P, Sievert H. Left  
4236 atrial appendage closure with the Watchman device in patients with a contraindication for oral  
4237 anticoagulation: the ASAP study (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage  
4238 Closure Technology). *J Am Coll Cardiol* 2013;**61**:2551-2556.
- 4239 455. Santoro G, Meucci F, Stolcova M, Rezzaghi M, Mori F, Palmieri C, Paradossi U, Pastormerlo  
4240 LE, Rosso G, Berti S. Percutaneous left atrial appendage occlusion in patients with non-valvular atrial  
4241 fibrillation: implantation and up to four years follow-up of the AMPLATZER Cardiac Plug.  
4242 *EuroIntervention* 2014.
- 4243 456. Badheka AO, Chothani A, Mehta K, Patel NJ, Deshmukh A, Hoosien M, Shah N, Singh V,  
4244 Grover P, Savani GT, Panaich SS, Rathod A, Patel N, Arora S, Bhalara V, Coffey JO, O'Neill W,  
4245 Makkar R, Grines CL, Schreiber T, Di Biase L, Natale A, Viles-Gonzalez JF. Utilization and adverse  
4246 outcomes of percutaneous left atrial appendage closure for stroke prevention in atrial fibrillation in the  
4247 United States: influence of hospital volume. *Circ Arrhythm Electrophysiol* 2015;**8**:42-48.
- 4248 457. Pison L, Potpara TS, Chen J, Larsen TB, Bongiorno MG, Blomstrom-Lundqvist C. Left atrial  
4249 appendage closure-indications, techniques, and outcomes: results of the European Heart Rhythm  
4250 Association Survey. *Europace* 2015;**17**:642-646.
- 4251 458. Price MJ, Gibson DN, Yakubov SJ, Schultz JC, Di Biase L, Natale A, Burkhardt JD, Pershad  
4252 A, Byrne TJ, Gidney B, Aragon JR, Goldstein J, Moulton K, Patel T, Knight B, Lin AC, Valderrabano  
4253 M. Early safety and efficacy of percutaneous left atrial appendage suture ligation: results from the  
4254 U.S. transcatheter LAA ligation consortium. *J Am Coll Cardiol* 2014;**64**:565-572.
- 4255 459. Boersma LV, Schmidt B, Betts TR, Sievert H, Tamburino C, Teiger E, Pokushalov E, Kische  
4256 S, Schmitz T, Stein KM, Bergmann MW, EWOLUTION investigators. Implant success and safety of

- 4257 left atrial appendage closure with the WATCHMAN device: peri-procedural outcomes from the  
4258 EWOLUTION registry. *Eur Heart J* 2016:[Epub ahead of print].
- 4259 460. Kuramatsu JB, Gerner ST, Schellinger PD, Glahn J, Endres M, Sobesky J, Flechsenhar J,  
4260 Neugebauer H, Juttler E, Grau A, Palm F, Rother J, Michels P, Hamann GF, Huwel J, Hagemann G,  
4261 Barber B, Terborg C, Trostdorf F, Bazner H, Roth A, Wohrle J, Keller M, Schwarz M, Reimann G,  
4262 Volkmann J, Mullges W, Kraft P, Classen J, Hobohm C, Horn M, Milewski A, Reichmann H, Schneider  
4263 H, Schimmel E, Fink GR, Dohmen C, Stetefeld H, Witte O, Gunther A, Neumann-Haefelin T, Racs  
4264 AE, Nueckel M, Erbguth F, Kloska SP, Dorfler A, Kohrmann M, Schwab S, Huttner HB. Anticoagulant  
4265 reversal, blood pressure levels, and anticoagulant resumption in patients with anticoagulation-related  
4266 intracerebral hemorrhage. *JAMA* 2015;**313**:824-836.
- 4267 461. Budera P, Straka Z, Osmancik P, Vanek T, Jelinek S, Hlavicka J, Fojt R, Cervinka P, Hulman  
4268 M, Smid M, Maly M, Widimsky P. Comparison of cardiac surgery with left atrial surgical ablation vs.  
4269 cardiac surgery without atrial ablation in patients with coronary and/or valvular heart disease plus  
4270 atrial fibrillation: final results of the PRAGUE-12 randomized multicentre study. *Eur Heart J*  
4271 2012;**33**:2644-2652.
- 4272 462. Healey JS, Crystal E, Lamy A, Teoh K, Semelhago L, Hohnloser SH, Cybulsky I, Abouzahr L,  
4273 Sawchuck C, Carroll S, Morillo C, Kleine P, Chu V, Lonn E, Connolly SJ. Left Atrial Appendage  
4274 Occlusion Study (LAAOS): results of a randomized controlled pilot study of left atrial appendage  
4275 occlusion during coronary bypass surgery in patients at risk for stroke. *Am Heart J* 2005;**150**:288-293.
- 4276 463. Tsai YC, Phan K, Munkholm-Larsen S, Tian DH, La Meir M, Yan TD. Surgical left atrial  
4277 appendage occlusion during cardiac surgery for patients with atrial fibrillation: a meta-analysis. *Eur J*  
4278 *Cardiothorac Surg* 2015;**47**:847-854.
- 4279 464. Whitlock RP, Vincent J, Blackall MH, Hirsh J, Fremes S, Novick R, Devereaux PJ, Teoh K,  
4280 Lamy A, Connolly SJ, Yusuf S, Carrier M, Healey JS. Left Atrial Appendage Occlusion Study II  
4281 (LAAOS II). *Can J Cardiol* 2013;**29**:1443-1447.
- 4282 465. Aryana A, Singh SK, Singh SM, Gearoid O'Neill P, Bowers MR, Allen SL, Lewandowski SL,  
4283 Vierra EC, d'Avila A. Association between incomplete surgical ligation of left atrial appendage and  
4284 stroke and systemic embolization. *Heart Rhythm* 2015;**12**:1431-1437.
- 4285 466. Gillinov AM, Gelijns AC, Parides MK, DeRose JJ, Jr., Moskowitz AJ, Voisine P, Ailawadi G,  
4286 Bouchard D, Smith PK, Mack MJ, Acker MA, Mullen JC, Rose EA, Chang HL, Puskas JD, Couderc  
4287 JP, Gardner TJ, Varghese R, Horvath KA, Bolling SF, Michler RE, Geller NL, Ascheim DD, Miller MA,  
4288 Bagiella E, Moquete EG, Williams P, Taddei-Peters WC, O'Gara PT, Blackstone EH, Argenziano M,  
4289 CTSN Investigators. Surgical ablation of atrial fibrillation during mitral-valve surgery. *N Engl J Med*  
4290 2015;**372**:1399-1409.
- 4291 467. Whitlock R, Healey J, Vincent J, Brady K, Teoh K, Royse A, Shah P, Guo Y, Alings M,  
4292 Folkeringa RJ, Paparella D, Colli A, Meyer SR, Legare JF, Lamontagne F, Reents W, Boning A,  
4293 Connolly S. Rationale and design of the Left Atrial Appendage Occlusion Study (LAAOS) III. *Ann*  
4294 *Cardiothorac Surg* 2014;**3**:45-54.
- 4295 468. Boersma LV, Castella M, van Boven W, Berruezo A, Yilmaz A, Nadal M, Sandoval E, Calvo  
4296 N, Brugada J, Kelder J, Wijffels M, Mont L. Atrial fibrillation catheter ablation versus surgical ablation  
4297 treatment (FAST): a 2-center randomized clinical trial. *Circulation* 2012;**125**:23-30.
- 4298 469. Grau AJ, Weimar C, Buggle F, Heinrich A, Goertler M, Neumaier S, Glahn J, Brandt T, Hacke  
4299 W, Diener H. Risk factors, outcome, and treatment in subtypes of ischemic stroke: the German stroke  
4300 data bank. *Stroke* 2001;**32**:2559-2566.
- 4301 470. Giles MF, Rothwell PM. Risk of stroke early after transient ischaemic attack: a systematic  
4302 review and meta-analysis. *Lancet Neurol* 2007;**6**:1063-1072.
- 4303 471. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, Brott T, Cohen G, Davis S,  
4304 Donnan G, Grotta J, Howard G, Kaste M, Koga M, von Kummer R, Lansberg M, Lindley RI, Murray G,  
4305 Olivot JM, Parsons M, Tilley B, Toni D, Toyoda K, Wahlgren N, Wardlaw J, Whiteley W, Del Zoppo  
4306 GJ, Baigent C, Sandercock P, Hacke W, Stroke Thrombolysis Trialists' Collaborative Group. Effect of  
4307 treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for  
4308 acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet*  
4309 2014.
- 4310 472. Diener HC, Stanford S, Abdul-Rahim A, Christensen L, Hougaard KD, Bakhai A, Veltkamp R,  
4311 Worthmann H. Anti-thrombotic therapy in patients with atrial fibrillation and intracranial hemorrhage.  
4312 *Expert Rev Neurother* 2014;**14**:1019-1028.
- 4313 473. Hankey GJ, Norrving B, Hacke W, Steiner T. Management of acute stroke in patients taking  
4314 novel oral anticoagulants. *Int J Stroke* 2014;**9**:627-632.
- 4315 474. Xian Y, Liang L, Smith EE, Schwamm LH, Reeves MJ, Olson DM, Hernandez AF, Fonarow  
4316 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, Rochweg 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 Caulfield 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

- 4377 G, Gielen S, Haller H, Hoes AW, Jordan J, Kahan T, Komajda M, Lovic D, Mahrholdt H, Olsen MH,  
4378 Ostergren J, Parati G, Perk J, Polonia J, Popescu BA, Reiner Z, Ryden L, Sirenko Y, Stanton A,  
4379 Struijker-Boudier H, Tsioufis C, van de Borne P, Vlachopoulos C, Volpe M, Wood DA. 2013 ESH/ESC  
4380 guidelines for the management of arterial hypertension: the Task Force for the Management of  
4381 Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of  
4382 Cardiology (ESC). *Eur Heart J* 2013;**34**:2159-2219.
- 4383 490. Eikelboom JW, Wallentin L, Connolly SJ, Ezekowitz M, Healey JS, Oldgren J, Yang S, Alings  
4384 M, Kaatz S, Hohnloser SH, Diener HC, Franzosi MG, Huber K, Reilly P, Varrone J, Yusuf S. Risk of  
4385 bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial  
4386 fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial.  
4387 *Circulation* 2011;**123**:2363-2372.
- 4388 491. Goodman SG, Wojdyla DM, Piccini JP, White HD, Paolini JF, Nessel CC, Berkowitz SD,  
4389 Mahaffey KW, Patel MR, Sherwood MW, Becker RC, Halperin JL, Hacke W, Singer DE, Hankey GJ,  
4390 Breithardt G, Fox KA, Califf RM, ROCKET AF Investigators. Factors associated with major bleeding  
4391 events: insights from the ROCKET AF trial (rivaroxaban once-daily oral direct factor Xa inhibition  
4392 compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation). *J*  
4393 *Am Coll Cardiol* 2014;**63**:891-900.
- 4394 492. Chang HY, Zhou M, Tang W, Alexander GC, Singh S. Risk of gastrointestinal bleeding  
4395 associated with oral anticoagulants: population based retrospective cohort study. *BMJ*  
4396 2015;**350**:h1585.
- 4397 493. Abraham NS, Singh S, Alexander GC, Heien H, Haas LR, Crown W, Shah ND. Comparative  
4398 risk of gastrointestinal bleeding with dabigatran, rivaroxaban, and warfarin: population based cohort  
4399 study. *Bmj* 2015;**350**:h1857.
- 4400 494. Björck F, Renlund H, Lip GYH, Wester P, Svensson PJ, Själander A. Outcomes in a Warfarin-  
4401 Treated Population With Atrial Fibrillation. *JAMA Cardiology* 2016.
- 4402 495. Jacobs LG, Billett HH, Freeman K, Dinglas C, Jumaquio L. Anticoagulation for stroke  
4403 prevention in elderly patients with atrial fibrillation, including those with falls and/or early-stage  
4404 dementia: a single-center, retrospective, observational study. *Am J Geriatr Pharmacother* 2009;**7**:159-  
4405 166.
- 4406 496. Banerjee A, Clementy N, Haguenoer K, Fauchier L, Lip GY. Prior history of falls and risk of  
4407 outcomes in atrial fibrillation: the Loire Valley Atrial Fibrillation Project. *Am J Med* 2014;**127**:972-978.
- 4408 497. Palareti G, Cosmi B. Bleeding with anticoagulation therapy - who is at risk, and how best to  
4409 identify such patients. *Thromb Haemost* 2009;**102**:268-278.
- 4410 498. van Schie RM, Wadelius MI, Kamali F, Daly AK, Manolopoulos VG, de Boer A, Barallon R,  
4411 Verhoef TI, Kirchheiner J, Haschke-Becher E, Briz M, Rosendaal FR, Redekop WK, Pirmohamed M,  
4412 Maitland van der Zee AH. Genotype-guided dosing of coumarin derivatives: the European  
4413 pharmacogenetics of anticoagulant therapy (EU-PACT) trial design. *Pharmacogenomics*  
4414 2009;**10**:1687-1695.
- 4415 499. International Warfarin Pharmacogenetics Consortium, Klein TE, Altman RB, Eriksson N,  
4416 Gage BF, Kimmel SE, Lee MT, Limdi NA, Page D, Roden DM, Wagner MJ, Caldwell MD, Johnson  
4417 JA. Estimation of the warfarin dose with clinical and pharmacogenetic data. *N Engl J Med*  
4418 2009;**360**:753-764.
- 4419 500. Schwarz UI, Ritchie MD, Bradford Y, Li C, Dudek SM, Frye-Anderson A, Kim RB, Roden DM,  
4420 Stein CM. Genetic determinants of response to warfarin during initial anticoagulation. *N Engl J Med*  
4421 2008;**358**:999-1008.
- 4422 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.  
4423 Genotype-Guided Dosing of Coumarin Anticoagulants: A Meta-analysis of Randomized Controlled  
4424 Trials. *J Cardiovasc Pharmacol Ther* 2015;**20**:387-394.
- 4425 502. Douketis JD, Spyropoulos AC, Kaatz S, Becker RC, Caprini JA, Dunn AS, Garcia DA,  
4426 Jacobson A, Jaffer AK, Kong DF, Schulman S, Turpie AG, Hasselblad V, Ortel TL, BRIDGE  
4427 Investigators. Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation. *N Engl J Med*  
4428 2015;**373**:823-833.
- 4429 503. Cuker A, Siegal DM, Crowther MA, Garcia DA. Laboratory measurement of the anticoagulant  
4430 activity of the non-vitamin K oral anticoagulants. *J Am Coll Cardiol* 2014;**64**:1128-1139.
- 4431 504. Niessner A, Tamargo J, Morais J, Koller L, Wassmann S, Husted SE, Torp-Pedersen C,  
4432 Kjeldsen K, Lewis BS, Drexel H, Kaski JC, Atar D, Storey RF, Lip GY, Verheugt FW, Agewall S.  
4433 Reversal strategies for non-vitamin K antagonist oral anticoagulants: a critical appraisal of available  
4434 evidence and recommendations for clinical management-a joint position paper of the European  
4435 Society of Cardiology Working Group on Cardiovascular Pharmacotherapy and European Society of  
4436 Cardiology Working Group on Thrombosis. *Eur Heart J* 2015:[Epub ahead of print].

- 4437 505. Hanley JP. Warfarin reversal. *J Clin Pathol* 2004;**57**:1132-1139.
- 4438 506. Parry-Jones AR, Di Napoli M, Goldstein JN, Schreuder FH, Tetri S, Tatlisumak T, Yan B, van  
4439 Nieuwenhuizen KM, Dequatre-Ponchelle N, Lee-Archer M, Horstmann S, Wilson D, Pomeroy F,  
4440 Masotti L, Lerpiniere C, Godoy DA, Cohen AS, Houben R, Salman RA, Pennati P, Fenoglio L,  
4441 Werring D, Veltkamp R, Wood E, Dewey HM, Cordonnier C, Klijn CJ, Meligeni F, Davis SM,  
4442 Huhtakangas J, Staals J, Rosand J, Meretoja A. Reversal strategies for vitamin K antagonists in acute  
4443 intracerebral hemorrhage. *Ann Neurol* 2015;**78**:54-62.
- 4444 507. Goldstein JN, Refaai MA, Milling TJ, Jr., Lewis B, Goldberg-Alberts R, Hug BA, Sarode R.  
4445 Four-factor prothrombin complex concentrate versus plasma for rapid vitamin K antagonist reversal in  
4446 patients needing urgent surgical or invasive interventions: a phase 3b, open-label, non-inferiority,  
4447 randomised trial. *Lancet* 2015;**385**:2077-2087.
- 4448 508. Siegal DM, Curnutte JT, Connolly SJ, Lu G, Conley PB, Wiens BL, Mathur VS, Castillo J,  
4449 Bronson MD, Leeds JM, Mar FA, Gold A, Crowther MA. Andexanet Alfa for the Reversal of Factor Xa  
4450 Inhibitor Activity. *N Engl J Med* 2015;**373**:2413-2424.
- 4451 509. Crowther M, Crowther MA. Antidotes for novel oral anticoagulants: current status and future  
4452 potential. *Arterioscler Thromb Vasc Biol* 2015;**35**:1736-1745.
- 4453 510. Staerk L, Lip GY, Olesen JB, Fosbol EL, Pallisgaard JL, Bonde AN, Gundlund A, Lindhardt  
4454 TB, Hansen ML, Torp-Pedersen C, Gislason GH. Stroke and recurrent haemorrhage associated with  
4455 antithrombotic treatment after gastrointestinal bleeding in patients with atrial fibrillation: nationwide  
4456 cohort study. *BMJ* 2015;**351**:h5876.
- 4457 511. Felmeden DC, Lip GY. Antithrombotic therapy in hypertension: a Cochrane Systematic  
4458 review. *J Hum Hypertens* 2005;**19**:185-196.
- 4459 512. Sharma M, Cornelius VR, Patel JP, Davies JG, Molokhia M. Efficacy and Harms of Direct  
4460 Oral Anticoagulants in the Elderly for Stroke Prevention in Atrial Fibrillation and Secondary Prevention  
4461 of Venous Thromboembolism: Systematic Review and Meta-Analysis. *Circulation* 2015;**132**:194-204.
- 4462 513. Ruiz-Nodar JM, Marin F, Hurtado JA, Valencia J, Pinar E, Pineda J, Gimeno JR, Sogorb F,  
4463 Valdes M, Lip GYH. Anticoagulant and antiplatelet therapy use in 426 patients with atrial fibrillation  
4464 undergoing percutaneous coronary intervention and stent implantation implications for bleeding risk  
4465 and prognosis. *J Am Coll Cardiol* 2008;**51**:818-825.
- 4466 514. Hansen ML, Sorensen R, Clausen MT, Fog-Petersen ML, Raunso J, Gadsboll N, Gislason  
4467 GH, Folke F, Andersen SS, Schramm TK, Abildstrom SZ, Poulsen HE, Kober L, Torp-Pedersen C.  
4468 Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients  
4469 with atrial fibrillation. *Arch Intern Med* 2010;**170**:1433-1441.
- 4470 515. Lamberts M, Olesen JB, Ruwald MH, Hansen CM, Karasoy D, Kristensen SL, Kober L, Torp-  
4471 Pedersen C, Gislason GH, Hansen ML. Bleeding after initiation of multiple antithrombotic drugs,  
4472 including triple therapy, in atrial fibrillation patients following myocardial infarction and coronary  
4473 intervention: a nationwide cohort study. *Circulation* 2012;**126**:1185-1193.
- 4474 516. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head  
4475 SJ, Juni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ,  
4476 Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski  
4477 A. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial  
4478 Revascularization of the European Society of Cardiology (ESC) and the European Association for  
4479 Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European  
4480 Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2014;**35**:2541-2619.
- 4481 517. Vandvik PO, Lincoff AM, Gore JM, Gutterman DD, Sonnenberg FA, Alonso-Coello P, Akl EA,  
4482 Lansberg MG, Guyatt GH, Spencer FA, American College of Chest Physicians. Primary and  
4483 secondary prevention of cardiovascular disease: Antithrombotic Therapy and Prevention of  
4484 Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice  
4485 Guidelines. *Chest* 2012;**141**:e637S-668S.
- 4486 518. Rubboli A, Faxon DP, Juhani Airaksinen KE, Schlitt A, Marin F, Bhatt DL, Lip GYH. The  
4487 optimal management of patients on oral anticoagulation undergoing coronary artery stenting. The  
4488 10th Anniversary Overview. *Thromb Haemost* 2014;**112**:1080-1087.
- 4489 519. Oldgren J, Wallentin L, Alexander JH, James S, Jonelid B, Steg G, Sundstrom J. New oral  
4490 anticoagulants in addition to single or dual antiplatelet therapy after an acute coronary syndrome: a  
4491 systematic review and meta-analysis. *Eur Heart J* 2013;**34**:1670-1680.
- 4492 520. Lip GY, Windecker S, Huber K, Kirchhof P, Marin F, Ten Berg JM, Haeusler KG, Boriani G,  
4493 Capodanno D, Gilard M, Zeymer U, Lane D, Storey RF, Bueno H, Collet JP, Fauchier L, Halvorsen S,  
4494 Lettino M, Morais J, Mueller C, Potpara TS, Rasmussen LH, Rubboli A, Tamargo J, Valgimigli M,  
4495 Zamorano JL. Management of antithrombotic therapy in atrial fibrillation patients presenting with acute  
4496 coronary syndrome and/or undergoing percutaneous coronary or valve interventions: a joint

