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ESC GUIDELINES

2012 focused update of the ESC Guidelines for the management of atrial fibrillation

An update of the 2010 ESC Guidelines for the management of atrial fibrillation
Developed with the special contribution of the European Heart Rhythm Association

Authors/Task Force Members: A. John Camm (Chairperson) (UK)*, Gregory Y.H. Lip (UK), Raffaele De Caterina (Italy), Irene Savelieva (UK), Dan Atar (Norway), Stefan H. Hohnloser (Germany), Gerhard Hindricks (Germany), Paulus Kirchhof (UK)

ESC Committee for Practice Guidelines (CPG): Jeroen J. Bax (CPG Chairperson) (The Netherlands), Helmut Baumgartner (Germany), Claudio Ceconi (Italy), Veronica Dean (France), Christi Deaton (UK), Robert Fagard (Belgium), Christian Funck-Brentano (France), David Hasdai (Israel), Arno Hoes (The Netherlands), Paulus Kirchhof (Germany/UK), Juhani Knuuti (Finland), Philippe Kolh (Belgium), Theresa McDonagh (UK), Cyril Moulin (France), Bogdan A. Popescu (Romania), Željko Reiner (Croatia), Udo Sechtem (Germany), Per Anton Sirnes (Norway), Michal Tendera (Poland), Adam Torbicki (Poland), Alec Vahanian (France), Stephan Windecker (Switzerland)

Document Reviewers: Panos Vardas (Review Coordinator) (Greece), Nawwar Al-Attar (France), Ottavio Alfieri† (Italy), Annalisa Angelini (Italy), Carina Blömstrom-Lundqvist (Sweden), Paolo Colonna (Italy), Johan De Sutter (Belgium), Sabine Ernst (UK), Andreas Goette (Germany), Bulent Gorenek (Turkey), Robert Hatala (Slovak Republic), Hein Heidbüchel (Belgium), Magnus Heldal (Norway), Steen Dalby Kristensen (Denmark), Philippe Kolh† (Belgium), Jean-Yves Le Heuzey (France), Hercules Mavrakis (Greece), Lluís Mont (Spain), Pasquale Perrone Filardi (Italy), Piotr Ponikowski (Poland), Bernard Prendergast (UK), Frans H. Rutten (The Netherlands), Ulrich Schotten (The Netherlands), Isabelle C. Van Gelder (The Netherlands), Freek W.A. Verheugt (The Netherlands)

The disclosure forms of the authors and reviewers are available on the ESC website www.escardio.org/guidelines

* Corresponding authors: A. John Camm, Division of Clinical Sciences, St.George's University of London, Cranmer Terrace, London SW17 0RE, United Kingdom. Tel.: +44 20 8725 3414. Fax: +44 20 8725 3416, Email: jcamm@sgul.ac.uk

† Representing the European Association for Cardio-Thoracic Surgery (EACTS).

Other ESC entities having participated in the development of this document:.

Associations: European Association of Echocardiography (EAE), European Association for Cardiovascular Prevention and Rehabilitation (EAPCR), Heart Failure Association (HFA).

Councils: Council for Cardiology Practice, Council on Primary Cardiovascular Care.

Working Groups: Acute Cardiac Care, Cardiovascular Surgery, Development, Anatomy and Pathology, Nuclear Cardiology and Cardiac Computed Tomography, Pharmacology and Drug Therapy, Thrombosis, Valvular Heart Disease.