- 4497 consensus document of the European Society of Cardiology Working Group on Thrombosis,  
4498 European Heart Rhythm Association (EHRA), European Association of Percutaneous Cardiovascular  
4499 Interventions (EAPCI) and European Association of Acute Cardiac Care (ACCA) endorsed by the  
4500 Heart Rhythm Society (HRS) and Asia-Pacific Heart Rhythm Society (APHRs). *Eur Heart J*  
4501 2014;**35**:3155-3179.
- 4502 521. Mega JL, Braunwald E, Mohanavelu S, Burton P, Poulter R, Misselwitz F, Hricak V,  
4503 Barnathan ES, Bordes P, Witkowski A, Markov V, Oppenheimer L, Gibson CM, ATLAS ACS-TIMI 46  
4504 study group. Rivaroxaban versus placebo in patients with acute coronary syndromes (ATLAS ACS-  
4505 TIMI 46): a randomised, double-blind, phase II trial. *Lancet* 2009;**374**:29-38.
- 4506 522. Sarafoff N, Martischinig A, Wealer J, Mayer K, Mehilli J, Sibbing D, Kastrati A. Triple therapy  
4507 with aspirin, prasugrel, and vitamin K antagonists in patients with drug-eluting stent implantation and  
4508 an indication for oral anticoagulation. *J Am Coll Cardiol* 2013;**61**:2060-2066.
- 4509 523. Jackson LR, 2nd, Ju C, Zettler M, Messenger JC, Cohen DJ, Stone GW, Baker BA, Efron M,  
4510 Peterson ED, Wang TY. Outcomes of Patients With Acute Myocardial Infarction Undergoing  
4511 Percutaneous Coronary Intervention Receiving an Oral Anticoagulant and Dual Antiplatelet Therapy:  
4512 A Comparison of Clopidogrel Versus Prasugrel From the TRANSLATE-ACS Study. *JACC Cardiovasc*  
4513 *Interv* 2015;**8**:1880-1889.
- 4514 524. Dewilde WJM, Oirbans T, Verheugt FWA, Kelder JC, De Smet BJGL, Herrman J-P,  
4515 Adriaenssens T, Vrolix M, Heestermans AACM, Vis MM, Tijssen JGP, van 't Hof AW, ten Berg JM. Use  
4516 of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing  
4517 percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet*  
4518 2013;**381**:1107-1115.
- 4519 525. Braun OÖ, Bico B, Chaudhry U, Wagner H, Koul S, Tyden P, Schersten F, Jovinge S,  
4520 Svensson PJ, Gustav Smith J, van der Pals J. Concomitant use of warfarin and ticagrelor as an  
4521 alternative to triple antithrombotic therapy after an acute coronary syndrome. *Thromb Res*  
4522 2015;**135**:26-30.
- 4523 526. Nikolaidou T, Channer KS. Chronic atrial fibrillation: a systematic review of medical heart rate  
4524 control management. *Postgrad Med J* 2009;**85**:303-312.
- 4525 527. Tamariz LJ, Bass EB. Pharmacological rate control of atrial fibrillation. *Cardiol Clin*  
4526 2004;**22**:35-45.
- 4527 528. Segal JB, McNamara RL, Miller MR, Kim N, Goodman SN, Powe NR, Robinson K, Yu D,  
4528 Bass EB. The evidence regarding the drugs used for ventricular rate control. In. *J Fam Practice*; 2000,  
4529 47-59.
- 4530 529. Schreck DM, Rivera AR, Tricarico VJ. Emergency management of atrial fibrillation and flutter:  
4531 intravenous diltiazem versus intravenous digoxin. *Ann Emerg Med* 1997;**29**:135-140.
- 4532 530. Siu CW, Lau CP, Lee WL, Lam KF, Tse HF. Intravenous diltiazem is superior to intravenous  
4533 amiodarone or digoxin for achieving ventricular rate control in patients with acute uncomplicated atrial  
4534 fibrillation. *Crit Care Med* 2009;**37**:2174-2179; quiz 2180.
- 4535 531. Tisdale JE, Padhi ID, Goldberg AD, Silverman NA, Webb CR, Higgins RS, Paone G, Frank  
4536 DM, Borzak S. A randomized, double-blind comparison of intravenous diltiazem and digoxin for atrial  
4537 fibrillation after coronary artery bypass surgery. *Am Heart J* 1998;**135**:739-747.
- 4538 532. Scheuermeyer FX, Grafstein E, Stenstrom R, Christenson J, Heslop C, Heilbron B, McGrath  
4539 L, Innes G. Safety and efficiency of calcium channel blockers versus beta-blockers for rate control in  
4540 patients with atrial fibrillation and no acute underlying medical illness. *Acad Emerg Med* 2013;**20**:222-  
4541 230.
- 4542 533. Darby AE, Dimarco JP. Management of atrial fibrillation in patients with structural heart  
4543 disease. *Circulation* 2012;**125**:945-957.
- 4544 534. Elkayam U. Calcium channel blockers in heart failure. *Cardiology* 1998;**89 Suppl 1**:38-46.
- 4545 535. Goldstein RE, Boccuzzi SJ, Cruess D, Nattel S. Diltiazem increases late-onset congestive  
4546 heart failure in postinfarction patients with early reduction in ejection fraction. The Adverse Experience  
4547 Committee; and the Multicenter Diltiazem Postinfarction Research Group. *Circulation* 1991;**83**:52-60.
- 4548 536. Clemo HF, Wood MA, Gilligan DM, Ellenbogen KA. Intravenous amiodarone for acute heart  
4549 rate control in the critically ill patient with atrial tachyarrhythmias. *Am J Cardiol* 1998;**81**:594-598.
- 4550 537. Delle Karth G, Geppert A, Neunteufl T, Priglinger U, Haumer M, Gschwandtner M,  
4551 Siostrzonek P, Heinz G. Amiodarone versus diltiazem for rate control in critically ill patients with atrial  
4552 tachyarrhythmias. *Crit Care Med* 2001;**29**:1149-1153.
- 4553 538. Hou ZY, Chang MS, Chen CY, Tu MS, Lin SL, Chiang HT, Woosley RL. Acute treatment of  
4554 recent-onset atrial fibrillation and flutter with a tailored dosing regimen of intravenous amiodarone. A  
4555 randomized, digoxin-controlled study. *Eur Heart J* 1995;**16**:521-528.

- 4556 539. National Institute for Health and Care Excellence (NICE). *Atrial fibrillation: management*.  
4557 *NICE guidelines [CG180]*. <http://www.nice.org.uk/guidance/cg180/>. Date last accessed 5 May  
4558 2016 Accessed 15/09/2014; <http://www.nice.org.uk/guidance/cg180/>  
4559 540. Kotecha D, Manzano L, Krum H, Rosano G, Holmes J, Altman DG, Collins P, Packer M,  
4560 Wikstrand J, Coats AJS, Cleland JGF, Kirchhof P, von Lueder TG, Rigby A, Andersson B, Lip GYH,  
4561 van Veldhuisen DJ, Shibata MC, Wedel H, Böhm M, Flather MD, Beta-Blockers in Heart Failure  
4562 Collaborative Group. Effect of age and sex on efficacy and tolerability of  $\beta$  blockers in patients with  
4563 heart failure with reduced ejection fraction: individual patient data meta-analysis. *BMJ*  
4564 2016;**353**:i1855.
- 4565 541. Ulimoen SR, Enger S, Carlson J, Platonov PG, Pripp AH, Abdelnoor M, Arnesen H, Gjesdal  
4566 K, Tveit A. Comparison of four single-drug regimens on ventricular rate and arrhythmia-related  
4567 symptoms in patients with permanent atrial fibrillation. *Am J Cardiol* 2013;**111**:225-230.
- 4568 542. Ulimoen SR, Enger S, Pripp AH, Abdelnoor M, Arnesen H, Gjesdal K, Tveit A. Calcium  
4569 channel blockers improve exercise capacity and reduce N-terminal Pro-B-type natriuretic peptide  
4570 levels compared with beta-blockers in patients with permanent atrial fibrillation. *Eur Heart J*  
4571 2014;**35**:517-524.
- 4572 543. Goldberger ZD, Alexander GC. Digitalis use in contemporary clinical practice: refitting the  
4573 foxglove. *JAMA Intern Med* 2014;**174**:151-154.
- 4574 544. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients  
4575 with heart failure. *N Engl J Med* 1997;**336**:525-533.
- 4576 545. Ahmed A, Rich MW, Fleg JL, Zile MR, Young JB, Kitzman DW, Love TE, Aronow WS, Adams  
4577 KF, Jr., Gheorghiade M. Effects of digoxin on morbidity and mortality in diastolic heart failure: the  
4578 ancillary digitalis investigation group trial. *Circulation* 2006;**114**:397-403.
- 4579 546. Ziff OJ, Kotecha D. Digoxin: The good and the bad. *Trends in Cardiovascular Medicine*  
4580 2016:[Epub ahead of print].
- 4581 547. Turakhia MP, Santangeli P, Winkelmayr WC, Xu X, Ullal AJ, Than CT, Schmitt S, Holmes  
4582 TH, Frayne SM, Phibbs CS, Yang F, Hoang DD, Ho PM, Heidenreich PA. Increased mortality  
4583 associated with digoxin in contemporary patients with atrial fibrillation: findings from the TREAT-AF  
4584 study. *J Am Coll Cardiol* 2014;**64**:660-668.
- 4585 548. Hallberg P, Lindback J, Lindahl B, Stenström U, Melhus H. Digoxin and mortality in atrial  
4586 fibrillation: a prospective cohort study. *Eur J Clin Pharmacol* 2007;**63**:959-971.
- 4587 549. Whitbeck MG, Charnigo RJ, Khairy P, Ziada K, Bailey AL, Zegarra MM, Shah J, Morales G,  
4588 Macaulay T, Sorrell VL, Campbell CL, Gurley J, Anaya P, Nasr H, Bai R, Di Biase L, Booth DC,  
4589 Jondeau G, Natale A, Roy D, Smyth S, Moliterno DJ, Elayi CS. Increased mortality among patients  
4590 taking digoxin--analysis from the AFFIRM study. *Eur Heart J* 2013;**34**:1481-1488.
- 4591 550. Gheorghiade M, Fonarow GC, van Veldhuisen DJ, Cleland JG, Butler J, Epstein AE, Patel K,  
4592 Aban IB, Aronow WS, Anker SD, Ahmed A. Lack of evidence of increased mortality among patients  
4593 with atrial fibrillation taking digoxin: findings from post hoc propensity-matched analysis of the  
4594 AFFIRM trial. *Eur Heart J* 2013;**34**:1489-1497.
- 4595 551. Flory JH, Ky B, Haynes K, S MB, Munson J, Rowan C, Strom BL, Hennessy S. Observational  
4596 cohort study of the safety of digoxin use in women with heart failure. *BMJ Open* 2012;**2**:e000888.
- 4597 552. Andrey JL, Romero S, Garcia-Egido A, Escobar MA, Corzo R, Garcia-Dominguez G, Lechuga  
4598 V, Gomez F. Mortality and morbidity of heart failure treated with digoxin. A propensity-matched study.  
4599 *Int J Clin Pract* 2011;**65**:1250-1258.
- 4600 553. Allen LA, Fonarow GC, Simon DN, Thomas LE, Marzec LN, Pokorney SD, Gersh BJ, Go AS,  
4601 Hylek EM, Kowey PR, Mahaffey KW, Chang P, Peterson ED, Piccini JP, ORBIT-AF Investigators.  
4602 Digoxin Use and Subsequent Outcomes Among Patients in a Contemporary Atrial Fibrillation Cohort.  
4603 *J Am Coll Cardiol* 2015;**65**:2691-2698.
- 4604 554. Khand AU, Rankin AC, Martin W, Taylor J, Gemmell I, Cleland JG. Carvedilol alone or in  
4605 combination with digoxin for the management of atrial fibrillation in patients with heart failure? *J Am*  
4606 *Coll Cardiol* 2003;**42**:1944-1951.
- 4607 555. Farshi R, Kistner D, Sarma JS, Longmate JA, Singh BN. Ventricular rate control in chronic  
4608 atrial fibrillation during daily activity and programmed exercise: a crossover open-label study of five  
4609 drug regimens. *J Am Coll Cardiol* 1999;**33**:304-310.
- 4610 556. Koh KK, Kwon KS, Park HB, Baik SH, Park SJ, Lee KH, Kim EJ, Kim SH, Cho SK, Kim SS.  
4611 Efficacy and safety of digoxin alone and in combination with low-dose diltiazem or betaxolol to control  
4612 ventricular rate in chronic atrial fibrillation. *Am J Cardiol* 1995;**75**:88-90.
- 4613 557. Lewis RV, McMurray J, McDevitt DG. Effects of atenolol, verapamil, and xamoterol on heart  
4614 rate and exercise tolerance in digitalised patients with chronic atrial fibrillation. *J Cardiovasc*  
4615 *Pharmacol* 1989;**13**:1-6.

- 4616 558. Tsuneda T, Yamashita T, Fukunami M, Kumagai K, Niwano S, Okumura K, Inoue H. Rate  
4617 control and quality of life in patients with permanent atrial fibrillation: the Quality of Life and Atrial  
4618 Fibrillation (QOLAF) Study. *Circ J* 2006;**70**:965-970.
- 4619 559. ClinicalTrials.gov. *Rate Control Therapy Evaluation in Permanent Atrial Fibrillation (RATE-*  
4620 *AF)*. <https://clinicaltrials.gov/ct2/show/NCT02391337>. Date last accessed 5 May 2016
- 4621 560. Van Gelder IC, Groenveld HF, Crijns HJ, Tuininga YS, Tijssen JG, Alings AM, Hillege HL,  
4622 Bergsma-Kadijk JA, Cornel JH, Kamp O, Tukkie R, Bosker HA, Van Veldhuisen DJ, Van den Berg  
4623 MP, RACE II Investigators. Lenient versus strict rate control in patients with atrial fibrillation. *N Engl J*  
4624 *Med* 2010;**362**:1363-1373.
- 4625 561. Groenveld HF, Crijns HJ, Van den Berg MP, Van Sonderen E, Alings AM, Tijssen JG, Hillege  
4626 HL, Tuininga YS, Van Veldhuisen DJ, Ranchor AV, Van Gelder IC, RACE II Investigators. The effect  
4627 of rate control on quality of life in patients with permanent atrial fibrillation: data from the RACE II  
4628 (Rate Control Efficacy in Permanent Atrial Fibrillation II) study. *J Am Coll Cardiol* 2011;**58**:1795-1803.
- 4629 562. Van Gelder IC, Wyse DG, Chandler ML, Cooper HA, Olshansky B, Hagens VE, Crijns HJ,  
4630 RACE and AFFIRM Investigators. Does intensity of rate-control influence outcome in atrial fibrillation?  
4631 An analysis of pooled data from the RACE and AFFIRM studies. *Europace* 2006;**8**:935-942.
- 4632 563. Queiroga A, Marshall HJ, Clune M, Gammage MD. Ablate and pace revisited: long term  
4633 survival and predictors of permanent atrial fibrillation. *Heart* 2003;**89**:1035-1038.
- 4634 564. Lim KT, Davis MJ, Powell A, Arnold L, Moulden K, Bulsara M, Weerasooriya R. Ablate and  
4635 pace strategy for atrial fibrillation: long-term outcome of AIRCRAFT trial. *Europace* 2007;**9**:498-505.
- 4636 565. Geelen P, Brugada J, Andries E, Brugada P. Ventricular fibrillation and sudden death after  
4637 radiofrequency catheter ablation of the atrioventricular junction. *Pacing Clin Electrophysiol*  
4638 1997;**20**:343-348.
- 4639 566. Wang RX, Lee HC, Hodge DO, Cha YM, Friedman PA, Rea RF, Munger TM, Jahangir A,  
4640 Srivathsan K, Shen WK. Effect of pacing method on risk of sudden death after atrioventricular node  
4641 ablation and pacemaker implantation in patients with atrial fibrillation. *Heart Rhythm* 2013;**10**:696-701.
- 4642 567. Chatterjee NA, Upadhyay GA, Ellenbogen KA, McAlister FA, Choudhry NK, Singh JP.  
4643 Atrioventricular nodal ablation in atrial fibrillation: a meta-analysis and systematic review. *Circ*  
4644 *Arrhythm Electrophysiol* 2012;**5**:68-76.
- 4645 568. Bradley DJ, Shen WK. Overview of management of atrial fibrillation in symptomatic elderly  
4646 patients: pharmacologic therapy versus AV node ablation. *Clin Pharmacol Ther* 2007;**81**:284-287.
- 4647 569. Wood MA, Brown-Mahoney C, Kay GN, Ellenbogen KA. Clinical outcomes after ablation and  
4648 pacing therapy for atrial fibrillation : a meta-analysis. *Circulation* 2000;**101**:1138-1144.
- 4649 570. Ozcan C, Jahangir A, Friedman PA, Patel PJ, Munger TM, Rea RF, Lloyd MA, Packer DL,  
4650 Hodge DO, Gersh BJ, Hammill SC, Shen WK. Long-term survival after ablation of the atrioventricular  
4651 node and implantation of a permanent pacemaker in patients with atrial fibrillation. *N Engl J Med*  
4652 2001;**344**:1043-1051.
- 4653 571. Hess PL, Jackson KP, Hasselblad V, Al-Khatib SM. Is cardiac resynchronization therapy an  
4654 antiarrhythmic therapy for atrial fibrillation? A systematic review and meta-analysis. *Curr Cardiol Rep*  
4655 2013;**15**:330.
- 4656 572. Hoppe UC, Casares JM, Eiskjaer H, Hagemann A, Cleland JG, Freemantle N, Erdmann E.  
4657 Effect of cardiac resynchronization on the incidence of atrial fibrillation in patients with severe heart  
4658 failure. *Circulation* 2006;**114**:18-25.
- 4659 573. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, Cleland  
4660 J, Deharo JC, Delgado V, Elliott PM, Gorenek B, Israel CW, Leclercq C, Linde C, Mont L, Padeletti L,  
4661 Sutton R, Vardas PE, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V,  
4662 Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti  
4663 P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendra M,  
4664 Torbicki A, Wijns W, Windecker S, Kirchhof P, Blomstrom-Lundqvist C, Badano LP, Aliyev F, Bansch  
4665 D, Baumgartner H, Bsata W, Buser P, Charron P, Daubert JC, Dobreanu D, Faerstrand S, Hasdai D,  
4666 Hoes AW, Le Heuzey JY, Mavrakis H, McDonagh T, Merino JL, Nawar MM, Nielsen JC, Pieske B,  
4667 Poposka L, Ruschitzka F, Tendra M, Van Gelder IC, Wilson CM. 2013 ESC Guidelines on cardiac  
4668 pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and  
4669 resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration  
4670 with the European Heart Rhythm Association (EHRA). *Eur Heart J* 2013;**34**:2281-2329.
- 4671 574. Chatterjee NA, Upadhyay GA, Ellenbogen KA, Hayes DL, Singh JP. Atrioventricular nodal  
4672 ablation in atrial fibrillation: a meta-analysis of biventricular vs. right ventricular pacing mode. *Eur J*  
4673 *Heart Fail* 2012;**14**:661-667.

- 4674 575. Lewis RV, Irvine N, McDevitt DG. Relationships between heart rate, exercise tolerance and  
4675 cardiac output in atrial fibrillation: the effects of treatment with digoxin, verapamil and diltiazem. *Eur*  
4676 *Heart J* 1988;**9**:777-781.
- 4677 576. Mulder BA, Van Veldhuisen DJ, Crijns HJ, Tijssen JG, Hillege HL, Alings M, Rienstra M, Van  
4678 den Berg MP, Van Gelder IC, RACE II Investigators. Digoxin in patients with permanent atrial  
4679 fibrillation: data from the RACE II study. *Heart Rhythm* 2014;**11**:1543-1550.
- 4680 577. Koh KK, Song JH, Kwon KS, Park HB, Baik SH, Park YS, In HH, Moon TH, Park GS, Cho SK,  
4681 Kim SS. Comparative study of efficacy and safety of low-dose diltiazem or betaxolol in combination  
4682 with digoxin to control ventricular rate in chronic atrial fibrillation: randomized crossover study. *Int J*  
4683 *Cardiol* 1995;**52**:167-174.
- 4684 578. Chatterjee S, Sardar P, Lichstein E, Mukherjee D, Aikat S. Pharmacologic rate versus rhythm-  
4685 control strategies in atrial fibrillation: an updated comprehensive review and meta-analysis. *PACE*  
4686 2013;**36**:122-133.
- 4687 579. de Denus S, Sanoski CA, Carlsson J, Opolski G, Spinler SA. Rate vs rhythm control in  
4688 patients with atrial fibrillation: a meta-analysis. *Arch Intern Med* 2005;**165**:258-262.
- 4689 580. Lafuente-Lafuente C, Longas-Tejero MA, Bergmann JF, Belmin J. Antiarrhythmics for  
4690 maintaining sinus rhythm after cardioversion of atrial fibrillation. *Cochrane Database Syst Rev*  
4691 2012;**5**:CD005049.
- 4692 581. Roy D, Talajic M, Dorian P, Connolly S, Eisenberg MJ, Green M, Kus T, Lambert J, Dubuc M,  
4693 Gagne P, Nattel S, Thibault B. Amiodarone to prevent recurrence of atrial fibrillation. Canadian Trial of  
4694 Atrial Fibrillation Investigators. *N Engl J Med* 2000;**342**:913-920.
- 4695 582. Roy D, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, Bourassa MG, Arnold JM, Buxton  
4696 AE, Camm AJ, Connolly SJ, Dubuc M, Ducharme A, Guerra PG, Hohnloser SH, Lambert J, Le  
4697 Heuzey JY, O'Hara G, Pedersen OD, Rouleau JL, Singh BN, Stevenson LW, Stevenson WG, Thibault  
4698 B, Waldo AL. Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med*  
4699 2008;**358**:2667-2677.
- 4700 583. Singh BN, Connolly SJ, Crijns HJ, Roy D, Kowey PR, Capucci A, Radzik D, Aliot EM,  
4701 Hohnloser SH. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. *N Engl J*  
4702 *Med* 2007;**357**:987-999.
- 4703 584. Kirchhof P, Andresen D, Bosch R, Borggrefe M, Meinertz T, Parade U, Ravens U, Samol A,  
4704 Steinbeck G, Treszl A, Wegscheider K, Breithardt G. Short-term versus long-term antiarrhythmic drug  
4705 treatment after cardioversion of atrial fibrillation (Flec-SL): a prospective, randomised, open-label,  
4706 blinded endpoint assessment trial. *Lancet* 2012;**380**:238-246.
- 4707 585. Cosedis Nielsen J, Johannessen A, Raatikainen P, Hindricks G, Walfridsson H, Kongstad O,  
4708 Pehrson S, Englund A, Hartikainen J, Mortensen LS, Hansen PS. Radiofrequency ablation as initial  
4709 therapy in paroxysmal atrial fibrillation. *N Engl J Med* 2012;**367**:1587-1595.
- 4710 586. Wilber DJ, Pappone C, Neuzil P, De Paola A, Marchlinski F, Natale A, Macle L, Daoud EG,  
4711 Calkins H, Hall B, Reddy V, Augello G, Reynolds MR, Vinekar C, Liu CY, Berry SM, Berry DA,  
4712 ThermoCool AF Trial Investigators. Comparison of antiarrhythmic drug therapy and radiofrequency  
4713 catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. *JAMA*  
4714 2010;**303**:333-340.
- 4715 587. Arbelo E, Brugada J, Hindricks G, Maggioni AP, Tavazzi L, Vardas P, Laroche C, Anselme F,  
4716 Inama G, Jais P, Kalarus Z, Kautzner J, Lewalter T, Mairesse GH, Perez-Villacastin J, Riahi S,  
4717 Taborsky M, Theodorakis G, Trines SA, Atrial Fibrillation Ablation Pilot Study Investigators. The atrial  
4718 fibrillation ablation pilot study: a European Survey on Methodology and results of catheter ablation for  
4719 atrial fibrillation conducted by the European Heart Rhythm Association. *Eur Heart J* 2014;**35**:1466-  
4720 1478.
- 4721 588. Hohnloser SH, Crijns HJ, van Eickels M, Gaudin C, Page RL, Torp-Pedersen C, Connolly SJ.  
4722 Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med* 2009;**360**:668-678.
- 4723 589. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, Kellen JC,  
4724 Greene HL, Mickel MC, Dalquist JE, Corley SD. A comparison of rate control and rhythm control in  
4725 patients with atrial fibrillation. *N Engl J Med* 2002;**347**:1825-1833.
- 4726 590. Van Gelder IC, Hagens VE, Bosker HA, Kingma JH, Kamp O, Kingma T, Said SA, Darmanata  
4727 JI, Timmermans AJ, Tijssen JG, Crijns HJ, Rate Control versus Electrical Cardioversion for Persistent  
4728 Atrial Fibrillation Study Group. A comparison of rate control and rhythm control in patients with  
4729 recurrent persistent atrial fibrillation. *N Engl J Med* 2002;**347**:1834-1840.
- 4730 591. Opolski G, Torbicki A, Kosior DA, Szulc M, Wozakowska-Kaplon B, Kolodziej P, Achremczyk  
4731 P, Investigators of the Polish How to Treat Chronic Atrial Fibrillation Study. Rate control vs rhythm  
4732 control in patients with nonvalvular persistent atrial fibrillation: the results of the Polish How to Treat  
4733 Chronic Atrial Fibrillation (HOT CAFE) Study. *Chest* 2004;**126**:476-486.

- 4734 592. Kong MH, Shaw LK, O'Connor C, Califf RM, Blazing MA, Al-Khatib SM. Is rhythm-control  
4735 superior to rate-control in patients with atrial fibrillation and diastolic heart failure? *Ann Noninvasive*  
4736 *Electrocardiol* 2010;**15**:209-217.
- 4737 593. Kotecha D, Kirchhof P. Rate and rhythm control have comparable effects on mortality and  
4738 stroke in atrial fibrillation but better data are needed. *Evid Based Med* 2014;**19**:222-223.
- 4739 594. ClinicalTrials.gov. *Catheter Ablation vs Anti-arrhythmic Drug Therapy for Atrial Fibrillation*  
4740 *Trial (CABANA)*. <https://clinicaltrials.gov/ct2/show/NCT00911508>. Date last accessed 5 May  
4741 2016 NLM Identifier: NCT00911508 [Accessed 20-May-2015]
- 4742 595. Khan IA. Oral loading single dose flecainide for pharmacological cardioversion of recent-onset  
4743 atrial fibrillation. *Int J Cardiol* 2003;**87**:121-128.
- 4744 596. Chevalier P, Durand-Dubief A, Burri H, Cucherat M, Kirkorian G, Touboul P. Amiodarone  
4745 versus placebo and class Ic drugs for cardioversion of recent-onset atrial fibrillation: a meta-analysis.  
4746 *J Am Coll Cardiol* 2003;**41**:255-262.
- 4747 597. Letelier LM, Udol K, Ena J, Weaver B, Guyatt GH. Effectiveness of amiodarone for  
4748 conversion of atrial fibrillation to sinus rhythm: a meta-analysis. *Arch Intern Med* 2003;**163**:777-785.
- 4749 598. Khan IA, Mehta NJ, Gowda RM. Amiodarone for pharmacological cardioversion of recent-  
4750 onset atrial fibrillation. *Int J Cardiol* 2003;**89**:239-248.
- 4751 599. Thomas SP, Guy D, Wallace E, Crompton R, Kijvanit P, Eipper V, Ross DL, Cooper MJ.  
4752 Rapid loading of sotalol or amiodarone for management of recent onset symptomatic atrial fibrillation:  
4753 a randomized, digoxin-controlled trial. *Am Heart J* 2004;**147**:E3.
- 4754 600. Vijayalakshmi K, Whittaker VJ, Sutton A, Campbell P, Wright RA, Hall JA, Harcombe AA,  
4755 Linker NJ, Stewart MJ, Davies A, de Belder MA. A randomized trial of prophylactic antiarrhythmic  
4756 agents (amiodarone and sotalol) in patients with atrial fibrillation for whom direct current cardioversion  
4757 is planned. *Am Heart J* 2006;**151**:863 e861-866.
- 4758 601. Singh BN, Singh SN, Reda DJ, Tang XC, Lopez B, Harris CL, Fletcher RD, Sharma SC,  
4759 Atwood JE, Jacobson AK, Lewis HD, Jr., Raisch DW, Ezekowitz MD. Amiodarone versus sotalol for  
4760 atrial fibrillation. *N Engl J Med* 2005;**352**:1861-1872.
- 4761 602. Roy D, Pratt CM, Torp-Pedersen C, Wyse DG, Toft E, Juul-Moller S, Nielsen T, Rasmussen  
4762 SL, Stiell IG, Coutu B, Ip JH, Pritchett EL, Camm AJ. Vernakalant hydrochloride for rapid conversion  
4763 of atrial fibrillation: a phase 3, randomized, placebo-controlled trial. *Circulation* 2008;**117**:1518-1525.
- 4764 603. Kowey PR, Dorian P, Mitchell LB, Pratt CM, Roy D, Schwartz PJ, Sadowski J, Sobczyk D,  
4765 Bochenek A, Toft E. Vernakalant hydrochloride for the rapid conversion of atrial fibrillation after  
4766 cardiac surgery: a randomized, double-blind, placebo-controlled trial. *Circ Arrhythm Electrophysiol*  
4767 2009;**2**:652-659.
- 4768 604. Camm AJ, Capucci A, Hohnloser SH, Torp-Pedersen C, Van Gelder IC, Mangal B, Beatch G.  
4769 A randomized active-controlled study comparing the efficacy and safety of vernakalant to amiodarone  
4770 in recent-onset atrial fibrillation. *J Am Coll Cardiol* 2011;**57**:313-321.
- 4771 605. Bash LD, Buono JL, Davies GM, Martin A, Fahrbach K, Phatak H, Avetisyan R, Mwamburi M.  
4772 Systematic review and meta-analysis of the efficacy of cardioversion by vernakalant and comparators  
4773 in patients with atrial fibrillation. *Cardiovasc Drugs Ther* 2012;**26**:167-179.
- 4774 606. Falk RH, Pollak A, Singh SN, Friedrich T. Intravenous dofetilide, a class III antiarrhythmic  
4775 agent, for the termination of sustained atrial fibrillation or flutter. Intravenous Dofetilide Investigators  
4776 [see comments]. *J Am Coll Cardiol* 1997;**29**:385-390.
- 4777 607. Dankner R, Shahar A, Novikov I, Agmon U, Ziv A, Hod H. Treatment of stable atrial fibrillation  
4778 in the emergency department: a population-based comparison of electrical direct-current versus  
4779 pharmacological cardioversion or conservative management. *Cardiology* 2009;**112**:270-278.
- 4780 608. Chen WS, Gao BR, Chen WQ, Li ZZ, Xu ZY, Zhang YH, Yang K, Guan XQ. Comparison of  
4781 pharmacological and electrical cardioversion in permanent atrial fibrillation after prosthetic cardiac  
4782 valve replacement: a prospective randomized trial. *J Int Med Res* 2013;**41**:1067-1073.
- 4783 609. Gitt AK, Smolka W, Michailov G, Bernhardt A, Pittrow D, Lewalter T. Types and outcomes of  
4784 cardioversion in patients admitted to hospital for atrial fibrillation: results of the German RHYTHM-AF  
4785 Study. *Clin Res Cardiol* 2013;**102**:713-723.
- 4786 610. Cristoni L, Tampieri A, Mucci F, Iannone P, Venturi A, Cavazza M, Lenzi T. Cardioversion of  
4787 acute atrial fibrillation in the short observation unit: comparison of a protocol focused on electrical  
4788 cardioversion with simple antiarrhythmic treatment. *Emerg Med J* 2011;**28**:932-937.
- 4789 611. Bellone A, Eteri M, Vettorello M, Bonetti C, Clerici D, Gini G, Maino C, Mariani M, Natalizi A,  
4790 Nessi I, Rampoldi A, Colombo L. Cardioversion of acute atrial fibrillation in the emergency  
4791 department: a prospective randomised trial. *Emerg Med J* 2012;**29**:188-191.
- 4792 612. Crijns HJ, Weijs B, Fairley AM, Lewalter T, Maggioni AP, Martin A, Ponikowski P, Rosenqvist  
4793 M, Sanders P, Scanavacca M, Bash LD, Chazelle F, Bernhardt A, Gitt AK, Lip GY, Le Heuzey JY.

- 4794 Contemporary real life cardioversion of atrial fibrillation: Results from the multinational RHYTHM-AF  
4795 study. *Int J Cardiol* 2014;**172**:588-594.
- 4796 613. Lip GY, Gitt AK, Le Heuzey JY, Bash LD, Morabito CJ, Bernhardt AA, Sisk CM, Chazelle F,  
4797 Crijns HJ. Overtreatment and undertreatment with anticoagulation in relation to cardioversion of atrial  
4798 fibrillation (the RHYTHM-AF study). *Am J Cardiol* 2014;**113**:480-484.
- 4799 614. Reisinger J, Gatterer E, Lang W, Vanicek T, Eisserer G, Bachleitner T, Niemeth C, Aicher F,  
4800 Grandner W, Heinze G, Kuhn P, Siostrzonek P. Flecainide versus ibutilide for immediate cardioversion  
4801 of atrial fibrillation of recent onset. *Eur Heart J* 2004;**25**:1318-1324.
- 4802 615. Stambler BS, Wood MA, Ellenbogen KA, Perry KT, Wakefield LK, VanderLugt JT. Efficacy  
4803 and safety of repeated intravenous doses of ibutilide for rapid conversion of atrial flutter or fibrillation.  
4804 Ibutilide Repeat Dose Study Investigators. *Circulation* 1996;**94**:1613-1621.
- 4805 616. Torp-Pedersen C, Camm AJ, Butterfield NN, Dickinson G, Beatch GN. Vernakalant:  
4806 conversion of atrial fibrillation in patients with ischemic heart disease. *Int J Cardiol* 2013;**166**:147-151.
- 4807 617. Savelieva I, Graydon R, Camm AJ. Pharmacological cardioversion of atrial fibrillation with  
4808 vernakalant: evidence in support of the ESC Guidelines. *Europace* 2014;**16**:162-173.
- 4809 618. Simon A, Niederdoeckl J, Skyllouriotis E, Schuetz N, Herkner H, Weiser C, Laggner AN,  
4810 Domanovits H, Spiel AO. Vernakalant is superior to ibutilide for achieving sinus rhythm in patients  
4811 with recent-onset atrial fibrillation: a randomized controlled trial at the emergency department.  
4812 *Europace* 2016;**10.1093/europace/euw052**: [Epub ahead of print].
- 4813 619. Reisinger J, Gatterer E, Heinze G, Wiesinger K, Zeindlhofer E, Gattermeier M, Poelzl G,  
4814 Kratzer H, Ebner A, Hohenwallner W, Lenz K, Slany J, Kuhn P. Prospective comparison of flecainide  
4815 versus sotalol for immediate cardioversion of atrial fibrillation. *Am J Cardiol* 1998;**81**:1450-1454.
- 4816 620. Alboni P, Botto GL, Baldi N, Luzi M, Russo V, Gianfranchi L, Marchi P, Calzolari M, Solano A,  
4817 Baroffio R, Gaggioli G. Outpatient treatment of recent-onset atrial fibrillation with the "pill-in-the-  
4818 pocket" approach. *N Engl J Med* 2004;**351**:2384-2391.
- 4819 621. Saborido CM, Hockenhull J, Bagust A, Boland A, Dickson R, Todd D. Systematic review and  
4820 cost-effectiveness evaluation of 'pill-in-the-pocket' strategy for paroxysmal atrial fibrillation compared  
4821 to episodic in-hospital treatment or continuous antiarrhythmic drug therapy. *Health Technol Assess*  
4822 2010;**14**:iii-iv, 1-75.
- 4823 622. Khan IA. Single oral loading dose of propafenone for pharmacological cardioversion of recent-  
4824 onset atrial fibrillation. *J Am Coll Cardiol* 2001;**37**:542-547.
- 4825 623. Stroobandt R, Stiels B, Hoebrechts R. Propafenone for conversion and prophylaxis of atrial  
4826 fibrillation. Propafenone Atrial Fibrillation Trial Investigators. *Am J Cardiol* 1997;**79**:418-423.
- 4827 624. Hughes C, Sunderji R, Gin K. Oral propafenone for rapid conversion of recent onset atrial  
4828 fibrillation - A review. *CAN J CARDIOL. Canadian Journal of Cardiology* 1997;**13**:839-842.
- 4829 625. Zhang N, Guo JH, Zhang H, Li XB, Zhang P, Xn Y. Comparison of intravenous ibutilide vs.  
4830 propafenone for rapid termination of recent onset atrial fibrillation. *Int J Clin Pract* 2005;**59**:1395-1400.
- 4831 626. Mittal S, Ayati S, Stein KM, Schwartzman D, Cavlovich D, Tchou PJ, Markowitz SM, Slotwiner  
4832 DJ, Scheiner MA, Lerman BB. Transthoracic cardioversion of atrial fibrillation: comparison of  
4833 rectilinear biphasic versus damped sine wave monophasic shocks. *Circulation* 2000;**101**:1282-1287.
- 4834 627. Kirchhof P, Eckardt L, Loh P, Weber K, Fischer RJ, Seidl KH, Böcker D, Breithardt G,  
4835 Haverkamp W, Borggrefe M. Anterior-posterior versus anterior-lateral electrode positions for external  
4836 cardioversion of atrial fibrillation: a randomised trial. *Lancet* 2002;**360**:1275-1279.
- 4837 628. Kirchhof P, Monnig G, Wasmer K, Heinecke A, Breithardt G, Eckardt L, Bocker D. A trial of  
4838 self-adhesive patch electrodes and hand-held paddle electrodes for external cardioversion of atrial  
4839 fibrillation (MOBIPAPA). *Eur Heart J* 2005;**26**:1292-1297.
- 4840 629. Furniss SS, Sneyd JR. Safe sedation in modern cardiological practice. *Heart* 2015;**101**:1526-  
4841 1530.
- 4842 630. Alp N, Rahman S, Bell J, Shahi M. Randomised comparison of antero-lateral versus antero-  
4843 posterior paddle positions for DC cardioversion of persistent atrial fibrillation. *Int J Cardiol*  
4844 2000;**75**:211-216.
- 4845 631. Singh SN, Tang XC, Reda D, Singh BN. Systematic electrocardioversion for atrial fibrillation  
4846 and role of antiarrhythmic drugs: a substudy of the SAFE-T trial. *Heart Rhythm* 2009;**6**:152-155.
- 4847 632. Channer KS, Birchall A, Steeds RP, Walters SJ, Yeo WW, West JN, Muthusamy R, Rhoden  
4848 WE, Saeed BT, Batin P, Brooksby WP, Wilson I, Grant S. A randomized placebo-controlled trial of  
4849 pre-treatment and short- or long-term maintenance therapy with amiodarone supporting DC  
4850 cardioversion for persistent atrial fibrillation. *Eur Heart J* 2004;**25**:144-150.
- 4851 633. Oral H, Souza JJ, Michaud GF, Knight BP, Goyal R, Strickberger SA, Morady F. Facilitating  
4852 transthoracic cardioversion of atrial fibrillation with ibutilide pretreatment. *N Engl J Med*  
4853 1999;**340**:1849-1854.

- 4854 634. Mussigbrodt A, John S, Kosiuk J, Richter S, Hindricks G, Bollmann A. Vernakalant-facilitated  
4855 electrical cardioversion: comparison of intravenous vernakalant and amiodarone for drug-enhanced  
4856 electrical cardioversion of atrial fibrillation after failed electrical cardioversion. *Europace* 2016;**18**:51-  
4857 56.
- 4858 635. Bianconi L, Mennuni M, Lukic V, Castro A, Chieffi M, Santini M. Effects of oral propafenone  
4859 administration before electrical cardioversion of chronic atrial fibrillation: a placebo-controlled study. *J*  
4860 *Am Coll Cardiol* 1996;**28**:700-706.
- 4861 636. Nergardh AK, Rosenqvist M, Nordlander R, Frick M. Maintenance of sinus rhythm with  
4862 metoprolol CR initiated before cardioversion and repeated cardioversion of atrial fibrillation: a  
4863 randomized double-blind placebo-controlled study. *Eur Heart J* 2007;**28**:1351-1357.
- 4864 637. Hemels ME, Van Noord T, Crijns HJ, Van Veldhuisen DJ, Veeger NJ, Bosker HA, Wiesfeld  
4865 AC, Van den Berg MP, Ranchor AV, Van Gelder IC. Verapamil versus digoxin and acute versus  
4866 routine serial cardioversion for the improvement of rhythm control for persistent atrial fibrillation. *J Am*  
4867 *Coll Cardiol* 2006;**48**:1001-1009.
- 4868 638. Villani GQ, Piepoli MF, Terracciano C, Capucci A. Effects of diltiazem pretreatment on direct-  
4869 current cardioversion in patients with persistent atrial fibrillation: a single-blind, randomized, controlled  
4870 study. *Am Heart J* 2000;**140**:e12.
- 4871 639. De Simone A, Stabile G, Vitale DF, Turco P, Di Stasio M, Petrazzuoli F, Gasparini M, De  
4872 Matteis C, Rotunno R, Di Napoli T. Pretreatment with verapamil in patients with persistent or chronic  
4873 atrial fibrillation who underwent electrical cardioversion. *J Am Coll Cardiol* 1999;**34**:810-814.
- 4874 640. The Digitalis in Acute Atrial Fibrillation (DAAF) Trial Group. Intravenous digoxin in acute atrial  
4875 fibrillation. Results of a randomized, placebo-controlled multicentre trial in 239 patients. *Eur Heart J*  
4876 1997;**18**:649-654.
- 4877 641. Atarashi H, Inoue H, Fukunami M, Sugi K, Hamada C, Origasa H. Double-blind placebo-  
4878 controlled trial of aprindine and digoxin for the prevention of symptomatic atrial fibrillation. *Circ J*  
4879 2002;**66**:553-556.
- 4880 642. Airaksinen KE, Gronberg T, Nuotio I, Nikkinen M, Ylitalo A, Biancari F, Hartikainen JE.  
4881 Thromboembolic complications after cardioversion of acute atrial fibrillation: the FinCV (Finnish  
4882 CardioVersion) study. *J Am Coll Cardiol* 2013;**62**:1187-1192.
- 4883 643. Hansen ML, Jepsen RM, Olesen JB, Ruwald MH, Karasoy D, Gislason GH, Hansen J, Kober  
4884 L, Husted S, Torp-Pedersen C. Thromboembolic risk in 16 274 atrial fibrillation patients undergoing  
4885 direct current cardioversion with and without oral anticoagulant therapy. *Europace* 2015;**17**:18-23.
- 4886 644. Schadlich PK, Schmidt-Lucke C, Huppertz E, Lehmacher W, Nixdorff U, Stellbrink C, Brecht  
4887 JG. Economic evaluation of enoxaparin for anticoagulation in early cardioversion of persisting  
4888 nonvalvular atrial fibrillation: a statutory health insurance perspective from Germany. *Am J Cardiovasc*  
4889 *Drugs* 2007;**7**:199-217.
- 4890 645. Schmidt-Lucke C, Paar WD, Stellbrink C, Nixdorff U, Hofmann T, Meurer J, Grewe R, Daniel  
4891 WG, Hanrath P, Mugge A, Klein HU, Schmidt-Lucke JA. Quality of anticoagulation with unfractionated  
4892 heparin plus phenprocoumon for the prevention of thromboembolic complications in cardioversion for  
4893 non-valvular atrial fibrillation. Sub-analysis from the Anticoagulation in Cardioversion using  
4894 Enoxaparin (ACE) trial. *Thromb Res* 2007;**119**:27-34.
- 4895 646. Stellbrink C, Nixdorff U, Hofmann T, Lehmacher W, Daniel WG, Hanrath P, Geller C, Mugge  
4896 A, Sehnert W, Schmidt-Lucke C, Schmidt-Lucke JA. Safety and efficacy of enoxaparin compared with  
4897 unfractionated heparin and oral anticoagulants for prevention of thromboembolic complications in  
4898 cardioversion of nonvalvular atrial fibrillation: the Anticoagulation in Cardioversion using Enoxaparin  
4899 (ACE) trial. *Circulation* 2004;**109**:997-1003.
- 4900 647. Nuotio I, Hartikainen JE, Gronberg T, Biancari F, Airaksinen KE. Time to cardioversion for  
4901 acute atrial fibrillation and thromboembolic complications. *JAMA* 2014;**312**:647-649.
- 4902 648. Klein AL, Grimm RA, Murray RD, Apperson-Hansen C, Asinger RW, Black IW, Davidoff R,  
4903 Erbel R, Halperin JL, Orsinelli DA, Porter TR, Stoddard MF. Use of transesophageal  
4904 echocardiography to guide cardioversion in patients with atrial fibrillation. *N Engl J Med*  
4905 2001;**344**:1411-1420.
- 4906 649. Cappato R, Ezekowitz MD, Klein AL, Camm AJ, Ma CS, Le Heuzey JY, Talajic M,  
4907 Scanavacca M, Vardas PE, Kirchhof P, Hemmrich M, Lanius V, Meng IL, Wildgoose P, van Eickels M,  
4908 Hohnloser SH, Investigators XV. Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial  
4909 fibrillation. *Eur Heart J* 2014;**35**:3346-3355.
- 4910 650. Darkner S, Chen X, Hansen J, Pehrson S, Johannessen A, Nielsen JB, Svendsen JH.  
4911 Recurrence of arrhythmia following short-term oral AMIOdarone after CATHeter ablation for atrial  
4912 fibrillation: a double-blind, randomized, placebo-controlled study (AMIO-CAT trial). *Eur Heart J*  
4913 2014;**35**:3356-3364.