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Abbreviations and acronyms

ACCF	American College of Cardiology Foundation
ACCP	American College of Chest Physicians
ACS	acute coronary syndrome
ACT	Atrial arrhythmia Conversion Trial
ADONIS	American–Australian–African trial with DronedarONe In atrial fibrillation or flutter for the maintenance of Sinus rhythm
AF	atrial fibrillation
AHA	American Heart Association
ANDROMEDA	ANtiarrhythmic trial with DROnedarone in Moderate-to-severe congestive heart failure Evaluating morbidity DecreAse
APHRS	Asia Pacific Heart Rhythm Society
aPTT	activated partial thromboplastin time
ARB	angiotensin-receptor blocker
ARISTOTLE	Apixaban for Reduction In STroke and Other ThromboembоLic Events in atrial fibrillation
ATHENA	A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg b.i.d. for the prevention of cardiovascular Hospitalization or death from any cause in patiENts with Atrial fibrillation/atrial flutter
ATRIA	AnTicoagulation and Risk factors In Atrial fibrillation
AVERROES	Apixaban VErsus acetylsalicylic acid (ASA) to Reduce the Rate Of Embolic Stroke in atrial fibrillation patients who have failed or are unsuitable for vitamin K antagonist treatment
AVRO	A prospective, randomized, double-blind, Active-controlled, superiority study of Vernakalant vs. amiodarone in Recent Onset atrial fibrillation
b.i.d	*bis in die* (twice daily)
b.p.m.	beats per minute
CABANA	Catheter ABlation vs. ANtiarrhythmic drug therapy for Atrial fibrillation
CABG	coronary artery bypass graft
CAP	Continued Access to Protect AF
CHA_2DS_2-VASc	Congestive heart failure or left ventricular dysfunction Hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled)-Vascular disease, Age 65–74, Sex category (female)
$CHADS_2$	Congestive heart failure, Hypertension, Age ≥75, Diabetes, Stroke (doubled)
CI	confidence interval
CRAFT	Controlled Randomized Atrial Fibrillation Trial
CrCl	creatinine clearance
DAFNE	Dronedarone Atrial FibrillatioN study after Electrical cardioversion
DIONYSOS	Randomized Double blind trIal to evaluate efficacy and safety of drOnedarone (400 mg b.i.d.) vs. amiodaroNe (600 mg q.d. for 28 daYS, then 200 mg qd thereafter) for at least 6 mOnths for the maintenance of Sinus rhythm in patients with atrial fibrillation
EAST	Early treatment of Atrial fibrillation for Stroke prevention Trial
EHRA	European Heart Rhythm Association
ECG	electrocardiogram
EMA	European Medicines Agency
ERATO	Efficacy and safety of dRonedArone for The cOntrol of ventricular rate during atrial fibrillation

EURIDIS	EUROpean trial In atrial fibrillation or flutter patients receiving Dronedarone for the maIntenance of Sinus rhythm
FAST	atrial Fibrillation catheter Ablation vs. Surgical ablation Treatment
FDA	Food and Drug Administration
Flec-SL	Flecainide Short-Long trial
HAS-BLED	Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol concomitantly
HF-PEF	heart failure with preserved ejection fraction
HF-REF	heart failure with reduced ejection fraction
HR	hazard ratio
HRS	Heart Rhythm Society
ICH	intracranial haemorrhage
INR	international normalized ratio
i.v.	intravenous
J-RHYTHM	Japanese RHYTHM management trial for atrial fibrillation
LAA	left atrial appendage
LoE	level of evidence
LVEF	left ventricular ejection fraction
MANTRA-PAF	Medical ANtiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation
NICE	National Institute for Health and Clinical Excellence
NOAC	novel oral anticoagulant
NSAID	non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
OAC	oral anticoagulant or oral anticoagulation
o.d.	*omni die* (every day)
PALLAS	Permanent Atrial fibriLLAtion outcome Study using dronedarone on top of standard therapy
PCI	percutaneous coronary intervention
PREVAIL	Prospective Randomized EVAluation of the LAA closure device In patients with atrial fibrillation vs. Long-term warfarin therapy
PROTECT AF	WATCHMAN LAA system for embolic PROTECTion in patients with Atrial Fibrillation
PT	prothrombin time
RAAFT	Radio frequency Ablation Atrial Fibrillation Trial
RE-LY	Randomized Evaluation of Long-term anticoagulant therapY with dabigatran etexilate
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
RRR	relative risk reduction
TE	thromboembolism
TIA	transient ischaemic attack
t.i.d.	*ter in die* (three times daily)
TOE	transoesophageal echocardiogram
TTR	time in therapeutic range
VKA	vitamin K antagonist

1. Preamble

Guidelines summarize and evaluate all currently available evidence on a particular issue with the aim of assisting physicians in selecting the best management strategy for an individual patient suffering from a given condition, taking into account the impact on outcome, as well as the risk–benefit ratio of particular diagnostic or therapeutic means. Guidelines are no substitutes for textbooks. The legal implications of medical guidelines have been discussed previously.

A large number of guidelines have been issued in recent years by the European Society of Cardiology (ESC) as well as by other societies and organizations. Because of the impact on clinical practice, quality criteria for 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 web site (http://www.escardio.org/guidelines-surveys/esc-guidelines/about/Pages/rules-writing.aspx).