- 4914 651. Singh SN, Fletcher RD, Fisher SG, Singh BN, Lewis HD, Deedwania PC, Massie BM, Colling  
4915 C, Lazzeri D. Amiodarone in patients with congestive heart failure and asymptomatic ventricular  
4916 arrhythmia. Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure. *N Engl J Med*  
4917 1995;**333**:77-82.
- 4918 652. Kirchhof P, Franz MR, Bardai A, Wilde AM. Giant T-U waves precede torsades de pointes in  
4919 long QT syndrome: a systematic electrocardiographic analysis in patients with acquired and  
4920 congenital QT prolongation. *J Am Coll Cardiol* 2009;**54**:143-149.
- 4921 653. Goldschlager N, Epstein AE, Naccarelli GV, Olshansky B, Singh B, Collard HR, Murphy E. A  
4922 practical guide for clinicians who treat patients with amiodarone: 2007. *Heart Rhythm* 2007;**4**:1250-  
4923 1259.
- 4924 654. Wolkove N, Baltzan M. Amiodarone pulmonary toxicity. *Can Respir J* 2009;**16**:43-48.
- 4925 655. Ahmed S, Rienstra M, Crijns HJ, Links TP, Wiesfeld AC, Hillege HL, Bosker HA, Lok DJ, Van  
4926 Veldhuisen DJ, Van Gelder IC. Continuous vs episodic prophylactic treatment with amiodarone for the  
4927 prevention of atrial fibrillation: a randomized trial. *JAMA* 2008;**300**:1784-1792.
- 4928 656. Davy JM, Herold M, Hognlund C, Timmermans A, Alings A, Radzik D, Van Kempen L.  
4929 Dronedarone for the control of ventricular rate in permanent atrial fibrillation: the Efficacy and safety of  
4930 dRonedArone for the cOntrol of ventricular rate during atrial fibrillation (ERATO) study. *Am Heart J*  
4931 2008;**156**:527 e521-529.
- 4932 657. Kober L, Torp-Pedersen C, McMurray JJ, Gotzsche O, Levy S, Crijns H, Amlie J, Carlsen J,  
4933 Dronedarone Study Group. Increased mortality after dronedarone therapy for severe heart failure. *N*  
4934 *Engl J Med* 2008;**358**:2678-2687.
- 4935 658. Connolly SJ, Camm AJ, Halperin JL, Joyner C, Alings M, Amerena J, Atar D, Avezum A,  
4936 Blomstrom P, Borggrefe M, Budaj A, Chen SA, Ching CK, Commerford P, Dans A, Davy JM,  
4937 Delacretaz E, Di Pasquale G, Diaz R, Dorian P, Flaker G, Golitsyn S, Gonzalez-Hermosillo A,  
4938 Granger CB, Heidbuchel H, Kautzner J, Kim JS, Lanan F, Lewis BS, Merino JL, Morillo C, Murin J,  
4939 Narasimhan C, Paolasso E, Parkhomenko A, Peters NS, Sim KH, Stiles MK, Tanomsup S, Toivonen  
4940 L, Tomcsanyi J, Torp-Pedersen C, Tse HF, Vardas P, Vinereanu D, Xavier D, Zhu J, Zhu JR, Baret-  
4941 Cormel L, Weinling E, Staiger C, Yusuf S, Chrolavicius S, Afzal R, Hohnloser SH. Dronedarone in  
4942 high-risk permanent atrial fibrillation. *N Engl J Med* 2011;**365**:2268-2276.
- 4943 659. Tschuppert Y, Buclin T, Rothuizen LE, Decosterd LA, Galleyrand J, Gaud C, Biollaz J. Effect  
4944 of dronedarone on renal function in healthy subjects. *Br J Clin Pharmacol* 2007;**64**:785-791.
- 4945 660. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of  
4946 encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial  
4947 infarction. *N Engl J Med* 1989;**321**:406-412.
- 4948 661. Freemantle N, Lafuente-Lafuente C, Mitchell S, Eckert L, Reynolds M. Mixed treatment  
4949 comparison of dronedarone, amiodarone, sotalol, flecainide, and propafenone, for the management of  
4950 atrial fibrillation. *Europace* 2011;**13**:329-345.
- 4951 662. Sherrid MV, Barac I, McKenna WJ, Elliott PM, Dickie S, Chojnowska L, Casey S, Maron BJ.  
4952 Multicenter study of the efficacy and safety of disopyramide in obstructive hypertrophic  
4953 cardiomyopathy. *J Am Coll Cardiol* 2005;**45**:1251-1258.
- 4954 663. Sirak TE, Sherrid MV. Oral disopyramide for the acute treatment of severe outflow obstruction  
4955 in hypertrophic cardiomyopathy in the ICU setting. *Chest* 2008;**133**:1243-1246.
- 4956 664. Sherrid MV, Shetty A, Winson G, Kim B, Musat D, Alviar CL, Homel P, Balaram SK, Swistel  
4957 DG. Treatment of obstructive hypertrophic cardiomyopathy symptoms and gradient resistant to first-  
4958 line therapy with beta-blockade or verapamil. *Circ Heart Fail* 2013;**6**:694-702.
- 4959 665. Waldo AL, Camm AJ, deRuyter H, Friedman PL, MacNeil DJ, Pauls JF, Pitt B, Pratt CM,  
4960 Schwartz PJ, Veltri EP. Effect of d-sotalol on mortality in patients with left ventricular dysfunction after  
4961 recent and remote myocardial infarction. The SWORD Investigators. Survival With Oral d-Sotalol.  
4962 *Lancet* 1996;**348**:7-12.
- 4963 666. Pedersen OD, Bagger H, Keller N, Marchant B, Kober L, Torp-Pedersen C. Efficacy of  
4964 dofetilide in the treatment of atrial fibrillation-flutter in patients with reduced left ventricular function: a  
4965 Danish investigations of arrhythmia and mortality on dofetilide (diamond) substudy. *Circulation*  
4966 2001;**104**:292-296.
- 4967 667. Shamiss Y, Khaykin Y, Oosthuizen R, Tunney D, Sarak B, Beardsall M, Seabrook C, Frost L,  
4968 Wulffhart Z, Tsang B, Verma A. Dofetilide is safe and effective in preventing atrial fibrillation  
4969 recurrences in patients accepted for catheter ablation. *Europace* 2009;**11**:1448-1455.
- 4970 668. Haverkamp W, Breithardt G, Camm AJ, Janse MJ, Rosen MR, Antzelevitch C, Escande D,  
4971 Franz M, Malik M, Moss A, Shah R. The potential for QT prolongation and pro-arrhythmia by non-anti-  
4972 arrhythmic drugs: clinical and regulatory implications. Report on a Policy Conference of the European  
4973 Society of Cardiology. *Cardiovasc Res* 2000;**47**:219-233.

- 4974 669. Käab S, Hinterseer M, Näbauer M, Steinbeck G. Sotalol testing unmasks altered  
4975 repolarization in patients with suspected acquired long-QT-syndrome-a case-control pilot study using  
4976 i.v. sotalol. *Eur Heart J* 2003;**24**:649-657.
- 4977 670. Fabritz L, Kirchhof P. Predictable and less predictable unwanted cardiac drugs effects:  
4978 individual pre-disposition and transient precipitating factors. *Basic Clin Pharmacol Toxicol*  
4979 2010;**106**:263-268.
- 4980 671. Choy AM, Darbar D, Dell'Orto S, Roden DM. Exaggerated QT prolongation after  
4981 cardioversion of atrial fibrillation. *J Am Coll Cardiol* 1999;**34**:396-401.
- 4982 672. Patten M, Maas R, Bauer P, Luderitz B, Sonntag F, Dluzniewski M, Hatala R, Opolski G,  
4983 Muller HW, Meinertz T. Suppression of paroxysmal atrial tachyarrhythmias--results of the SOPAT trial.  
4984 *Eur Heart J* 2004;**25**:1395-1404.
- 4985 673. Burashnikov A, Barajas-Martinez H, Hu D, Nof E, Blazek J, Antzelevitch C. Atrial-selective  
4986 prolongation of refractory period with AVE0118 is due principally to inhibition of sodium channel  
4987 activity. *J Cardiovasc Pharmacol* 2012;**59**:539-546.
- 4988 674. Ford J, Milnes J, Wettwer E, Christ T, Rogers M, Sutton K, Madge D, Virag L, Jost N, Horvath  
4989 Z, Matschke K, Varro A, Ravens U. Human electrophysiological and pharmacological properties of  
4990 XEN-D0101: a novel atrial-selective Kv1.5/IKur inhibitor. *J Cardiovasc Pharmacol* 2013;**61**:408-415.
- 4991 675. Loose S, Mueller J, Wettwer E, Knaut M, Ford J, Milnes J, Ravens U. Effects of IKur blocker  
4992 MK-0448 on human right atrial action potentials from patients in sinus rhythm and in permanent atrial  
4993 fibrillation. *Front Pharmacol* 2014;**5**:26.
- 4994 676. Schram G, Zhang L, Derakhchan K, Ehrlich JR, Belardinelli L, Nattel S. Ranolazine: ion-  
4995 channel-blocking actions and in vivo electrophysiological effects. *Br J Pharmacol* 2004;**142**:1300-  
4996 1308.
- 4997 677. McCormack JG, Barr RL, Wolff AA, Lopaschuk GD. Ranolazine stimulates glucose oxidation  
4998 in normoxic, ischemic, and reperfused ischemic rat hearts. *Circulation* 1996;**93**:135-142.
- 4999 678. Scirica BM, Morrow DA, Hod H, Murphy SA, Belardinelli L, Hedgepeth CM, Molhoek P,  
5000 Verheugt FW, Gersh BJ, McCabe CH, Braunwald E. Effect of ranolazine, an antianginal agent with  
5001 novel electrophysiological properties, on the incidence of arrhythmias in patients with non ST-  
5002 segment elevation acute coronary syndrome: results from the Metabolic Efficiency With Ranolazine  
5003 for Less Ischemia in Non ST-Elevation Acute Coronary Syndrome Thrombolysis in Myocardial  
5004 Infarction 36 (MERLIN-TIMI 36) randomized controlled trial. *Circulation* 2007;**116**:1647-1652.
- 5005 679. Scirica BM, Belardinelli L, Chaitman BR, Waks JW, Volo S, Karwadowska-Prokopczuk E,  
5006 Murphy SA, Cheng ML, Braunwald E, Morrow DA. Effect of ranolazine on atrial fibrillation in patients  
5007 with non-ST elevation acute coronary syndromes: observations from the MERLIN-TIMI 36 trial.  
5008 *Europace* 2015;**17**:32-37.
- 5009 680. Reiffel JA, Camm AJ, Belardinelli L, Zeng D, Karwadowska-Prokopczuk E, Olmsted A, Zareba  
5010 W, Rosero S, Kowey P, HARMONY Investigators. The HARMONY Trial: Combined Ranolazine and  
5011 Dronedarone in the Management of Paroxysmal Atrial Fibrillation: Mechanistic and Therapeutic  
5012 Synergism. *Circ Arrhythm Electrophysiol* 2015;**8**:1048-1056.
- 5013 681. Fragakis N, Koskinas KC, Katritsis DG, Pagourelis ED, Zografos T, Geleris P. Comparison  
5014 of effectiveness of ranolazine plus amiodarone versus amiodarone alone for conversion of recent-  
5015 onset atrial fibrillation. *Am J Cardiol* 2012;**110**:673-677.
- 5016 682. Simopoulos V, Tagarakis GI, Daskalopoulou SS, Daskalopoulos ME, Lenos A, Chryssagis K,  
5017 Skouleringis I, Molyvdas PA, Tsilimingas NB, Aidonidis I. Ranolazine enhances the antiarrhythmic  
5018 activity of amiodarone by accelerating conversion of new-onset atrial fibrillation after cardiac surgery.  
5019 *Angiology* 2014;**65**:294-297.
- 5020 683. Koskinas KC, Fragakis N, Katritsis D, Skeberis V, Vassilikos V. Ranolazine enhances the  
5021 efficacy of amiodarone for conversion of recent-onset atrial fibrillation. *Europace* 2014;**16**:973-979.
- 5022 684. De Ferrari GM, Maier LS, Mont L, Schwartz PJ, Simonis G, Leschke M, Gronda E, Boriani G,  
5023 Darius H, Guillaumon Toran L, Savelieva I, Dusi V, Marchionni N, Quintana Rendon M, Schumacher K,  
5024 Tonini G, Melani L, Giannelli S, Alberto Maggi C, Camm AJ, RAFFAELLO Investigators. Ranolazine in  
5025 the treatment of atrial fibrillation: Results of the dose-ranging RAFFAELLO (Ranolazine in Atrial  
5026 Fibrillation Following An Electrical Cardioversion) study. *Heart Rhythm* 2015;**12**:872-878.
- 5027 685. Martin RI, Pogoryelova O, Koref MS, Bourke JP, Teare MD, Keavney BD. Atrial fibrillation  
5028 associated with ivabradine treatment: meta-analysis of randomised controlled trials. *Heart*  
5029 2014;**100**:1506-1510.
- 5030 686. Okin PM, Wachtell K, Devereux RB, Harris KE, Jern S, Kjeldsen SE, Julius S, Lindholm LH,  
5031 Nieminen MS, Edelman JM, Hille DA, Dahlof B. Regression of electrocardiographic left ventricular  
5032 hypertrophy and decreased incidence of new-onset atrial fibrillation in patients with hypertension.  
5033 *JAMA* 2006;**296**:1242-1248.

- 5034 687. Savelieva I, Kakouros N, Kourliouros A, Camm AJ. Upstream therapies for management of  
5035 atrial fibrillation: review of clinical evidence and implications for European Society of Cardiology  
5036 guidelines. Part II: secondary prevention. *Europace* 2011;**13**:610-625.
- 5037 688. Kuhlkamp V, Schirdewan A, Stangl K, Homberg M, Ploch M, Beck OA. Use of metoprolol  
5038 CR/XL to maintain sinus rhythm after conversion from persistent atrial fibrillation: a randomized,  
5039 double-blind, placebo-controlled study. *J Am Coll Cardiol* 2000;**36**:139-146.
- 5040 689. Liakopoulos OJ, Kuhn EW, Slottosch I, Wassmer G, Wahlers T. Preoperative statin therapy  
5041 for patients undergoing cardiac surgery. *Cochrane Database Syst Rev* 2012;**4**:Cd008493.
- 5042 690. Kuhn EW, Liakopoulos OJ, Stange S, Deppe AC, Slottosch I, Choi YH, Wahlers T.  
5043 Preoperative statin therapy in cardiac surgery: a meta-analysis of 90,000 patients. *Eur J Cardiothorac*  
5044 *Surg* 2014;**45**:17-26; discussion 26.
- 5045 691. Zheng Z, Jayaram R, Jiang L, Emberson J, Zhao Y, Li Q, Du J, Guarguagli S, Hill M, Chen Z,  
5046 Collins R, Casadei B. Perioperative Rosuvastatin in Cardiac Surgery. *N Engl J Med* 2016;**374**:1744-  
5047 1753.
- 5048 692. Rahimi K, Emberson J, McGale P, Majoni W, Merhi A, Asselbergs FW, Krane V, Macfarlane  
5049 PW, PROSPER Executive. Effect of statins on atrial fibrillation: collaborative meta-analysis of  
5050 published and unpublished evidence from randomised controlled trials. *BMJ* 2011;**342**:d1250.
- 5051 693. Pinho-Gomes AC, Reilly S, Brandes RP, Casadei B. Targeting inflammation and oxidative  
5052 stress in atrial fibrillation: role of 3-hydroxy-3-methylglutaryl-coenzyme a reductase inhibition with  
5053 statins. *Antioxid Redox Signal* 2014;**20**:1268-1285.
- 5054 694. Bianconi L, Calo L, Mennuni M, Santini L, Morosetti P, Azzolini P, Barbato G, Biscione F,  
5055 Romano P, Santini M. n-3 polyunsaturated fatty acids for the prevention of arrhythmia recurrence  
5056 after electrical cardioversion of chronic persistent atrial fibrillation: a randomized, double-blind,  
5057 multicentre study. *Europace* 2011;**13**:174-181.
- 5058 695. Kowey PR, Reiffel JA, Ellenbogen KA, Naccarelli GV, Pratt CM. Efficacy and safety of  
5059 prescription omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation: a  
5060 randomized controlled trial. *JAMA* 2010;**304**:2363-2372.
- 5061 696. Mozaffarian D, Marchioli R, Macchia A, Silletta MG, Ferrazzi P, Gardner TJ, Latini R, Libby P,  
5062 Lombardi F, O'Gara PT, Page RL, Tavazzi L, Tognoni G, OPERA Investigators. Fish oil and  
5063 postoperative atrial fibrillation: the Omega-3 Fatty Acids for Prevention of Post-operative Atrial  
5064 Fibrillation (OPERA) randomized trial. *JAMA* 2012;**308**:2001-2011.
- 5065 697. Yamashita T, Inoue H, Okumura K, Kodama I, Aizawa Y, Atarashi H, Ohe T, Ohtsu H, Kato T,  
5066 Kamakura S, Kumagai K, Kurachi Y, Koretsune Y, Saikawa T, Sakurai M, Sato T, Sugi K, Nakaya H,  
5067 Hirai M, Hirayama A, Fukatani M, Mitamura H, Yamazaki T, Watanabe E, Ogawa S, J-RHYTHM II  
5068 Investigators. Randomized trial of angiotensin II-receptor blocker vs. dihydropyridine calcium channel  
5069 blocker in the treatment of paroxysmal atrial fibrillation with hypertension (J-RHYTHM II study).  
5070 *Europace* 2011;**13**:473-479.
- 5071 698. Macchia A, Grancelli H, Varini S, Nul D, Laffaye N, Mariani J, Ferrante D, Badra R, Figal J,  
5072 Ramos S, Tognoni G, Doval HC, GESICA Investigators. Omega-3 fatty acids for the prevention of  
5073 recurrent symptomatic atrial fibrillation: results of the FORWARD (Randomized Trial to Assess  
5074 Efficacy of PUFA for the Maintenance of Sinus Rhythm in Persistent Atrial Fibrillation) trial. *J Am Coll*  
5075 *Cardiol* 2013;**61**:463-468.
- 5076 699. Dabrowski R, Borowiec A, Smolis-Bak E, Kowalik I, Sosnowski C, Kraska A, Kazimierska B,  
5077 Wozniak J, Zareba W, Szwed H. Effect of combined spironolactone- $\beta$ -blocker  $\pm$  enalapril treatment on  
5078 occurrence of symptomatic atrial fibrillation episodes in patients with a history of paroxysmal atrial  
5079 fibrillation (SPIR-AF study). *Am J Cardiol* 2010;**106**:1609-1614.
- 5080 700. Ito Y, Yamasaki H, Naruse Y, Yoshida K, Kaneshiro T, Murakoshi N, Igarashi M, Kuroki K,  
5081 Machino T, Xu D, Kunugita F, Sekiguchi Y, Sato A, Tada H, Aonuma K. Effect of eplerenone on  
5082 maintenance of sinus rhythm after catheter ablation in patients with long-standing persistent atrial  
5083 fibrillation. *Am J Cardiol* 2013;**111**:1012-1018.
- 5084 701. Swedberg K, Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Shi H, Vincent J, Pitt B,  
5085 EMPHASIS-Hf Study Investigators. Eplerenone and atrial fibrillation in mild systolic heart failure:  
5086 results from the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization And Survival Study in  
5087 Heart Failure) study. *J Am Coll Cardiol* 2012;**59**:1598-1603.
- 5088 702. Coll-Vinent B, Sala X, Fernandez C, Bragulat E, Espinosa G, Miro O, Milla J, Sanchez M.  
5089 Sedation for cardioversion in the emergency department: analysis of effectiveness in four protocols.  
5090 *Ann Emerg Med* 2003;**42**:767-772.
- 5091 703. del Arco C, Martin A, Laguna P, Gargantilla P. Analysis of current management of atrial  
5092 fibrillation in the acute setting: GEFAUR-1 study. *Ann Emerg Med* 2005;**46**:424-430.

- 5093 704. Scheuermeyer FX, Grafstein E, Heilbron B, Innes G. Emergency department management  
5094 and 1-year outcomes of patients with atrial flutter. *Ann Emerg Med* 2011;**57**:564-571 e562.
- 5095 705. Goldner BG, Baker J, Accordino A, Sabatino L, DiGiulio M, Kalenderian D, Lin D, Zambrotta  
5096 V, Stechel J, Maccaro P, Jadonath R. Electrical cardioversion of atrial fibrillation or flutter with  
5097 conscious sedation in the age of cost containment. *Am Heart J* 1998;**136**:961-964.
- 5098 706. Martinez-Marcos FJ, Garcia-Garmendia JL, Ortega-Carpio A, Fernandez-Gomez JM, Santos  
5099 JM, Camacho C. Comparison of intravenous flecainide, propafenone, and amiodarone for conversion  
5100 of acute atrial fibrillation to sinus rhythm. *Am J Cardiol* 2000;**86**:950-953.
- 5101 707. Buccelletti F, Iacomini P, Botta G, Marsiliani D, Carroccia A, Gentiloni Silveri N, Franceschi F.  
5102 Efficacy and safety of vernakalant in recent-onset atrial fibrillation after the European medicines  
5103 agency approval: systematic review and meta-analysis. *J Clin Pharmacol* 2012;**52**:1872-1878.
- 5104 708. Cappato R, Ezekowitz MD, Klein AL, Camm AJ, Ma CS, Le Heuzey JY, Talajic M,  
5105 Scanavacca M, Vardas PE, Kirchhof P, Hemmrich M, Lanius V, Meng IL, Wildgoose P, van Eickels M,  
5106 Hohnloser SH, X-VerT Investigators. Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial  
5107 fibrillation. *Eur Heart J* 2014.
- 5108 709. Nagarakanti R, Ezekowitz MD, Oldgren J, Yang S, Chernick M, Aikens TH, Flaker G, Brugada  
5109 J, Kamensky G, Parekh A, Reilly PA, Yusuf S, Connolly SJ. Dabigatran versus warfarin in patients  
5110 with atrial fibrillation: an analysis of patients undergoing cardioversion. *Circulation* 2011;**123**:131-136.
- 5111 710. Steinberg JS, Sadaniantz A, Kron J, Krahn A, Denny DM, Daubert J, Campbell WB, Havranek  
5112 E, Murray K, Olshansky B, O'Neill G, Sami M, Schmidt S, Storm R, Zabalgoitia M, Miller J, Chandler  
5113 M, Nasco EM, Greene HL. Analysis of cause-specific mortality in the Atrial Fibrillation Follow-up  
5114 Investigation of Rhythm Management (AFFIRM) study. *Circulation* 2004;**109**:1973-1980.
- 5115 711. Andersen HR, Nielsen JC, Thomsen PE, Thuesen L, Mortensen PT, Vesterlund T, Pedersen  
5116 AK. Long-term follow-up of patients from a randomised trial of atrial versus ventricular pacing for sick-  
5117 sinus syndrome. *Lancet* 1997;**350**:1210-1216.
- 5118 712. Connolly SJ, Kerr CR, Gent M, Roberts RS, Yusuf S, Gillis AM, Sami MH, Talajic M, Tang  
5119 AS, Klein GJ, Lau C, Newman DM. Effects of physiologic pacing versus ventricular pacing on the risk  
5120 of stroke and death due to cardiovascular causes. Canadian Trial of Physiologic Pacing Investigators.  
5121 *N Engl J Med* 2000;**342**:1385-1391.
- 5122 713. Calkins H, Reynolds MR, Spector P, Sondhi M, Xu Y, Martin A, Williams CJ, Sledge I.  
5123 Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation: two systematic  
5124 literature reviews and meta-analyses. *Circ Arrhythm Electrophysiol* 2009;**2**:349-361.
- 5125 714. Schmieder RE, Kjeldsen SE, Julius S, McInnes GT, Zanchetti A, Hua TA. Reduced incidence  
5126 of new-onset atrial fibrillation with angiotensin II receptor blockade: the VALUE trial. *J Hypertens*  
5127 2008;**26**:403-411.
- 5128 715. Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA, Crijns HJ, Damiano RJ, Jr.,  
5129 Davies DW, DiMarco J, Edgerton J, Ellenbogen K, Ezekowitz MD, Haines DE, Haissaguerre M,  
5130 Hindricks G, Iesaka Y, Jackman W, Jalife J, Jais P, Kalman J, Keane D, Kim YH, Kirchhof P, Klein G,  
5131 Kottkamp H, Kumagai K, Lindsay BD, Mansour M, Marchlinski FE, McCarthy PM, Mont JL, Morady F,  
5132 Nademanee K, Nakagawa H, Natale A, Nattel S, Packer DL, Pappone C, Prystowsky E, Raviele A,  
5133 Reddy V, Ruskin JN, Shemin RJ, Tsao HM, Wilber D. 2012 HRS/EHRA/ECAS Expert Consensus  
5134 Statement on Catheter and Surgical Ablation of Atrial Fibrillation: recommendations for patient  
5135 selection, procedural techniques, patient management and follow-up, definitions, endpoints, and  
5136 research trial design. *Europace* 2012;**14**:528-606.
- 5137 716. Kuck KH, Hoffmann BA, Ernst S, Wegscheider K, Treszl A, Metzner A, Eckardt L, Lewalter T,  
5138 Breithardt G, Willems S, Gap-AF-AFNET 1 Investigators. Impact of Complete Versus Incomplete  
5139 Circumferential Lines Around the Pulmonary Veins During Catheter Ablation of Paroxysmal Atrial  
5140 Fibrillation: Results From the Gap-Atrial Fibrillation-German Atrial Fibrillation Competence Network 1  
5141 Trial. *Circ Arrhythm Electrophysiol* 2016;**9**:e003337.
- 5142 717. Mont L, Bisbal F, Hernandez-Madrid A, Perez-Castellano N, Vinolas X, Arenal A, Arribas F,  
5143 Fernandez-Lozano I, Bodegas A, Cobos A, Matia R, Perez-Villacastin J, Guerra JM, Avila P, Lopez-  
5144 Gil M, Castro V, Arana JI, Brugada J, SARA investigators. Catheter ablation vs. antiarrhythmic drug  
5145 treatment of persistent atrial fibrillation: a multicentre, randomized, controlled trial (SARA study). *Eur*  
5146 *Heart J* 2014;**35**:501-507.
- 5147 718. Schreiber D, Rostock T, Frohlich M, Sultan A, Servatius H, Hoffmann BA, Luker J, Berner I,  
5148 Schaffer B, Wegscheider K, Lezius S, Willems S, Steven D. Five-year follow-up after catheter ablation  
5149 of persistent atrial fibrillation using the stepwise approach and prognostic factors for success. *Circ*  
5150 *Arrhythm Electrophysiol* 2015;**8**:308-317.
- 5151 719. Scherr D, Khairy P, Miyazaki S, Aurillac-Lavignolle V, Pascale P, Wilton SB, Ramoul K,  
5152 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

- 5212 Investigators. Approaches to catheter ablation for persistent atrial fibrillation. *N Engl J Med*  
5213 2015;**372**:1812-1822.
- 5214 736. Dong JZ, Sang CH, Yu RH, Long DY, Tang RB, Jiang CX, Ning M, Liu N, Liu XP, Du X, Tse  
5215 HF, Ma CS. Prospective randomized comparison between a fixed '2C3L' approach vs. stepwise  
5216 approach for catheter ablation of persistent atrial fibrillation. *Europace* 2015;**17**:1798-1806.
- 5217 737. Hunter RJ, McCreedy J, Diab I, Page SP, Finlay M, Richmond L, French A, Earley MJ,  
5218 Sporton S, Jones M, Joseph JP, Bashir Y, Betts TR, Thomas G, Staniforth A, Lee G, Kistler P,  
5219 Rajappan K, Chow A, Schilling RJ. Maintenance of sinus rhythm with an ablation strategy in patients  
5220 with atrial fibrillation is associated with a lower risk of stroke and death. *Heart* 2012;**98**:48-53.
- 5221 738. Providencia R, Lambiase PD, Srinivasan N, Ganesh Babu G, Bronis K, Ahsan S, Khan FZ,  
5222 Chow AW, Rowland E, Lowe M, Segal OR. Is There Still a Role for Complex Fractionated Atrial  
5223 Electrogram Ablation in Addition to Pulmonary Vein Isolation in Patients With Paroxysmal and  
5224 Persistent Atrial Fibrillation? Meta-Analysis of 1415 Patients. *Circ Arrhythm Electrophysiol*  
5225 2015;**8**:1017-1029.
- 5226 739. Mohanty S, Gianni C, Mohanty P, Halbfass P, Metz T, Trivedi C, Deneke T, Tomassoni G, Bai  
5227 R, Al-Ahmad A, Bailey S, Burkhardt JD, Gallingshouse GJ, Horton R, Hranitzky PM, Sanchez JE, Di  
5228 Biase L, Natale A. Impact of Rotor Ablation in Non-Paroxysmal AF Patients: Results from a  
5229 Randomized Trial (OASIS). *J Am Coll Cardiol* 2016.
- 5230 740. Rolf S, Kircher S, Arya A, Eitel C, Sommer P, Richter S, Gaspar T, Bollmann A, Altmann D,  
5231 Piedra C, Hindricks G, Piorkowski C. Tailored atrial substrate modification based on low-voltage areas  
5232 in catheter ablation of atrial fibrillation. *Circ Arrhythm Electrophysiol* 2014;**7**:825-833.
- 5233 741. Shah AJ, Pascale P, Miyazaki S, Liu X, Roten L, Derval N, Jadidi AS, Scherr D, Wilton SB,  
5234 Pedersen M, Knecht S, Sacher F, Jais P, Haissaguerre M, Hocini M. Prevalence and types of pitfall in  
5235 the assessment of mitral isthmus linear conduction block. *Circ Arrhythm Electrophysiol* 2012;**5**:957-  
5236 967.
- 5237 742. Macle L, Khairy P, Weerasooriya R, Novak P, Verma A, Willems S, Arentz T, Deisenhofer I,  
5238 Veenhuyzen G, Scavee C, Jais P, Puererfellner H, Levesque S, Andrade JG, Rivard L, Guerra PG,  
5239 Dubuc M, Thibault B, Talajic M, Roy D, Nattel S, ADVICE trial investigators. Adenosine-guided  
5240 pulmonary vein isolation for the treatment of paroxysmal atrial fibrillation: an international, multicentre,  
5241 randomised superiority trial. *Lancet* 2015;**386**:672-679.
- 5242 743. Kobori A, Shizuta S, Inoue K, Kaitani K, Morimoto T, Nakazawa Y, Ozawa T, Kurotobi T,  
5243 Morishima I, Miura F, Watanabe T, Masuda M, Naito M, Fujimoto H, Nishida T, Furukawa Y,  
5244 Shirayama T, Tanaka M, Okajima K, Yao T, Egami Y, Satomi K, Noda T, Miyamoto K, Haruna T,  
5245 Kawaji T, Yoshizawa T, Toyota T, Yahata M, Nakai K, Sugiyama H, Higashi Y, Ito M, Horie M, Kusano  
5246 KF, Shimizu W, Kamakura S, Kimura T, UNDER-ATP Trial Investigators. Adenosine triphosphate-  
5247 guided pulmonary vein isolation for atrial fibrillation: the UNmasking Dormant Electrical Reconnection  
5248 by Adenosine TriPhosphate (UNDER-ATP) trial. *Eur Heart J* 2015;**36**:3276-3287.
- 5249 744. Berntsen RF, Haland TF, Skardal R, Holm T. Focal impulse and rotor modulation as a stand-  
5250 alone procedure for treatment of paroxysmal atrial fibrillation. A within-patient controlled study with  
5251 implanted cardiac monitoring. *Heart Rhythm* 2016.
- 5252 745. Lee G, Sparks PB, Morton JB, Kistler PM, Vohra JK, Medi C, Rosso R, Teh A, Halloran K,  
5253 Kalman JM. Low risk of major complications associated with pulmonary vein antral isolation for atrial  
5254 fibrillation: results of 500 consecutive ablation procedures in patients with low prevalence of structural  
5255 heart disease from a single center. *J Cardiovasc Electrophysiol* 2011;**22**:163-168.
- 5256 746. Wynn GJ, Das M, Bonnett LJ, Panikker S, Wong T, Gupta D. Efficacy of catheter ablation for  
5257 persistent atrial fibrillation: a systematic review and meta-analysis of evidence from randomized and  
5258 nonrandomized controlled trials. *Circ Arrhythm Electrophysiol* 2014;**7**:841-852.
- 5259 747. Seaburg L, Hess EP, Coylewright M, Ting HH, McLeod CJ, Montori VM. Shared decision  
5260 making in atrial fibrillation: where we are and where we should be going. *Circulation* 2014;**129**:704-  
5261 710.
- 5262 748. Dagres N, Hindricks G, Kottkamp H, Sommer P, Gaspar T, Bode K, Arya A, Husser D,  
5263 Rallidis LS, Kremastinos DT, Piorkowski C. Complications of atrial fibrillation ablation in a high-volume  
5264 center in 1,000 procedures: still cause for concern? *J Cardiovasc Electrophysiol* 2009;**20**:1014-1019.
- 5265 749. Deneke T, Jais P, Scaglione M, Schmitt R, L DIB, Christopoulos G, Schade A, Mugge A,  
5266 Bansmann M, Nentwich K, Muller P, Roos M, Halbfass P, Natale A, Gaita F, Haines D. Silent  
5267 cerebral events/lesions related to atrial fibrillation ablation: a clinical review. *J Cardiovasc*  
5268 *Electrophysiol* 2015;**26**:455-463.
- 5269 750. Gupta A, Perera T, Ganesan A, Sullivan T, Lau DH, Roberts-Thomson KC, Brooks AG,  
5270 Sanders P. Complications of catheter ablation of atrial fibrillation: a systematic review. *Circ Arrhythm*  
5271 *Electrophysiol* 2013;**6**:1082-1088.

- 5272 751. Cappato R, Calkins H, Chen SA, Davies W, Iesaka Y, Kalman J, Kim YH, Klein G, Natale A,  
5273 Packer D, Ricci C, Skanes A, Ranucci M. Delayed cardiac tamponade after radiofrequency catheter  
5274 ablation of atrial fibrillation: a worldwide report. *J Am Coll Cardiol* 2011;**58**:2696-2697.
- 5275 752. Haeusler KG, Kirchhof P, Endres M. Left atrial catheter ablation and ischemic stroke. *Stroke*  
5276 2012;**43**:265-270.
- 5277 753. Kosiuk J, Kornej J, Bollmann A, Piorkowski C, Myrda K, Arya A, Sommer P, Richter S, Rolf S,  
5278 Husser D, Gaspar T, Lip GY, Hindricks G. Early cerebral thromboembolic complications after  
5279 radiofrequency catheter ablation of atrial fibrillation: incidence, characteristics, and risk factors. *Heart*  
5280 *Rhythm* 2014;**11**:1934-1940.
- 5281 754. Gaita F, Leclercq JF, Schumacher B, Scaglione M, Toso E, Halimi F, Schade A, Froehner S,  
5282 Ziegler V, Sergi D, Cesarani F, Blandino A. Incidence of silent cerebral thromboembolic lesions after  
5283 atrial fibrillation ablation may change according to technology used: comparison of irrigated  
5284 radiofrequency, multipolar nonirrigated catheter and cryoballoon. *J Cardiovasc Electrophysiol*  
5285 2011;**22**:961-968.
- 5286 755. Hsu LF, Jais P, Hocini M, Sanders P, Scavee C, Sacher F, Takahashi Y, Rotter M, Pasquie  
5287 JL, Clementy J, Haissaguerre M. Incidence and prevention of cardiac tamponade complicating  
5288 ablation for atrial fibrillation. *Pacing Clin Electrophysiol* 2005;**28 Suppl 1**:S106-109.
- 5289 756. Michowitz Y, Rahkovich M, Oral H, Zado ES, Tiltz R, John S, Denis A, Di Biase L, Winkle RA,  
5290 Mikhaylov EN, Ruskin JN, Yao Y, Josephson ME, Tanner H, Miller JM, Champagne J, Della Bella P,  
5291 Kumagai K, Defaye P, Luria D, Lebedev DS, Natale A, Jais P, Hindricks G, Kuck KH, Marchlinski FE,  
5292 Morady F, Belhassen B. Effects of sex on the incidence of cardiac tamponade after catheter ablation  
5293 of atrial fibrillation: results from a worldwide survey in 34 943 atrial fibrillation ablation procedures. *Circ*  
5294 *Arrhythm Electrophysiol* 2014;**7**:274-280.
- 5295 757. Nair KK, Shurrab M, Skanes A, Danon A, Birnie D, Morillo C, Chauhan V, Mangat I, Ayala-  
5296 Paredes F, Champagne J, Nault I, Tang A, Verma A, Lashevsky I, Singh SM, Crystal E. The  
5297 prevalence and risk factors for atrioesophageal fistula after percutaneous radiofrequency catheter  
5298 ablation for atrial fibrillation: the Canadian experience. *J Interv Card Electrophysiol* 2014;**39**:139-144.
- 5299 758. Shah RU, Freeman JV, Shilane D, Wang PJ, Go AS, Hlatky MA. Procedural complications,  
5300 rehospitalizations, and repeat procedures after catheter ablation for atrial fibrillation. *J Am Coll Cardiol*  
5301 2012;**59**:143-149.
- 5302 759. Straube F, Dorwarth U, Schmidt M, Wankel M, Ebersberger U, Hoffmann E. Comparison of  
5303 the first and second cryoballoon: high-volume single-center safety and efficacy analysis. *Circ*  
5304 *Arrhythm Electrophysiol* 2014;**7**:293-299.
- 5305 760. Di Biase L, Burkhardt JD, Santangeli P, Mohanty P, Sanchez JE, Horton R, Gallinhouse GJ,  
5306 Themistoclakis S, Rossillo A, Lakkireddy D, Reddy M, Hao S, Hongo R, Beheiry S, Zagrodzky J,  
5307 Rong B, Mohanty S, Elayi CS, Forleo G, Pelargonio G, Narducci ML, Dello Russo A, Casella M,  
5308 Fassini G, Tondo C, Schweikert RA, Natale A. Periprocedural Stroke and Bleeding Complications in  
5309 Patients Undergoing Catheter Ablation of Atrial Fibrillation With Different Anticoagulation  
5310 Management: Results From the Role of Coumadin in Preventing Thromboembolism in Atrial  
5311 Fibrillation (AF) Patients Undergoing Catheter Ablation (COMPARE) Randomized Trial. *Circulation*  
5312 2014;**129**:2638-2644.
- 5313 761. Di Biase L, Lakkireddy D, Trivedi C, Deneke T, Martinek M, Mohanty S, Mohanty P, Prakash  
5314 S, Bai R, Reddy M, Gianni C, Horton R, Bailey S, Sigmund E, Derndorfer M, Schade A, Mueller P,  
5315 Szoelloes A, Sanchez J, Al-Ahmad A, Hranitzky P, Gallinhouse GJ, Hongo RH, Beheiry S,  
5316 Purefellner H, Burkhardt JD, Natale A. Feasibility and safety of uninterrupted periprocedural  
5317 apixaban administration in patients undergoing radiofrequency catheter ablation for atrial fibrillation:  
5318 Results from a multicenter study. *Heart Rhythm* 2015;**12**:1162-1168.
- 5319 762. Hohnloser SH, Camm AJ. Safety and efficacy of dabigatran etexilate during catheter ablation  
5320 of atrial fibrillation: a meta-analysis of the literature. *Europace* 2013;**15**:1407-1411.
- 5321 763. Lakkireddy D, Reddy YM, Di Biase L, Vallakati A, Mansour MC, Santangeli P, Gangireddy S,  
5322 Swarup V, Chalhoub F, Atkins D, Bommana S, Verma A, Sanchez JE, Burkhardt JD, Barrett CD,  
5323 Baheiry S, Ruskin J, Reddy V, Natale A. Feasibility and safety of uninterrupted rivaroxaban for  
5324 periprocedural anticoagulation in patients undergoing radiofrequency ablation for atrial fibrillation:  
5325 results from a multicenter prospective registry. *J Am Coll Cardiol* 2014;**63**:982-988.
- 5326 764. Providencia R, Marijon E, Albenque JP, Combes S, Combes N, Jourda F, Hireche H, Morais  
5327 J, Boveda S. Rivaroxaban and dabigatran in patients undergoing catheter ablation of atrial fibrillation.  
5328 *Europace* 2014;**16**:1137-1144.
- 5329 765. Stepanyan G, Badhwar N, Lee RJ, Marcus GM, Lee BK, Tseng ZH, Vedantham V, Olgin J,  
5330 Scheinman M, Gerstenfeld EP. Safety of new oral anticoagulants for patients undergoing atrial  
5331 fibrillation ablation. *J Interv Card Electrophysiol* 2014;**40**:33-38.

- 5332 766. Aryal MR, Ukaigwe A, Pandit A, Karmacharya P, Pradhan R, Mainali NR, Pathak R, Jalota L,  
5333 Bhandari Y, Donato A. Meta-analysis of efficacy and safety of rivaroxaban compared with warfarin or  
5334 dabigatran in patients undergoing catheter ablation for atrial fibrillation. *Am J Cardiol* 2014;**114**:577-  
5335 582.
- 5336 767. Kaess BM, Ammar S, Reents T, Dillier R, Lennerz C, Semmler V, Grebmer C, Bourier F,  
5337 Buiatti A, Kolb C, Deisenhofer I, Hessling G. Comparison of safety of left atrial catheter ablation  
5338 procedures for atrial arrhythmias under continuous anticoagulation with apixaban versus  
5339 phenprocoumon. *Am J Cardiol* 2015;**115**:47-51.
- 5340 768. Cappato R, Marchlinski FE, Hohnloser SH, Naccarelli GV, Xiang J, Wilber DJ, Ma CS, Hess  
5341 S, Wells DS, Juang G, Vijgen J, Hugl BJ, Balasubramaniam R, De Chillou C, Davies DW, Fields LE,  
5342 Natale A, VENTURE-AF Investigators. Uninterrupted rivaroxaban vs. uninterrupted vitamin K  
5343 antagonists for catheter ablation in non-valvular atrial fibrillation. *Eur Heart J* 2015;**36**:1805-1811.
- 5344 769. Wu S, Yang YM, Zhu J, Wan HB, Wang J, Zhang H, Shao XH. Meta-Analysis of Efficacy and  
5345 Safety of New Oral Anticoagulants Compared With Uninterrupted Vitamin K Antagonists in Patients  
5346 Undergoing Catheter Ablation for Atrial Fibrillation. *Am J Cardiol* 2016;**117**:926-934.
- 5347 770. Santarpia G, De Rosa S, Polimeni A, Giampa S, Micieli M, Curcio A, Indolfi C. Efficacy and  
5348 Safety of Non-Vitamin K Antagonist Oral Anticoagulants versus Vitamin K Antagonist Oral  
5349 Anticoagulants in Patients Undergoing Radiofrequency Catheter Ablation of Atrial Fibrillation: A Meta-  
5350 Analysis. *PLoS One* 2015;**10**:e0126512.
- 5351 771. Karasoy D, Gislason GH, Hansen J, Johannessen A, Kober L, Hvidtfeldt M, Ozcan C, Torp-  
5352 Pedersen C, Hansen ML. Oral anticoagulation therapy after radiofrequency ablation of atrial fibrillation  
5353 and the risk of thromboembolism and serious bleeding: long-term follow-up in nationwide cohort of  
5354 Denmark. *Eur Heart J* 2015;**36**:307-314a.
- 5355 772. Themistoclakis S, Corrado A, Marchlinski FE, Jais P, Zado E, Rossillo A, Di Biase L,  
5356 Schweikert RA, Saliba WJ, Horton R, Mohanty P, Patel D, Burkhardt DJ, Wazni OM, Bonso A, Callans  
5357 DJ, Haissaguerre M, Raviele A, Natale A. The risk of thromboembolism and need for oral  
5358 anticoagulation after successful atrial fibrillation ablation. *J Am Coll Cardiol* 2010;**55**:735-743.
- 5359 773. Bunch TJ, May HT, Bair TL, Weiss JP, Crandall BG, Osborn JS, Mallender C, Anderson JL,  
5360 Muhlestein BJ, Lappe DL, Day JD. Atrial fibrillation ablation patients have long-term stroke rates  
5361 similar to patients without atrial fibrillation regardless of CHADS2 score. *Heart Rhythm* 2013;**10**:1272-  
5362 1277.
- 5363 774. Nedios S, Kornej J, Koutalas E, Bertagnoli L, Kosiuk J, Rolf S, Arya A, Sommer P, Husser D,  
5364 Hindricks G, Bollmann A. Left atrial appendage morphology and thromboembolic risk after catheter  
5365 ablation for atrial fibrillation. *Heart Rhythm* 2014;**11**:2239-2246.
- 5366 775. Reynolds MR, Gunnarsson CL, Hunter TD, Ladapo JA, March JL, Zhang M, Hao SC. Health  
5367 outcomes with catheter ablation or antiarrhythmic drug therapy in atrial fibrillation: results of a  
5368 propensity-matched analysis. *Circ Cardiovasc Qual Outcomes* 2012;**5**:171-181.
- 5369 776. Gallo C, Battaglia A, Anselmino M, Bianchi F, Grossi S, Nangeroni G, Toso E, Gaido L,  
5370 Scaglione M, Ferraris F, Gaita F. Long-term events following atrial fibrillation rate control or  
5371 transcatheter ablation: a multicenter observational study. *J Cardiovasc Med (Hagerstown)*  
5372 2016;**17**:187-193.
- 5373 777. Di Biase L, Mohanty P, Mohanty S, Santangeli P, Trivedi C, Lakkireddy D, Reddy M, Jais P,  
5374 Themistoclakis S, Dello Russo A, Casella M, Pelargonio G, Narducci ML, Schweikert R, Neuzil P,  
5375 Sanchez J, Horton R, Beheiry S, Hongo R, Hao S, Rossillo A, Forleo G, Tondo C, Burkhardt JD,  
5376 Haissaguerre M, Natale A. Ablation vs. Amiodarone for Treatment of Persistent Atrial Fibrillation in  
5377 Patients With Congestive Heart Failure and an Implanted Device: Results From the AATAC  
5378 Multicenter Randomized Trial. *Circulation* 2016.
- 5379 778. Hunter RJ, Berriman TJ, Diab I, Kamdar R, Richmond L, Baker V, Goromonzi F, Sawhney V,  
5380 Duncan E, Page SP, Ullah W, Unsworth B, Mayet J, Dhinoja M, Earley MJ, Sporton S, Schilling RJ. A  
5381 randomized controlled trial of catheter ablation versus medical treatment of atrial fibrillation in heart  
5382 failure (the CAMTAF trial). *Circ Arrhythm Electrophysiol* 2014;**7**:31-38.
- 5383 779. MacDonald MR, Connelly DT, Hawkins NM, Steedman T, Payne J, Shaw M, Denvir M,  
5384 Bhagra S, Small S, Martin W, McMurray JJ, Petrie MC. Radiofrequency ablation for persistent atrial  
5385 fibrillation in patients with advanced heart failure and severe left ventricular systolic dysfunction: a  
5386 randomised controlled trial. *Heart* 2011;**97**:740-747.
- 5387 780. Dagues N, Varounis C, Gaspar T, Piorkowski C, Eitel C, Iliodromitis EK, Lekakis JP, Flevari P,  
5388 Simeonidou E, Rallidis LS, Tsougos E, Hindricks G, Sommer P, Anastasiou-Nana M. Catheter  
5389 ablation for atrial fibrillation in patients with left ventricular systolic dysfunction. A systematic review  
5390 and meta-analysis. *J Card Fail* 2011;**17**:964-970.

- 5391 781. Piorkowski C, Kottkamp H, Tanner H, Kobza R, Nielsen JC, Arya A, Hindricks G. Value of  
5392 different follow-up strategies to assess the efficacy of circumferential pulmonary vein ablation for the  
5393 curative treatment of atrial fibrillation. *J Cardiovasc Electrophysiol* 2005;**16**:1286-1292.
- 5394 782. Verma A, Champagne J, Sapp J, Essebag V, Novak P, Skanes A, Morillo CA, Khaykin Y,  
5395 Birnie D. Discerning the incidence of symptomatic and asymptomatic episodes of atrial fibrillation  
5396 before and after catheter ablation (DISCERN AF): a prospective, multicenter study. *JAMA Intern Med*  
5397 2013;**173**:149-156.
- 5398 783. Cox JL, Boineau JP, Schuessler RB, Ferguson TB, Jr., Cain ME, Lindsay BD, Corr PB, Kater  
5399 KM, Lappas DG. Successful surgical treatment of atrial fibrillation. Review and clinical update. *JAMA*  
5400 1991;**266**:1976-1980.
- 5401 784. Cox JL, Schuessler RB, D'Agostino HJ, Jr., Stone CM, Chang BC, Cain ME, Corr PB,  
5402 Boineau JP. The surgical treatment of atrial fibrillation. III. Development of a definitive surgical  
5403 procedure. *J Thorac Cardiovasc Surg* 1991;**101**:569-583.
- 5404 785. Stulak JM, Suri RM, Burkhardt HM, Daly RC, Dearani JA, Greason KL, Joyce LD, Park SJ,  
5405 Schaff HV. Surgical ablation for atrial fibrillation for two decades: are the results of new techniques  
5406 equivalent to the Cox maze III procedure? *J Thorac Cardiovasc Surg* 2014;**147**:1478-1486.
- 5407 786. Basu S, Nagendran M, Maruthappu M. How effective is bipolar radiofrequency ablation for  
5408 atrial fibrillation during concomitant cardiac surgery? *Interact Cardiovasc Thorac Surg* 2012;**15**:741-  
5409 748.
- 5410 787. Lin Z, Shan ZG, Liao CX, Chen LW. The effect of microwave and bipolar radio-frequency  
5411 ablation in the surgical treatment of permanent atrial fibrillation during valve surgery. *Thorac*  
5412 *Cardiovasc Surg* 2011;**59**:460-464.
- 5413 788. McCarthy PM, Kruse J, Shalji S, Ilkhanoff L, Goldberger JJ, Kadish AH, Arora R, Lee R.  
5414 Where does atrial fibrillation surgery fail? Implications for increasing effectiveness of ablation. *J*  
5415 *Thorac Cardiovasc Surg* 2010;**139**:860-867.
- 5416 789. Abreu Filho CA, Lisboa LA, Dallan LA, Spina GS, Grinberg M, Scanavacca M, Sosa EA,  
5417 Ramires JA, Oliveira SA. Effectiveness of the maze procedure using cooled-tip radiofrequency  
5418 ablation in patients with permanent atrial fibrillation and rheumatic mitral valve disease. *Circulation*  
5419 2005;**112**:I20-25.
- 5420 790. Blomstrom-Lundqvist C, Johansson B, Berglin E, Nilsson L, Jensen SM, Thelin S, Holmgren  
5421 A, Edvardsson N, Kallner G, Blomstrom P. A randomized double-blind study of epicardial left atrial  
5422 cryoablation for permanent atrial fibrillation in patients undergoing mitral valve surgery: the SWEDish  
5423 Multicentre Atrial Fibrillation study (SWEDMAF). *Eur Heart J* 2007;**28**:2902-2908.
- 5424 791. Chevalier P, Leizorovicz A, Maureira P, Carreaux JP, Corbineau H, Caus T, DeBreyne B,  
5425 Mabot P, Dechillou C, Deharo JC, Barry S, Touboul P, Villemot JP, Obadia JF. Left atrial  
5426 radiofrequency ablation during mitral valve surgery: a prospective randomized multicentre study  
5427 (SAFIR). *Arch Cardiovasc Dis* 2009;**102**:769-775.
- 5428 792. Deneke T, Khargi K, Grewe PH, Laczkovics A, von Dryander S, Lawo T, Muller KM, Lemke B.  
5429 Efficacy of an additional MAZE procedure using cooled-tip radiofrequency ablation in patients with  
5430 chronic atrial fibrillation and mitral valve disease. A randomized, prospective trial. *Eur Heart J*  
5431 2002;**23**:558-566.
- 5432 793. Doukas G, Samani NJ, Alexiou C, Oc M, Chin DT, Stafford PG, Ng LL, Spyt TJ. Left atrial  
5433 radiofrequency ablation during mitral valve surgery for continuous atrial fibrillation: a randomized  
5434 controlled trial. *JAMA* 2005;**294**:2323-2329.
- 5435 794. Schuetz A, Schulze CJ, Sarvanakis KK, Mair H, Plazer H, Kilger E, Reichart B, Wildhirt SM.  
5436 Surgical treatment of permanent atrial fibrillation using microwave energy ablation: a prospective  
5437 randomized clinical trial. *Eur J Cardiothorac Surg* 2003;**24**:475-480; discussion 480.
- 5438 795. Liu X, Tan HW, Wang XH, Shi HF, Li YZ, Li F, Zhou L, Gu JN. Efficacy of catheter ablation  
5439 and surgical CryoMaze procedure in patients with long-lasting persistent atrial fibrillation and  
5440 rheumatic heart disease: a randomized trial. *Eur Heart J* 2010;**31**:2633-2641.
- 5441 796. Cheng DC, Ad N, Martin J, Berglin EE, Chang BC, Doukas G, Gammie JS, Nitta T, Wolf RK,  
5442 Puskas JD. Surgical ablation for atrial fibrillation in cardiac surgery: a meta-analysis and systematic  
5443 review. *Innovations (Phila)* 2010;**5**:84-96.
- 5444 797. Barnett SD, Ad N. Surgical ablation as treatment for the elimination of atrial fibrillation: a  
5445 meta-analysis. *J Thorac Cardiovasc Surg* 2006;**131**:1029-1035.
- 5446 798. Ad N, Henry L, Massimiano P, Pritchard G, Holmes SD. The state of surgical ablation for  
5447 atrial fibrillation in patients with mitral valve disease. *Curr Opin Cardiol* 2013;**28**:170-180.
- 5448 799. Gammie JS, Haddad M, Milford-Beland S, Welke KF, Ferguson TB, Jr., O'Brien SM, Griffith  
5449 BP, Peterson ED. Atrial fibrillation correction surgery: lessons from the Society of Thoracic Surgeons  
5450 National Cardiac Database. *Ann Thorac Surg* 2008;**85**:909-914.

- 5451 800. Chen MC, Chang JP, Chang HW. Preoperative atrial size predicts the success of  
5452 radiofrequency maze procedure for permanent atrial fibrillation in patients undergoing concomitant  
5453 valvular surgery. *Chest* 2004;**125**:2129-2134.
- 5454 801. Sunderland N, Maruthappu M, Nagendran M. What size of left atrium significantly impairs the  
5455 success of maze surgery for atrial fibrillation? *Interact Cardiovasc Thorac Surg* 2011;**13**:332-338.
- 5456 802. Chaiyaraj S, Ngarmukos T, Lertsithichai P. Predictors of sinus rhythm after radiofrequency  
5457 maze and mitral valve surgery. *Asian Cardiovasc Thorac Ann* 2008;**16**:292-297.
- 5458 803. Gillinov AM, Bhavani S, Blackstone EH, Rajeswaran J, Svensson LG, Navia JL, Pettersson  
5459 BG, Sabik JF, 3rd, Smedira NG, Mihaljevic T, McCarthy PM, Shewchik J, Natale A. Surgery for  
5460 permanent atrial fibrillation: impact of patient factors and lesion set. *Ann Thorac Surg* 2006;**82**:502-  
5461 513; discussion 513-504.
- 5462 804. Beukema WP, Sie HT, Misier AR, Delnoy PP, Wellens HJ, Elvan A. Predictive factors of  
5463 sustained sinus rhythm and recurrent atrial fibrillation after a radiofrequency modified Maze  
5464 procedure. *Eur J Cardiothorac Surg* 2008;**34**:771-775.
- 5465 805. Gillinov AM, Bakaeen F, McCarthy PM, Blackstone EH, Rajeswaran J, Pettersson G, Sabik  
5466 JF, 3rd, Najam F, Hill KM, Svensson LG, Cosgrove DM, Marrouche N, Natale A. Surgery for  
5467 paroxysmal atrial fibrillation in the setting of mitral valve disease: a role for pulmonary vein isolation?  
5468 *Ann Thorac Surg* 2006;**81**:19-26; discussion 27-18.
- 5469 806. Onorati F, Mariscalco G, Rubino AS, Serraino F, Santini F, Musazzi A, Klersy C, Sala A,  
5470 Renzulli A. Impact of lesion sets on mid-term results of surgical ablation procedure for atrial fibrillation.  
5471 *J Am Coll Cardiol* 2011;**57**:931-940.
- 5472 807. Saint LL, Bailey MS, Prasad S, Guthrie TJ, Bell J, Moon MR, Lawton JS, Munfakh NA,  
5473 Schuessler RB, Damiano RJ, Jr., Maniar HS. Cox-Maze IV results for patients with lone atrial  
5474 fibrillation versus concomitant mitral disease. *Ann Thorac Surg* 2012;**93**:789-794; discussion 794-785.
- 5475 808. Lawrance CP, Henn MC, Miller JR, Sinn LA, Schuessler RB, Maniar HS, Damiano RJ, Jr. A  
5476 minimally invasive Cox maze IV procedure is as effective as sternotomy while decreasing major  
5477 morbidity and hospital stay. *J Thorac Cardiovasc Surg* 2014;**148**:955-961; discussion 962-952.
- 5478 809. Edgerton JR, Brinkman WT, Weaver T, Prince SL, Culica D, Herbert MA, Mack MJ.  
5479 Pulmonary vein isolation and autonomic denervation for the management of paroxysmal atrial  
5480 fibrillation by a minimally invasive surgical approach. *J Thorac Cardiovasc Surg* 2010;**140**:823-828.
- 5481 810. McClelland JH, Duke D, Reddy R. Preliminary results of a limited thoracotomy: new approach  
5482 to treat atrial fibrillation. *J Cardiovasc Electrophysiol* 2007;**18**:1289-1295.
- 5483 811. Castella M, Pereda D, Mestres CA, Gomez F, Quintana E, Mulet J. Thoracoscopic pulmonary  
5484 vein isolation in patients with atrial fibrillation and failed percutaneous ablation. *J Thorac Cardiovasc  
5485 Surg* 2010;**140**:633-638.
- 5486 812. Krul SP, Driessen AH, van Boven WJ, Linnenbank AC, Geuzebroek GS, Jackman WM, Wilde  
5487 AA, de Bakker JM, de Groot JR. Thoracoscopic video-assisted pulmonary vein antrum isolation,  
5488 ganglionated plexus ablation, and periprocedural confirmation of ablation lesions: first results of a  
5489 hybrid surgical-electrophysiological approach for atrial fibrillation. *Circ Arrhythm Electrophysiol*  
5490 2011;**4**:262-270.
- 5491 813. La Meir M, Gelsomino S, Lorusso R, Luca F, Pison L, Parise O, Wellens F, Gensini GF,  
5492 Maessen J. The hybrid approach for the surgical treatment of lone atrial fibrillation: one-year results  
5493 employing a monopolar radiofrequency source. *J Cardiothorac Surg* 2012;**7**:71.
- 5494 814. Wang S, Liu L, Zou C. Comparative study of video-assisted thoracoscopic surgery ablation  
5495 and radiofrequency catheter ablation on treating paroxysmal atrial fibrillation: a randomized, controlled  
5496 short-term trial. *Chin Med J (Engl)* 2014;**127**:2567-2570.
- 5497 815. Phan K, Phan S, Thiagalingam A, Medi C, Yan TD. Thoracoscopic surgical ablation versus  
5498 catheter ablation for atrial fibrillation. *Eur J Cardiothorac Surg* 2016;**49**:1044-1051.
- 5499 816. Hu QM, Li Y, Xu CL, Han J, Zhang HB, Han W, Meng X. Analysis of risk factors for  
5500 recurrence after video-assisted pulmonary vein isolation of lone atrial fibrillation-results of 5 years of  
5501 follow-up. *J Thorac Cardiovasc Surg* 2014;**148**:2174-2180.
- 5502 817. Edgerton JR, Edgerton ZJ, Weaver T, Reed K, Prince S, Herbert MA, Mack MJ. Minimally  
5503 invasive pulmonary vein isolation and partial autonomic denervation for surgical treatment of atrial  
5504 fibrillation. *Ann Thorac Surg* 2008;**86**:35-38; discussion 39.
- 5505 818. Wang J, Li Y, Shi J, Han J, Xu C, Ma C, Meng X. Minimally invasive surgical versus catheter  
5506 ablation for the long-lasting persistent atrial fibrillation. *PLoS One* 2011;**6**:e22122.
- 5507 819. Wang JG, Xin M, Han J, Li Y, Luo TG, Wang J, Meng F, Meng X. Ablation in selective  
5508 patients with long-standing persistent atrial fibrillation: medium-term results of the Dallas lesion set.  
5509 *Eur J Cardiothorac Surg* 2014;**46**:213-220.

- 5510 820. Sirak JH, Schwartzman D. Interim results of the 5-box thoracoscopic maze procedure. *Ann Thorac Surg* 2012;**94**:1880-1884.
- 5511
- 5512 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.
- 5513
- 5514
- 5515
- 5516 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.
- 5517
- 5518
- 5519 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.
- 5520
- 5521
- 5522
- 5523 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.
- 5524
- 5525
- 5526 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.
- 5527
- 5528 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.
- 5529
- 5530
- 5531 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.
- 5532
- 5533 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.
- 5534
- 5535
- 5536 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.
- 5537
- 5538
- 5539 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.
- 5540
- 5541
- 5542
- 5543 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.
- 5544
- 5545 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.
- 5546
- 5547
- 5548 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.
- 5549
- 5550
- 5551 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.
- 5552
- 5553
- 5554 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.
- 5555
- 5556
- 5557
- 5558 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.
- 5559
- 5560
- 5561
- 5562 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.
- 5563
- 5564
- 5565
- 5566 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.
- 5567
- 5568

- 5569 839. Saksena S, Prakash A, Ziegler P, Hummel JD, Friedman P, Plumb VJ, Wyse DG, Johnson E,  
5570 Fitts S, Mehra R. Improved suppression of recurrent atrial fibrillation with dual-site right atrial pacing  
5571 and antiarrhythmic drug therapy. *J Am Coll Cardiol* 2002;**40**:1140-1150; discussion 1151-1142.
- 5572 840. Wharton JM, Sorrentino RA, Campbell P, Gonzalez-Zuelgaray J, Keating E, Curtis A, Grill C,  
5573 Hafley G, Lee K. Effect of pacing modality on atrial tachyarrhythmia recurrence in the tachycardia-  
5574 bradycardia syndrome: preliminary results of the Pacemaker Atrial Tachycardia Trial. *Circulation*  
5575 1998;**98 (suppl I)**:I-494 (abstract).
- 5576 841. Marinigh R, Lip GY, Fiotti N, Giansante C, Lane DA. Age as a risk factor for stroke in atrial  
5577 fibrillation patients: implications for thromboprophylaxis. *J Am Coll Cardiol* 2010;**56**:827-837.
- 5578 842. Gage BF, Boechler M, Doggette AL, Fortune G, Flaker GC, Rich MW, Radford MJ. Adverse  
5579 outcomes and predictors of underuse of antithrombotic therapy in medicare beneficiaries with chronic  
5580 atrial fibrillation. *Stroke* 2000;**31**:822-827.
- 5581 843. Andreotti F, Rocca B, Husted S, Ajjan RA, Ten Berg J, Cattaneo M, Collet JP, De Caterina R,  
5582 Fox KA, Halvorsen S, Huber K, Hylek EM, Lip GY, Montalescot G, Morais J, Patrono C, Verheugt FW,  
5583 Wallentin L, Weiss TW, Storey RF, ESC Thrombosis Working Group. Antithrombotic therapy in the  
5584 elderly: expert position paper of the European Society of Cardiology Working Group on Thrombosis.  
5585 *Eur Heart J* 2015;**36**:3238-3249.
- 5586 844. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM,  
5587 Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen K, Kuck KH, Hernandez-Madrid A, Nikolaou  
5588 N, Norekval TM, Spaulding C, Van Veldhuisen DJ. 2015 ESC Guidelines for the management of  
5589 patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for  
5590 the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac  
5591 Death of the European Society of Cardiology (ESC). Endorsed by: Association for European  
5592 Paediatric and Congenital Cardiology (AEPC). *Eur Heart J* 2015;**36**:2793-2867.
- 5593 845. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont  
5594 A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG,  
5595 Pieske B, Rapezzi C, Rutten FH, Tillmanns C, Watkins H. 2014 ESC Guidelines on diagnosis and  
5596 management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of  
5597 Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J*  
5598 2014;**35**:2733-2779.
- 5599 846. Johnson JN, Tester DJ, Perry J, Salisbury BA, Reed CR, Ackerman MJ. Prevalence of early-  
5600 onset atrial fibrillation in congenital long QT syndrome. *Heart Rhythm* 2008;**5**:704-709.
- 5601 847. Kirchhof P, Eckardt L, Franz MR, Monnig G, Loh P, Wedekind H, Schulze-Bahr E, Breithardt  
5602 G, Haverkamp W. Prolonged atrial action potential durations and polymorphic atrial tachyarrhythmias  
5603 in patients with long QT syndrome. *J Cardiovasc Electrophysiol* 2003;**14**:1027-1033.
- 5604 848. Zellerhoff S, Pistulli R, Monnig G, Hinterseer M, Beckmann BM, Kobe J, Steinbeck G, Kaab  
5605 S, Haverkamp W, Fabritz L, Gradaus R, Breithardt G, Schulze-Bahr E, Bocker D, Kirchhof P. Atrial  
5606 Arrhythmias in long-QT syndrome under daily life conditions: a nested case control study. *J*  
5607 *Cardiovasc Electrophysiol* 2009;**20**:401-407.
- 5608 849. Moss AJ, Zareba W, Benhorin J, Locati EH, Hall WJ, Robinson JL, Schwartz PJ, Towbin JA,  
5609 Vincent GM, Lehmann MH. ECG T-wave patterns in genetically distinct forms of the hereditary long  
5610 QT syndrome. *Circulation* 1995;**92**:2929-2934.
- 5611 850. Schwartz PJ, Priori SG, Spazzolini C, Moss AJ, Vincent GM, Napolitano C, Denjoy I,  
5612 Guicheney P, Breithardt G, Keating MT, Towbin JA, Beggs AH, Brink P, Wilde AA, Toivonen L,  
5613 Zareba W, Robinson JL, Timothy KW, Corfield V, Wattanasirichaigoon D, Corbett C, Haverkamp W,  
5614 Schulze-Bahr E, Lehmann MH, Schwartz K, Coumel P, Bloise R. Genotype-phenotype correlation in  
5615 the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. *Circulation*  
5616 2001;**103**:89-95.
- 5617 851. Eckardt L, Kirchhof P, Loh P, Schulze-Bahr E, Johna R, Wichter T, Breithardt G, Haverkamp  
5618 W, Borggrefe M. Brugada syndrome and supraventricular tachyarrhythmias: a novel association? *J*  
5619 *Cardiovasc Electrophysiol* 2001;**12**:680-685.
- 5620 852. Kaufman ES. Mechanisms and clinical management of inherited channelopathies: long QT  
5621 syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, and short QT  
5622 syndrome. *Heart Rhythm* 2009;**6**:S51-55.
- 5623 853. Antzelevitch C, Pollevick GD, Cordeiro JM, Casis O, Sanguinetti MC, Aizawa Y, Guerchicoff  
5624 A, Pfeiffer R, Oliva A, Wollnik B, Gelber P, Bonaros EP, Jr., Burashnikov E, Wu Y, Sargent JD,  
5625 Schickel S, Oberheiden R, Bhatia A, Hsu LF, Haissaguerre M, Schimpf R, Borggrefe M, Wolpert C.  
5626 Loss-of-function mutations in the cardiac calcium channel underlie a new clinical entity characterized  
5627 by ST-segment elevation, short QT intervals, and sudden cardiac death. *Circulation* 2007;**115**:442-  
5628 449.

- 5629 854. London B, Michalec M, Mehdi H, Zhu X, Kerchner L, Sanyal S, Viswanathan PC, Pfahnl AE,  
5630 Shang LL, Madhusudanan M, Baty CJ, Lagana S, Aleong R, Gutmann R, Ackerman MJ, McNamara  
5631 DM, Weiss R, Dudley SC, Jr. Mutation in glycerol-3-phosphate dehydrogenase 1 like gene (GPD1-L)  
5632 decreases cardiac Na<sup>+</sup> current and causes inherited arrhythmias. *Circulation* 2007;**116**:2260-2268.
- 5633 855. Watanabe H, Koopmann TT, Le Scouarnec S, Yang T, Ingram CR, Schott JJ, Demolombe S,  
5634 Probst V, Anselme F, Escande D, Wiesfeld AC, Pfeufer A, Kaab S, Wichmann HE, Hasdemir C,  
5635 Aizawa Y, Wilde AA, Roden DM, Bezzina CR. Sodium channel beta1 subunit mutations associated  
5636 with Brugada syndrome and cardiac conduction disease in humans. *J Clin Invest* 2008;**118**:2260-  
5637 2268.
- 5638 856. Brugada R, Hong K, Dumaine R, Cordeiro J, Gaita F, Borggrefe M, Menendez TM, Brugada  
5639 J, Pollevick GD, Wolpert C, Burashnikov E, Matsuo K, Wu YS, Guerchicoff A, Bianchi F, Giustetto C,  
5640 Schimpf R, Brugada P, Antzelevitch C. Sudden death associated with short-QT syndrome linked to  
5641 mutations in HERG. *Circulation* 2004;**109**:30-35.
- 5642 857. Gaita F, Giustetto C, Bianchi F, Wolpert C, Schimpf R, Riccardi R, Grossi S, Richiardi E,  
5643 Borggrefe M. Short QT Syndrome: a familial cause of sudden death. *Circulation* 2003;**108**:965-970.
- 5644 858. Giustetto C, Di Monte F, Wolpert C, Borggrefe M, Schimpf R, Sbragia P, Leone G, Maury P,  
5645 Anttonen O, Haissaguerre M, Gaita F. Short QT syndrome: clinical findings and diagnostic-therapeutic  
5646 implications. *Eur Heart J* 2006;**27**:2440-2447.
- 5647 859. Bhuiyan ZA, van den Berg MP, van Tintelen JP, Bink-Boelkens MT, Wiesfeld AC, Alders M,  
5648 Postma AV, van Langen I, Mannens MM, Wilde AA. Expanding spectrum of human RYR2-related  
5649 disease: new electrocardiographic, structural, and genetic features. *Circulation* 2007;**116**:1569-1576.
- 5650 860. Napolitano C, Priori SG. Diagnosis and treatment of catecholaminergic polymorphic  
5651 ventricular tachycardia. *Heart Rhythm* 2007;**4**:675-678.
- 5652 861. Mohamed U, Napolitano C, Priori SG. Molecular and electrophysiological bases of  
5653 catecholaminergic polymorphic ventricular tachycardia. *J Cardiovasc Electrophysiol* 2007;**18**:791-797.
- 5654 862. Lee CH, Liu PY, Lin LJ, Chen JH, Tsai LM. Clinical characteristics and outcomes of  
5655 hypertrophic cardiomyopathy in Taiwan--a tertiary center experience. *Clin Cardiol* 2007;**30**:177-182.
- 5656 863. Losi MA, Betocchi S, Aversa M, Lombardi R, Miranda M, D'Alessandro G, Cacace A,  
5657 Tocchetti CG, Barbati G, Chiariello M. Determinants of atrial fibrillation development in patients with  
5658 hypertrophic cardiomyopathy. *Am J Cardiol* 2004;**94**:895-900.
- 5659 864. Maron BJ, Olivetto I, Bellone P, Conte MR, Cecchi F, Flygenring BP, Casey SA, Gohman TE,  
5660 Bongioanni S, Spirito P. Clinical profile of stroke in 900 patients with hypertrophic cardiomyopathy. *J*  
5661 *Am Coll Cardiol* 2002;**39**:301-307.
- 5662 865. Gollob MH, Seger JJ, Gollob TN, Tapscott T, Gonzales O, Bachinski L, Roberts R. Novel  
5663 PRKAG2 mutation responsible for the genetic syndrome of ventricular preexcitation and conduction  
5664 system disease with childhood onset and absence of cardiac hypertrophy. *Circulation* 2001;**104**:3030-  
5665 3033.
- 5666 866. Postma AV, van de Meerakker JB, Mathijssen IB, Barnett P, Christoffels VM, Ilgun A, Lam J,  
5667 Wilde AA, Lekanne Deprez RH, Moorman AF. A gain-of-function TBX5 mutation is associated with  
5668 atypical Holt-Oram syndrome and paroxysmal atrial fibrillation. *Circ Res* 2008;**102**:1433-1442.
- 5669 867. Marcus FI, Edson S, Towbin JA. Genetics of arrhythmogenic right ventricular cardiomyopathy:  
5670 a practical guide for physicians. *J Am Coll Cardiol* 2013;**61**:1945-1948.
- 5671 868. Chu AF, Zado E, Marchlinski FE. Atrial arrhythmias in patients with arrhythmogenic right  
5672 ventricular cardiomyopathy/dysplasia and ventricular tachycardia. *Am J Cardiol* 2010;**106**:720-722.
- 5673 869. Blomstrom-Lundqvist C, Scheinman MM, Aliot EM, Alpert JS, Calkins H, Camm AJ, Campbell  
5674 WB, Haines DE, Kuck KH, Lerman BB, Miller DD, Shaeffer CW, Stevenson WG, Tomaselli GF,  
5675 Antman EM, Smith SC, Jr., Alpert JS, Faxon DP, Fuster V, Gibbons RJ, Gregoratos G, Hiratzka LF,  
5676 Hunt SA, Jacobs AK, Russell RO, Jr., Priori SG, Blanc JJ, Budaj A, Burgos EF, Cowie M, Deckers  
5677 JW, Garcia MA, Klein WW, Lekakis J, Lindahl B, Mazzotta G, Morais JC, Oto A, Smiseth O, Trappe  
5678 HJ, European Society of Cardiology Committee, NASPE-Heart Rhythm Society. ACC/AHA/ESC  
5679 guidelines for the management of patients with supraventricular arrhythmias--executive summary. a  
5680 report of the American college of cardiology/American heart association task force on practice  
5681 guidelines and the European society of cardiology committee for practice guidelines (writing  
5682 committee to develop guidelines for the management of patients with supraventricular arrhythmias)  
5683 developed in collaboration with NASPE-Heart Rhythm Society. *J Am Coll Cardiol* 2003;**42**:1493-1531.
- 5684 870. Tischenko A, Fox DJ, Yee R, Krahn AD, Skanes AC, Gula LJ, Klein GJ. When should we  
5685 recommend catheter ablation for patients with the Wolff-Parkinson-White syndrome? *Curr Opin*  
5686 *Cardiol* 2008;**23**:32-37.
- 5687 871. Kibos A, Deharo JC, Adoubi A, Assouan X, Djiane P. [Clinical and electrophysiological study  
5688 of asymptomatic Wolff-Parkinson-White syndrome]. *Ann Cardiol Angeiol (Paris)* 2007;**56**:237-240.

- 5689 872. Pappone C, Santinelli V, Manguso F, Augello G, Santinelli O, Vicedomini G, Gulletta S,  
5690 Mazzone P, Tortoriello V, Pappone A, Dicandia C, Rosanio S. A randomized study of prophylactic  
5691 catheter ablation in asymptomatic patients with the Wolff-Parkinson-White syndrome. *N Engl J Med*  
5692 2003;**349**:1803-1811.
- 5693 873. Boahene KA, Klein GJ, Yee R, Sharma AD, Fujimura O. Termination of acute atrial fibrillation  
5694 in the Wolff-Parkinson-White syndrome by procainamide and propafenone: importance of atrial  
5695 fibrillatory cycle length. *J Am Coll Cardiol* 1990;**16**:1408-1414.
- 5696 874. O'Nunain S, Garratt CJ, Linker NJ, Gill J, Ward DE, Camm AJ. A comparison of intravenous  
5697 propafenone and flecainide in the treatment of tachycardias associated with the Wolff-Parkinson-  
5698 White syndrome. *Pacing Clin Electrophysiol* 1991;**14**:2028-2034.
- 5699 875. Manolis AS, Estes NA, 3rd. Supraventricular tachycardia. Mechanisms and therapy. *Arch*  
5700 *Intern Med* 1987;**147**:1706-1716.
- 5701 876. Simonian SM, Lotfipour S, Wall C, Langdorf MI. Challenging the superiority of amiodarone for  
5702 rate control in Wolff-Parkinson-White and atrial fibrillation. *Intern Emerg Med* 2010;**5**:421-426.
- 5703 877. Guttman OP, Rahman MS, O'Mahony C, Anastasakis A, Elliott PM. Atrial fibrillation and  
5704 thromboembolism in patients with hypertrophic cardiomyopathy: systematic review. *Heart*  
5705 2014;**100**:465-472.
- 5706 878. Olivetto I, Cecchi F, Casey SA, Dolara A, Traverse JH, Maron BJ. Impact of atrial fibrillation  
5707 on the clinical course of hypertrophic cardiomyopathy. *Circulation* 2001;**104**:2517-2524.
- 5708 879. Cecchi F, Olivetto I, Monteregeggi A, Squillatini G, Dolara A, Maron BJ. Prognostic value of non-  
5709 sustained ventricular tachycardia and the potential role of amiodarone treatment in hypertrophic  
5710 cardiomyopathy: assessment in an unselected non-referral based patient population. *Heart*  
5711 1998;**79**:331-336.
- 5712 880. Bunch TJ, Munger TM, Friedman PA, Asirvatham SJ, Brady PA, Cha YM, Rea RF, Shen WK,  
5713 Powell BD, Ommen SR, Monahan KH, Haroldson JM, Packer DL. Substrate and procedural  
5714 predictors of outcomes after catheter ablation for atrial fibrillation in patients with hypertrophic  
5715 cardiomyopathy. *J Cardiovasc Electrophysiol* 2008;**19**:1009-1014.
- 5716 881. Di Donna P, Olivetto I, Delcre SD, Caponi D, Scaglione M, Nault I, Montefusco A, Girolami F,  
5717 Cecchi F, Haissaguerre M, Gaita F. Efficacy of catheter ablation for atrial fibrillation in hypertrophic  
5718 cardiomyopathy: impact of age, atrial remodelling, and disease progression. *Europace* 2010;**12**:347-  
5719 355.
- 5720 882. Gaita F, Di Donna P, Olivetto I, Scaglione M, Ferrero I, Montefusco A, Caponi D, Conte MR,  
5721 Nistri S, Cecchi F. Usefulness and safety of transcatheter ablation of atrial fibrillation in patients with  
5722 hypertrophic cardiomyopathy. *Am J Cardiol* 2007;**99**:1575-1581.
- 5723 883. Kilicaslan F, Verma A, Saad E, Themistoclakis S, Bonso A, Raviele A, Bozbas H, Andrews  
5724 MW, Beheiry S, Hao S, Cummings JE, Marrouche NF, Lakkireddy D, Wazni O, Yamaji H, Saenz LC,  
5725 Saliba W, Schweikert RA, Natale A. Efficacy of catheter ablation of atrial fibrillation in patients with  
5726 hypertrophic obstructive cardiomyopathy. *Heart Rhythm* 2006;**3**:275-280.
- 5727 884. McCreedy JW, Smedley T, Lambiase PD, Ahsan SY, Segal OR, Rowland E, Lowe MD, Chow  
5728 AW. Predictors of recurrence following radiofrequency ablation for persistent atrial fibrillation.  
5729 *Europace* 2011;**13**:355-361.
- 5730 885. Ritchie MD, Rowan S, Kucera G, Stubblefield T, Blair M, Carter S, Roden DM, Darbar D.  
5731 Chromosome 4q25 variants are genetic modifiers of rare ion channel mutations associated with  
5732 familial atrial fibrillation. *J Am Coll Cardiol* 2012;**60**:1173-1181.
- 5733 886. Mann SA, Otway R, Guo G, Soka M, Karlsdotter L, Trivedi G, Ohanian M, Zodgekar P, Smith  
5734 RA, Wouters MA, Subbiah R, Walker B, Kuchar D, Sanders P, Griffiths L, Vandenberg JI, Fatkin D.  
5735 Epistatic effects of potassium channel variation on cardiac repolarization and atrial fibrillation risk. *J*  
5736 *Am Coll Cardiol* 2012;**59**:1017-1025.
- 5737 887. Giustetto C, Cerrato N, Gribaudo E, Scrocco C, Castagno D, Richiardi E, Giachino D, Bianchi  
5738 F, Barbonaglia L, Ferraro A. Atrial fibrillation in a large population with Brugada electrocardiographic  
5739 pattern: prevalence, management, and correlation with prognosis. *Heart Rhythm* 2014;**11**:259-265.
- 5740 888. Darbar D, Kannankeril PJ, Donahue BS, Kucera G, Stubblefield T, Haines JL, George AL, Jr.,  
5741 Roden DM. Cardiac sodium channel (SCN5A) variants associated with atrial fibrillation. *Circulation*  
5742 2008;**117**:1927-1935.
- 5743 889. Olson TM, Michels VV, Ballew JD, Reyna SP, Karst ML, Herron KJ, Horton SC, Rodeheffer  
5744 RJ, Anderson JL. Sodium channel mutations and susceptibility to heart failure and atrial fibrillation.  
5745 *JAMA* 2005;**293**:447-454.
- 5746 890. Ellinor PT, Moore RK, Patton KK, Ruskin JN, Pollak MR, Macrae CA. Mutations in the long  
5747 QT gene, KCNQ1, are an uncommon cause of atrial fibrillation. *Heart* 2004;**90**:1487-1488.

- 5748 891. Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, Blom N, Brugada J, Chiang CE,  
5749 Huikuri H, Kannankeril P, Krahn A, Leenhardt A, Moss A, Schwartz PJ, Shimizu W, Tomaselli G,  
5750 Tracy C, Ackerman M, Belhassen B, Estes NA, 3rd, Fatkin D, Kalman J, Kaufman E, Kirchhof P,  
5751 Schulze-Bahr E, Wolpert C, Vohra J, Refaat M, Etheridge SP, Campbell RM, Martin ET, Quek SC.  
5752 Executive summary: HRS/EHRA/APHRS expert consensus statement on the diagnosis and  
5753 management of patients with inherited primary arrhythmia syndromes. *Europace* 2013;**15**:1389-1406.
- 5754 892. Antz M, Weiss C, Volkmer M, Hebe J, Ernst S, Ouyang F, Kuck KH. Risk of sudden death  
5755 after successful accessory atrioventricular pathway ablation in resuscitated patients with Wolff-  
5756 Parkinson-White syndrome. *J Cardiovasc Electrophysiol* 2002;**13**:231-236.
- 5757 893. Timmermans C, Smeets JL, Rodriguez LM, Vrouchos G, van den Dool A, Wellens HJ.  
5758 Aborted sudden death in the Wolff-Parkinson-White syndrome. *Am J Cardiol* 1995;**76**:492-494.
- 5759 894. Bromberg BI, Lindsay BD, Cain ME, Cox JL. Impact of clinical history and electrophysiologic  
5760 characterization of accessory pathways on management strategies to reduce sudden death among  
5761 children with Wolff-Parkinson-White syndrome. *J Am Coll Cardiol* 1996;**27**:690-695.
- 5762 895. Al-Khatib SM, Arshad A, Balk EM, Das SR, Hsu JC, Joglar JA, Page RL. Risk stratification for  
5763 arrhythmic events in patients with asymptomatic pre-excitation: A systematic review for the 2015  
5764 ACC/AHA/HRS guideline for the management of adult patients with supraventricular tachycardia: A  
5765 Report of the American College of Cardiology/American Heart Association Task Force on Clinical  
5766 Practice Guidelines and the Heart Rhythm Society. *Heart Rhythm* 2016;**13**:e222-237.
- 5767 896. Maron BJ, Ommen SR, Semsarian C, Spirito P, Olivetto I, Maron MS. Hypertrophic  
5768 cardiomyopathy: present and future, with translation into contemporary cardiovascular medicine. *J Am  
5769 Coll Cardiol* 2014;**64**:83-99.
- 5770 897. Robinson K, Frenneaux MP, Stockins B, Karatasakis G, Poloniecki JD, McKenna WJ. Atrial  
5771 fibrillation in hypertrophic cardiomyopathy: a longitudinal study. *J Am Coll Cardiol* 1990;**15**:1279-1285.
- 5772 898. Mozaffarian D, Furberg CD, Psaty BM, Siscovick D. Physical activity and incidence of atrial  
5773 fibrillation in older adults: the cardiovascular health study. *Circulation* 2008;**118**:800-807.
- 5774 899. Elosua R, Arquer A, Mont L, Sambola A, Molina L, Garcia-Moran E, Brugada J, Marrugat J.  
5775 Sport practice and the risk of lone atrial fibrillation: a case-control study. *Int J Cardiol* 2006;**108**:332-  
5776 337.
- 5777 900. Mont L, Sambola A, Brugada J, Vacca M, Marrugat J, Elosua R, Pare C, Azqueta M, Sanz G.  
5778 Long-lasting sport practice and lone atrial fibrillation. *Eur Heart J* 2002;**23**:477-482.
- 5779 901. Abdulla J, Nielsen JR. Is the risk of atrial fibrillation higher in athletes than in the general  
5780 population? A systematic review and meta-analysis. *Europace* 2009;**11**:1156-1159.
- 5781 902. Thelle DS, Selmer R, Gjesdal K, Sakshaug S, Jugessur A, Graff-Iversen S, Tverdal A, Nystad  
5782 W. Resting heart rate and physical activity as risk factors for lone atrial fibrillation: a prospective study  
5783 of 309,540 men and women. *Heart* 2013;**99**:1755-1760.
- 5784 903. Wilhelm M, Roten L, Tanner H, Wilhelm I, Schmid JP, Saner H. Atrial remodeling, autonomic  
5785 tone, and lifetime training hours in nonelite athletes. *Am J Cardiol* 2011;**108**:580-585.
- 5786 904. Guasch E, Benito B, Qi X, Cifelli C, Naud P, Shi Y, Mighiu A, Tardif JC, Tadevosyan A, Chen  
5787 Y, Gillis MA, Iwasaki YK, Dobrev D, Mont L, Heximer S, Nattel S. Atrial fibrillation promotion by  
5788 endurance exercise: demonstration and mechanistic exploration in an animal model. *J Am Coll  
5789 Cardiol* 2013;**62**:68-77.
- 5790 905. Andersen K, Farahmand B, Ahlbom A, Held C, Ljunghall S, Michaelsson K, Sundstrom J.  
5791 Risk of arrhythmias in 52 755 long-distance cross-country skiers: a cohort study. *Eur Heart J  
5792* 2013;**34**:3624-3631.
- 5793 906. Karjalainen J, Kujala UM, Kaprio J, Sarna S, Viitasalo M. Lone atrial fibrillation in vigorously  
5794 exercising middle aged men: case-control study. *BMJ* 1998;**316**:1784-1785.
- 5795 907. Biffi A, Maron BJ, Culasso F, Verdile L, Fernando F, Di Giacinto B, Di Paolo FM, Spataro A,  
5796 Delise P, Pelliccia A. Patterns of ventricular tachyarrhythmias associated with training, deconditioning  
5797 and retraining in elite athletes without cardiovascular abnormalities. *Am J Cardiol* 2011;**107**:697-703.
- 5798 908. Calvo N, Mont L, Tamborero D, Berruezo A, Viola G, Guasch E, Nadal M, Andreu D, Vidal B,  
5799 Sitges M, Brugada J. Efficacy of circumferential pulmonary vein ablation of atrial fibrillation in  
5800 endurance athletes. *Europace* 2010;**12**:30-36.
- 5801 909. Koopman P, Nuyens D, Garweg C, La Gerche A, De Buck S, Van Casteren L, Alzand B,  
5802 Willems R, Heidebuchel H. Efficacy of radiofrequency catheter ablation in athletes with atrial fibrillation.  
5803 *Europace* 2011;**13**:1386-1393.
- 5804 910. Heidebuchel H, Panhuyzen-Goedkoop N, Corrado D, Hoffmann E, Biffi A, Delise P,  
5805 Blomstrom-Lundqvist C, Vanhees L, Ivarhoff P, Dorwarth U, Pelliccia A. Recommendations for  
5806 participation in leisure-time physical activity and competitive sports in patients with arrhythmias and

- 5807 potentially arrhythmogenic conditions Part I: Supraventricular arrhythmias and pacemakers. *Eur J*  
5808 *Cardiovasc Prev Rehabil* 2006;**13**:475-484.
- 5809 911. Silversides CK, Harris L, Haberer K, Sermer M, Colman JM, Siu SC. Recurrence rates of  
5810 arrhythmias during pregnancy in women with previous tachyarrhythmia and impact on fetal and  
5811 neonatal outcomes. *Am J Cardiol* 2006;**97**:1206-1212.
- 5812 912. Salam AM, Ertekin E, van Hagen IM, Al Suwaidi J, Ruys TPE, Johnson MR, Gumbiene L,  
5813 Frogoudaki AA, Sorour KA, Iserin L, Ladouceur M, van Oppen ACC, Hall R, Roos-Hesselink JW.  
5814 Atrial Fibrillation or Flutter During Pregnancy in Patients With Structural Heart Disease: Data From the  
5815 ROPAC (Registry on Pregnancy and Cardiac Disease). *JACC Clin Electrophysiol* 2015;**1**:284-292.
- 5816 913. Baumgartner H, Bonhoeffer P, De Groot NM, de Haan F, Deanfield JE, Galie N, Gatzoulis  
5817 MA, Gohlke-Baerwolf C, Kaemmerer H, Kilner P, Meijboom F, Mulder BJ, Oechslin E, Oliver JM,  
5818 Serraf A, Szatmari A, Thaulow E, Vouhe PR, Walma E. ESC Guidelines for the management of  
5819 grown-up congenital heart disease (new version 2010). *Eur Heart J* 2010;**31**:2915-2957.
- 5820 914. Page RL. Treatment of arrhythmias during pregnancy. *Am Heart J* 1995;**130**:871-876.
- 5821 915. Magee LA, Duley L. Oral beta-blockers for mild to moderate hypertension during pregnancy.  
5822 *Cochrane Database Syst Rev* 2003;**3**:CD002863.
- 5823 916. Mitani GM, Steinberg I, Lien EJ, Harrison EC, Elkayam U. The pharmacokinetics of  
5824 antiarrhythmic agents in pregnancy and lactation. *Clin Pharmacokinet* 1987;**12**:253-291.
- 5825 917. Gowda RM, Khan IA, Mehta NJ, Vasavada BC, Sacchi TJ. Cardiac arrhythmias in pregnancy:  
5826 clinical and therapeutic considerations. *Int J Cardiol* 2003;**88**:129-133.
- 5827 918. Joint Formulary Committee. *British National Formulary (online)*.  
5828 <http://www.medicinescomplete.com>. Date last accessed 02/12/2014 2014
- 5829 919. Bartalena L, Bogazzi F, Braverman LE, Martino E. Effects of amiodarone administration  
5830 during pregnancy on neonatal thyroid function and subsequent neurodevelopment. *J Endocrinol*  
5831 *Invest* 2001;**24**:116-130.
- 5832 920. Jaeggi ET, Carvalho JS, De Groot E, Api O, Clur SA, Rammeloo L, McCrindle BW, Ryan G,  
5833 Manlhiot C, Blom NA. Comparison of transplacental treatment of fetal supraventricular  
5834 tachyarrhythmias with digoxin, flecainide, and sotalol: results of a nonrandomized multicenter study.  
5835 *Circulation* 2011;**124**:1747-1754.
- 5836 921. Tromp CHN, Nanne ACM, Pernet PJM, Tukkie R, Bolte AC. Electrical cardioversion during  
5837 pregnancy: safe or not? *Neth Heart J* 2011;**19**:134-136.
- 5838 922. Ghosh N, Luk A, Derzko C, Dorian P, Chow CM. The acute treatment of maternal  
5839 supraventricular tachycardias during pregnancy: a review of the literature. *J Obstet Gynaecol Can*  
5840 2011;**33**:17-23.
- 5841 923. Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO, American  
5842 College of Chest Physicians. VTE, thrombophilia, antithrombotic therapy, and pregnancy:  
5843 Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians  
5844 Evidence-Based Clinical Practice Guidelines. *Chest* 2012;**141**:e691S-736S.
- 5845 924. Ahlsson AJ, Bodin L, Lundblad OH, Englund AG. Postoperative atrial fibrillation is not  
5846 correlated to C-reactive protein. *Ann Thorac Surg* 2007;**83**:1332-1337.
- 5847 925. Arsenault KA, Yusuf AM, Crystal E, Healey JS, Morillo CA, Nair GM, Whitlock RP.  
5848 Interventions for preventing postoperative atrial fibrillation in patients undergoing heart surgery.  
5849 *Cochrane Database Syst Rev* 2013;**1**:Cd003611.
- 5850 926. Mathew JP, Fontes ML, Tudor IC, Ramsay J, Duke P, Mazer CD, Barash PG, Hsu PH,  
5851 Mangano DT. A multicenter risk index for atrial fibrillation after cardiac surgery. *JAMA* 2004;**291**:1720-  
5852 1729.
- 5853 927. Steinberg BA, Zhao Y, He X, Hernandez AF, Fullerton DA, Thomas KL, Mills R, Klaskala W,  
5854 Peterson ED, Piccini JP. Management of postoperative atrial fibrillation and subsequent outcomes in  
5855 contemporary patients undergoing cardiac surgery: insights from the Society of Thoracic Surgeons  
5856 CAPS-Care Atrial Fibrillation Registry. *Clin Cardiol* 2014;**37**:7-13.
- 5857 928. Khan MF, Wendel CS, Movahed MR. Prevention of post-coronary artery bypass grafting  
5858 (CABG) atrial fibrillation: efficacy of prophylactic beta-blockers in the modern era: a meta-analysis of  
5859 latest randomized controlled trials. *Ann Noninvasive Electrocardiol* 2013;**18**:58-68.
- 5860 929. Burgess DC, Kilborn MJ, Keech AC. Interventions for prevention of post-operative atrial  
5861 fibrillation and its complications after cardiac surgery: a meta-analysis. *Eur Heart J* 2006;**27**:2846-  
5862 2857.
- 5863 930. Chatterjee S, Sardar P, Mukherjee D, Lichstein E, Aikat S. Timing and route of amiodarone  
5864 for prevention of postoperative atrial fibrillation after cardiac surgery: a network regression meta-  
5865 analysis. *Pacing Clin Electrophysiol* 2013;**36**:1017-1023.

- 5866 931. Zhu J, Wang C, Gao D, Zhang C, Zhang Y, Lu Y, Gao Y. Meta-analysis of amiodarone versus  
5867 beta-blocker as a prophylactic therapy against atrial fibrillation following cardiac surgery. *Intern Med J*  
5868 2012;**42**:1078-1087.
- 5869 932. Fauchier L, Clementy N, Babuty D. Statin therapy and atrial fibrillation: systematic review and  
5870 updated meta-analysis of published randomized controlled trials. *Curr Opin Cardiol* 2013;**28**:7-18.
- 5871 933. Zheng H, Xue S, Hu ZL, Shan JG, Yang WG. The use of statins to prevent postoperative  
5872 atrial fibrillation after coronary artery bypass grafting: a meta-analysis of 12 studies. *J Cardiovasc*  
5873 *Pharmacol* 2014;**64**:285-292.
- 5874 934. Casadei B, OTHERS. Statin Therapy In Cardiac Surgery (STICS) Trial. *N Engl J Med*  
5875 2016;**TO BE ADDED**.
- 5876 935. Cook RC, Yamashita MH, Kearns M, Ramanathan K, Gin K, Humphries KH. Prophylactic  
5877 magnesium does not prevent atrial fibrillation after cardiac surgery: a meta-analysis. *Ann Thorac Surg*  
5878 2013;**95**:533-541.
- 5879 936. De Oliveira GS, Jr., Knautz JS, Sherwani S, McCarthy RJ. Systemic magnesium to reduce  
5880 postoperative arrhythmias after coronary artery bypass graft surgery: a meta-analysis of randomized  
5881 controlled trials. *J Cardiothorac Vasc Anesth* 2012;**26**:643-650.
- 5882 937. Costanzo S, di Niro V, Di Castelnuovo A, Gianfagna F, Donati MB, de Gaetano G, Iacoviello  
5883 L. Prevention of postoperative atrial fibrillation in open heart surgery patients by preoperative  
5884 supplementation of n-3 polyunsaturated fatty acids: an updated meta-analysis. *J Thorac Cardiovasc*  
5885 *Surg* 2013;**146**:906-911.
- 5886 938. Farquharson AL, Metcalf RG, Sanders P, Stuklis R, Edwards JR, Gibson RA, Cleland LG,  
5887 Sullivan TR, James MJ, Young GD. Effect of dietary fish oil on atrial fibrillation after cardiac surgery.  
5888 *Am J Cardiol* 2011;**108**:851-856.
- 5889 939. Heidarsdottir R, Arnar DO, Skuladottir GV, Torfason B, Edvardsson V, Gottskalksson G,  
5890 Palsson R, Indridason OS. Does treatment with n-3 polyunsaturated fatty acids prevent atrial  
5891 fibrillation after open heart surgery? *Europace* 2010;**12**:356-363.
- 5892 940. Mariani J, Doval HC, Nul D, Varini S, Grancelli H, Ferrante D, Tognoni G, Macchia A. N-3  
5893 polyunsaturated fatty acids to prevent atrial fibrillation: updated systematic review and meta-analysis  
5894 of randomized controlled trials. *J Am Heart Assoc* 2013;**2**:e005033.
- 5895 941. Rodrigo R, Korantzopoulos P, Cereceda M, Asenjo R, Zamorano J, Villalabeitia E, Baeza C,  
5896 Aguayo R, Castillo R, Carrasco R, Gormaz JG. A randomized controlled trial to prevent post-operative  
5897 atrial fibrillation by antioxidant reinforcement. *J Am Coll Cardiol* 2013;**62**:1457-1465.
- 5898 942. Saravanan P, Bridgewater B, West AL, O'Neill SC, Calder PC, Davidson NC. Omega-3 fatty  
5899 acid supplementation does not reduce risk of atrial fibrillation after coronary artery bypass surgery: a  
5900 randomized, double-blind, placebo-controlled clinical trial. *Circ Arrhythm Electrophysiol* 2010;**3**:46-53.
- 5901 943. Wu JH, Marchioli R, Silletta MG, Macchia A, Song X, Siscovick DS, Harris WS, Masson S,  
5902 Latini R, Albert C, Brown NJ, Lamarra M, Favalaro RR, Mozaffarian D. Plasma phospholipid omega-3  
5903 fatty acids and incidence of postoperative atrial fibrillation in the OPERA trial. *J Am Heart Assoc*  
5904 2013;**2**:e000397.
- 5905 944. Xin W, Wei W, Lin Z, Zhang X, Yang H, Zhang T, Li B, Mi S. Fish oil and atrial fibrillation after  
5906 cardiac surgery: a meta-analysis of randomized controlled trials. *PLoS One* 2013;**8**:e72913.
- 5907 945. Zhang B, Zhen Y, Tao A, Bao Z, Zhang G. Polyunsaturated fatty acids for the prevention of  
5908 atrial fibrillation after cardiac surgery: an updated meta-analysis of randomized controlled trials. *J*  
5909 *Cardiol* 2014;**63**:53-59.
- 5910 946. Imazio M, Brucato A, Ferrazzi P, Pullara A, Adler Y, Barosi A, Caforio AL, Cemin R, Chirillo F,  
5911 Comoglio C, Cugola D, Cumetti D, Dyrda O, Ferrua S, Finkelstein Y, Flocco R, Gandino A, Hoit B,  
5912 Innocente F, Maestroni S, Musumeci F, Oh J, Pergolini A, Polizzi V, Ristic A, Simon C, Spodick DH,  
5913 Tarzia V, Trimboli S, Valenti A, Belli R, Gaita F, COPPS-2 Investigators. Colchicine for prevention of  
5914 postpericardiotomy syndrome and postoperative atrial fibrillation: the COPPS-2 randomized clinical  
5915 trial. *JAMA* 2014;**312**:1016-1023.
- 5916 947. Cappabianca G, Rotunno C, de Luca Tuppiti Schinosa L, Ranieri VM, Paparella D. Protective  
5917 effects of steroids in cardiac surgery: a meta-analysis of randomized double-blind trials. *J*  
5918 *Cardiothorac Vasc Anesth* 2011;**25**:156-165.
- 5919 948. Viviano A, Kanagasabay R, Zakkar M. Is perioperative corticosteroid administration  
5920 associated with a reduced incidence of postoperative atrial fibrillation in adult cardiac surgery?  
5921 *Interact Cardiovasc Thorac Surg* 2014;**18**:225-229.
- 5922 949. Kaleda VI, McCormack DJ, Shipolini AR. Does posterior pericardiotomy reduce the incidence  
5923 of atrial fibrillation after coronary artery bypass grafting surgery? *Interact Cardiovasc Thorac Surg*  
5924 2012;**14**:384-389.

- 5925 950. Dunning J, Treasure T, Versteegh M, Nashef SA. Guidelines on the prevention and  
5926 management of de novo atrial fibrillation after cardiac and thoracic surgery. *Eur J Cardiothorac Surg*  
5927 2006;**30**:852-872.
- 5928 951. LaPar DJ, Speir AM, Crosby IK, Fonner E, Jr., Brown M, Rich JB, Quader M, Kern JA, Kron  
5929 IL, Ailawadi G, Investigators for the Virginia Cardiac Surgery Quality Initiative. Postoperative atrial  
5930 fibrillation significantly increases mortality, hospital readmission, and hospital costs. *Ann Thorac Surg*  
5931 2014;**98**:527-533; discussion 533.
- 5932 952. Saxena A, Dinh DT, Smith JA, Shardey GC, Reid CM, Newcomb AE. Usefulness of  
5933 postoperative atrial fibrillation as an independent predictor for worse early and late outcomes after  
5934 isolated coronary artery bypass grafting (multicenter Australian study of 19,497 patients). *Am J*  
5935 *Cardiol* 2012;**109**:219-225.
- 5936 953. Gialdini G, Nearing K, Bhavne PD, Bonuccelli U, Iadecola C, Healey JS, Kamel H.  
5937 Perioperative atrial fibrillation and the long-term risk of ischemic stroke. *JAMA* 2014;**312**:616-622.
- 5938 954. Ahlsson A, Bodin L, Fengsrud E, Englund A. Patients with postoperative atrial fibrillation have  
5939 a doubled cardiovascular mortality. *Scand Cardiovasc J* 2009;**43**:330-336.
- 5940 955. Ahlsson A, Fengsrud E, Bodin L, Englund A. Postoperative atrial fibrillation in patients  
5941 undergoing aortocoronary bypass surgery carries an eightfold risk of future atrial fibrillation and a  
5942 doubled cardiovascular mortality. *Eur J Cardiothorac Surg* 2010;**37**:1353-1359.
- 5943 956. Mariscalco G, Klersy C, Zanobini M, Banach M, Ferrarese S, Borsani P, Cantore C, Biglioli P,  
5944 Sala A. Atrial fibrillation after isolated coronary surgery affects late survival. *Circulation*  
5945 2008;**118**:1612-1618.
- 5946 957. Villareal RP, Hariharan R, Liu BC, Kar B, Lee VV, Elayda M, Lopez JA, Rasekh A, Wilson JM,  
5947 Massumi A. Postoperative atrial fibrillation and mortality after coronary artery bypass surgery. *J Am*  
5948 *Coll Cardiol* 2004;**43**:742-748.
- 5949 958. Phan K, Ha HS, Phan S, Medi C, Thomas SP, Yan TD. New-onset atrial fibrillation following  
5950 coronary bypass surgery predicts long-term mortality: a systematic review and meta-analysis. *Eur J*  
5951 *Cardiothorac Surg* 2015;**48**:817-824.
- 5952 959. El-Chami MF, Kilgo P, Thourani V, Lattouf OM, Delurgio DB, Guyton RA, Leon AR, Puskas  
5953 JD. New-onset atrial fibrillation predicts long-term mortality after coronary artery bypass graft. *J Am*  
5954 *Coll Cardiol* 2010;**55**:1370-1376.
- 5955 960. Anderson E, Dyke C, Levy JH. Anticoagulation strategies for the management of  
5956 postoperative atrial fibrillation. *Clin Lab Med* 2014;**34**:537-561.
- 5957 961. Haldal M, Atar D. Pharmacological conversion of recent-onset atrial fibrillation: a systematic  
5958 review. *Scand Cardiovasc J Suppl* 2013;**47**:2-10.
- 5959 962. Gillinov AM, Bagiella E, Moskowitz AJ, Raiten JM, Groh MA, Bowdish ME, Ailawadi G,  
5960 Kirkwood KA, Perrault LP, Parides MK, Smith II RL, Kern JA, Dussault G, Hackmann AE, Jeffries NO,  
5961 Miller MA, Taddei-Peters WC, Rose EA, Weisel RD, Williams DL, Mangusan RF, Argenziano M,  
5962 Moquete EG, O'Sullivan KL, Pellerin M, Shah KJ, Gammie JS, Mayer ML, Voisine P, Gelijns AC,  
5963 O'Gara PT, Mack MJ, CTSN. Rate Control versus Rhythm Control for Atrial Fibrillation after Cardiac  
5964 Surgery. *N Engl J Med* 2016:[Epub ahead of print].
- 5965 963. Triedman JK. Arrhythmias in adults with congenital heart disease. *Heart* 2002;**87**:383-389.
- 5966 964. Ammash NM, Phillips SD, Hodge DO, Connolly HM, Grogan MA, Friedman PA, Warnes CA,  
5967 Asirvatham SJ. Outcome of direct current cardioversion for atrial arrhythmias in adults with congenital  
5968 heart disease. *Int J Cardiol* 2012;**154**:270-274.
- 5969 965. Greason KL, Dearani JA, Theodoro DA, Porter CB, Warnes CA, Danielson GK. Surgical  
5970 management of atrial tachyarrhythmias associated with congenital cardiac anomalies: Mayo Clinic  
5971 experience. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu* 2003;**6**:59-71.
- 5972 966. Payne L, Zeigler VL, Gillette PC. Acute cardiac arrhythmias following surgery for congenital  
5973 heart disease: mechanisms, diagnostic tools, and management. *Crit Care Nurs Clin North Am*  
5974 2011;**23**:255-272.
- 5975 967. Koyak Z, Harris L, de Groot JR, Silversides CK, Oechslin EN, Bouma BJ, Budts W,  
5976 Zwinderman AH, Van Gelder IC, Mulder BJ. Sudden cardiac death in adult congenital heart disease.  
5977 *Circulation* 2012;**126**:1944-1954.
- 5978 968. Jensen AS, Idorn L, Norager B, Vejlstrup N, Sondergaard L. Anticoagulation in adults with  
5979 congenital heart disease: The who, the when and the how? *Heart* 2014.
- 5980 969. Fujita S, Takahashi K, Takeuchi D, Manaka T, Shoda M, Hagiwara N, Kurosawa H, Nakanishi  
5981 T. Management of late atrial tachyarrhythmia long after Fontan operation. *J Cardiol* 2009;**53**:410-416.
- 5982 970. Feltes TF, Friedman RA. Transesophageal echocardiographic detection of atrial thrombi in  
5983 patients with nonfibrillation atrial tachyarrhythmias and congenital heart disease. *J Am Coll Cardiol*  
5984 1994;**24**:1365-1370.

- 5985 971. Nagao K, Tsuchihashi K, Tanaka S, Imura O. [Studies on atrial arrhythmias in atrial septal  
5986 defect. The influences of aging on atrial fibrillation]. *Nihon Ronen Igakkai Zasshi* 1995;**32**:27-32.
- 5987 972. Giamberti A, Chessa M, Abella R, Butera G, Negura D, Foresti S, Carminati M, Cappato R,  
5988 Frigiola A. Surgical treatment of arrhythmias in adults with congenital heart defects. *Int J Cardiol*  
5989 2008;**129**:37-41.
- 5990 973. Roos-Hesselink JW, Meijboom FJ, Spitaels SE, van Domburg R, van Rijen EH, Utens EM,  
5991 Bogers AJ, Simoons ML. Excellent survival and low incidence of arrhythmias, stroke and heart failure  
5992 long-term after surgical ASD closure at young age. A prospective follow-up study of 21-33 years. *Eur*  
5993 *Heart J* 2003;**24**:190-197.
- 5994 974. Yamada T, McElderry HT, Muto M, Murakami Y, Kay GN. Pulmonary vein isolation in patients  
5995 with paroxysmal atrial fibrillation after direct suture closure of congenital atrial septal defect. *Circ J*  
5996 2007;**71**:1989-1992.
- 5997 975. Van De Bruaene A, Delcroix M, Pasquet A, De Backer J, Paelinck B, Morissens M, Budts W.  
5998 The importance of pulmonary artery pressures on late atrial arrhythmia in transcatheter and surgically  
5999 closed ASD type secundum. *Int J Cardiol* 2011;**152**:192-195.
- 6000 976. de Salle P, Goenen M, Lecron J, Jaumin P, Tremouroux J. [Rhythm disorders occurring after  
6001 surgical closure of the interatrial communication]. *Acta Cardiol* 1975;**30**:239-249.
- 6002 977. Scaglione M, Caponi D, Ebrille E, Di Donna P, Di Clemente F, Battaglia A, Raimondo C,  
6003 Appendino M, Gaita F. Very long-term results of electroanatomic-guided radiofrequency ablation of  
6004 atrial arrhythmias in patients with surgically corrected atrial septal defect. *Europace* 2014;**16**:1800-  
6005 1807.
- 6006 978. Kanter RJ, Garson A, Jr. Atrial arrhythmias during chronic follow-up of surgery for complex  
6007 congenital heart disease. *Pacing Clin Electrophysiol* 1997;**20**:502-511.
- 6008 979. Porter CJ, Garson A. Incidence and management of dysrhythmias after Fontan procedure.  
6009 *Herz* 1993;**18**:318-327.
- 6010 980. Gelatt M, Hamilton RM, McCrindle BW, Gow RM, Williams WG, Trusler GA, Freedom RM.  
6011 Risk factors for atrial tachyarrhythmias after the Fontan operation. *J Am Coll Cardiol* 1994;**24**:1735-  
6012 1741.
- 6013 981. Peters NS, Somerville J. Arrhythmias after the Fontan procedure. *Br Heart J* 1992;**68**:199-  
6014 204.
- 6015 982. Kwak JG, Kim WH, Lee JR, Kim YJ. Surgical therapy of arrhythmias in single-ventricle  
6016 patients undergoing Fontan or Fontan conversion. *J Card Surg* 2009;**24**:738-741.
- 6017 983. Backer CL, Tsao S, Deal BJ, Mavroudis C. Maze procedure in single ventricle patients. *Semin*  
6018 *Thorac Cardiovasc Surg Pediatr Card Surg Annu* 2008:44-48.
- 6019 984. Deal BJ, Mavroudis C, Backer CL. The role of concomitant arrhythmia surgery in patients  
6020 undergoing repair of congenital heart disease. *Pacing Clin Electrophysiol* 2008;**31 Suppl 1**:S13-16.
- 6021 985. Gandhi SK. Atrial arrhythmia surgery in congenital heart disease. *J Interv Card Electrophysiol*  
6022 2007;**20**:119-125.
- 6023 986. Correa R, Sherwin ED, Kovach J, Mah DY, Alexander ME, Cecchin F, Walsh EP, Triedman  
6024 JK, Abrams DJ. Mechanism and ablation of arrhythmia following total cavopulmonary connection. *Circ*  
6025 *Arrhythm Electrophysiol* 2015;**8**:318-325.
- 6026 987. Khairy P, Aboulhosn J, Gurvitz MZ, Opatowsky AR, Mongeon FP, Kay J, Valente AM, Earing  
6027 MG, Lui G, Gersony DR, Cook S, Ting JG, Nickolaus MJ, Webb G, Landzberg MJ, Broberg CS,  
6028 Alliance for Adult Research in Congenital Cardiology. Arrhythmia burden in adults with surgically  
6029 repaired tetralogy of Fallot: a multi-institutional study. *Circulation* 2010;**122**:868-875.
- 6030 988. Kobayashi J, Yamamoto F, Nakano K, Sasako Y, Kitamura S, Kosakai Y. Maze procedure for  
6031 atrial fibrillation associated with atrial septal defect. *Circulation* 1998;**98**:II399-402.
- 6032 989. Shim H, Yang JH, Park PW, Jeong DS, Jun TG. Efficacy of the maze procedure for atrial  
6033 fibrillation associated with atrial septal defect. *Korean J Thorac Cardiovasc Surg* 2013;**46**:98-103.
- 6034 990. Gutierrez SD, Earing MG, Singh AK, Tweddell JS, Bartz PJ. Atrial tachyarrhythmias and the  
6035 Cox-maze procedure in congenital heart disease. *Congenit Heart Dis* 2013;**8**:434-439.
- 6036 991. Sherwin ED, Triedman JK, Walsh EP. Update on interventional electrophysiology in  
6037 congenital heart disease: evolving solutions for complex hearts. *Circ Arrhythm Electrophysiol*  
6038 2013;**6**:1032-1040.
- 6039 992. Wellens HJ. Contemporary management of atrial flutter. *Circulation* 2002;**106**:649-652.
- 6040 993. Bertaglia E, Zoppo F, Bonso A, Proclemer A, Verlato R, Coro L, Mantovan R, D'Este D, Zerbo  
6041 F, Pascotto P. Long term follow up of radiofrequency catheter ablation of atrial flutter: clinical course  
6042 and predictors of atrial fibrillation occurrence. *Heart* 2004;**90**:59-63.

- 6043 994. Seara JG, Roubin SR, Gude Sampedro F, Barreiro VB, Sande JM, Manero MR, Grandio PC,  
6044 Alvarez B, Juanatey JG. Risk of atrial fibrillation, stroke, and death after radiofrequency catheter  
6045 ablation of typical atrial flutter. *Clin Res Cardiol* 2014;**103**:543-552.
- 6046 995. Brembilla-Perrot B, Girerd N, Sellal JM, Olivier A, Manenti V, Villemin T, Beurrier D, de  
6047 Chillou C, Louis P, Selton O, de la Chaise AT. Risk of atrial fibrillation after atrial flutter ablation:  
6048 impact of AF history, gender, and antiarrhythmic drug medication. *J Cardiovasc Electrophysiol*  
6049 2014;**25**:813-820.
- 6050 996. Bronis K, Metaxa S, Koulouris S, Manolis AS. Vernakalant: review of a novel atrial selective  
6051 antiarrhythmic agent and its place in current treatment of atrial fibrillation. *Hosp Chronicles*  
6052 2012;**7**:171-181.
- 6053 997. Nair M, George LK, Koshy SK. Safety and efficacy of ibutilide in cardioversion of atrial flutter  
6054 and fibrillation. *J Am Board Fam Med* 2011;**24**:86-92.
- 6055 998. Reisinger J, Gstrein C, Winter T, Zeindlhofer E, Hollinger K, Mori M, Schiller A, Winter A,  
6056 Geiger H, Siostrzonek P. Optimization of initial energy for cardioversion of atrial tachyarrhythmias with  
6057 biphasic shocks. *Am J Emerg Med* 2010;**28**:159-165.
- 6058 999. Pinski SL, Sgarbossa EB, Ching E, Trohman RG. A comparison of 50-J versus 100-J shocks  
6059 for direct-current cardioversion of atrial flutter. *Am Heart J* 1999;**137**:439-442.
- 6060 1000. Manolis AS, Dragazis I, Kapelakis I, Papadimitriou P, Sakellaris N. Transesophageal  
6061 overdrive pacing: A simple and versatile tool. *Hosp Chronicles* 2013;**8**:143-145.
- 6062 1001. Poulidakis E, Manolis AS. Transvenous temporary cardiac pacing. *Rhythmos* 2014;**9**:20-27.
- 6063 1002. Spector P, Reynolds MR, Calkins H, Sondhi M, Xu Y, Martin A, Williams CJ, Sledge I. Meta-  
6064 analysis of ablation of atrial flutter and supraventricular tachycardia. *Am J Cardiol* 2009;**104**:671-677.
- 6065 1003. Schmieder S, Ndrepepa G, Dong J, Zrenner B, Schreieck J, Schneider MA, Karch MR,  
6066 Schmitt C. Acute and long-term results of radiofrequency ablation of common atrial flutter and the  
6067 influence of the right atrial isthmus ablation on the occurrence of atrial fibrillation. *Eur Heart J*  
6068 2003;**24**:956-962.
- 6069 1004. Bandini A, Golia P, Caroli E, Biancoli S, Galvani M. Atrial fibrillation after typical atrial flutter  
6070 ablation: a long-term follow-up. *J Cardiovasc Med (Hagerstown)* 2011;**12**:110-115.
- 6071 1005. Dewland TA, Glidden DV, Marcus GM. Healthcare utilization and clinical outcomes after  
6072 catheter ablation of atrial flutter. *PLoS One* 2014;**9**:e100509.
- 6073 1006. Esato M, Hindricks G, Sommer P, Arya A, Gaspar T, Bode K, Bollmann A, Wetzel U, Hilbert  
6074 S, Kircher S, Eitel C, Piorkowski C. Color-coded three-dimensional entrainment mapping for analysis  
6075 and treatment of atrial macroreentrant tachycardia. *Heart Rhythm* 2009;**6**:349-358.
- 6076 1007. Huo Y, Schoenbauer R, Richter S, Rolf S, Sommer P, Arya A, Rastan A, Doll N, Mohr FW,  
6077 Hindricks G, Piorkowski C, Gaspar T. Atrial Arrhythmias Following Surgical AF Ablation:  
6078 Electrophysiological Findings, Ablation Strategies, and Clinical Outcome. *J Cardiovasc Electrophysiol*  
6079 2014;**25**:725-738.
- 6080 1008. Institute of Medicine Committee on Quality of Health Care in America. *Crossing the Quality*  
6081 *Chasm: A New Health System for the 21st Century*. Washington (DC): National Academies Press  
6082 (US); 2001.
- 6083 1009. Bodenheimer T, Wagner EH, Grumbach K. Improving primary care for patients with chronic  
6084 illness. *JAMA* 2002;**288**:1775-1779.
- 6085 1010. Hibbard JH, Greene J. What the evidence shows about patient activation: better health  
6086 outcomes and care experiences; fewer data on costs. *Health Aff (Millwood)* 2013;**32**:207-214.
- 6087 1011. McCabe PJ. Self-management of atrial fibrillation: a new frontier for nursing research. *Prog*  
6088 *Cardiovasc Nurs* 2008;**23**:37-40.
- 6089 1012. Lip GY, Kamath S, Jafri M, Mohammed A, Bareford D. Ethnic differences in patient  
6090 perceptions of atrial fibrillation and anticoagulation therapy: the West Birmingham Atrial Fibrillation  
6091 Project. *Stroke* 2002;**33**:238-242.
- 6092 1013. Clarkesmith DE, Pattison HM, Lane DA. Educational and behavioural interventions for  
6093 anticoagulant therapy in patients with atrial fibrillation. *Cochrane Database Syst Rev*  
6094 2013;**6**:Cd008600.
- 6095 1014. Clarkesmith DE, Pattison HM, Lip GY, Lane DA. Educational intervention improves  
6096 anticoagulation control in atrial fibrillation patients: the TREAT randomised trial. *PLoS One*  
6097 2013;**8**:e74037.
- 6098 1015. Smith DE, Xuereb CB, Pattison HM, Lip GY, Lane DA. TRial of an Educational intervention on  
6099 patients' knowledge of Atrial fibrillation and anticoagulant therapy, INR control, and outcome of  
6100 Treatment with warfarin (TREAT). *BMC Cardiovasc Disord* 2010;**10**:21.
- 6101 1016. Smith MB, Christensen N, Wang S, Strohecker J, Day JD, Weiss JP, Crandall BG, Osborn  
6102 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)