In brief, experts in the field are selected and undertake a comprehensive review of the published evidence for management and/or prevention of a given condition. A critical evaluation of diagnostic and therapeutic procedures is performed, including assessment of the risk–benefit ratio. Estimates of expected health outcomes for larger societies are included, where data exist. The level of evidence and the strength of recommendation of particular treatment options are weighed and graded according to pre-defined scales, as outlined in *Tables 1* and *2*.

The experts of the writing panels have provided disclosure statements of all relationships they may have that might be perceived as real or potential sources of conflicts of interest. These disclosure forms are kept on file at the European Heart House, headquarters of the ESC. Any changes in conflict of interest that arise during the writing period must be notified to the ESC. The Task Force report received its entire financial support from the ESC and was developed without any involvement of the pharmaceutical, device, or surgical industries.

The ESC Committee for Practice Guidelines (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 or statements. Once the document has been finalized and approved by all the experts involved in the Task Force, it is submitted to outside specialists for review. The document is revised, finally approved by the CPG, and subsequently published.

After publication, dissemination of the message is of paramount importance. Pocket-sized versions and personal digital assistant (PDA) downloadable versions are useful at the point of care. Some surveys have shown that the intended users are sometimes unaware of the existence of guidelines, or simply do not translate them into practice. Thus, implementation programmes for new guidelines form an important component of knowledge dissemination. Meetings are organized by the ESC and directed towards its member National Societies and key opinion leaders in Europe. Implementation meetings can also be undertaken at national levels, once the guidelines have been endorsed by the ESC member societies and translated into the national language. Implementation programmes are needed because it has been shown that

Table 1 Classes of recommendations

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

Table 2 Levels of evidence

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

the outcome of disease may be favourably influenced by the thorough application of clinical recommendations.

Thus, the task of writing guidelines covers not only the integration of the most recent research, but also the creation of educational tools and implementation programmes for the recommendations. The loop between clinical research, writing of guidelines, and implementing them into clinical practice can then only be completed if surveys and registries are performed to verify that real-life daily practice is in keeping with what is recommended in the guidelines. Such surveys and registries also make it possible to evaluate the impact of implementation of the guidelines on patient outcomes. Guidelines and recommendations should help the physicians to make decisions in their daily practice; however, the ultimate judgment regarding the care of an individual patient must be made by the physician in charge of their care.

2. Introduction

The current estimate of the prevalence of atrial fibrillation (AF) in the developed world is approximately 1.5–2% of the general population, with the average age of patients with this condition steadily rising, such that it now averages between 75 and 85 years. The arrhythmia is associated with a five-fold risk of stroke and a three-fold incidence of congestive heart failure, and higher mortality. Hospitalization of patients with AF is also very common. This arrhythmia is a major cardiovascular challenge in modern society and its medical, social and economic aspects are all set to worsen over the coming decades. Fortunately a number of valuable treatments have been devised in recent years that may offer some solution to this problem.

In 2010, when the ESC Guidelines for the Management of Atrial Fibrillation were first issued,[1] it was already realized that an update would be necessary in 2012 because, for example, European regulatory approvals of several new drugs were anticipated, such as vernakalant and dabigatran. In addition, reports from major clinical trials of the novel oral anticoagulants, such as AVERROES (Apixaban VErsus acetylsalicylic acid (ASA) to Reduce the Rate Of Embolic Stroke in atrial fibrillation patients who have failed or are unsuitable for vitamin K antagonist treatment),[2] 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),[3] and ARISTOTLE (Apixaban for Reduction In STroke and Other ThromboembolLic Events in atrial fibrillation),[4] were expected, paving the way for potentially yet more regulatory approvals. What was not necessarily expected was the early discontinuation of the PALLAS (Permanent Atrial fibriLLAtion outcome Study) of dronedarone,[5] nor the reports of hepatotoxicity associated with this drug.

The American College of Cardiology Foundation (ACCF), American Heart Association (AHA), and the Heart Rhythm Society (HRS) have jointly published two major updates, one concerning dronedarone and left atrial ablation,[6] and another focusing on dabigatran.[7] Early in 2012, the American College of Chest Physicians (ACCP) published its 9th version of Antithrombotic Therapy for Atrial Fibrillation,[8] and the Canadian Cardiovascular

Society guideline writers have issued a focused update of their AF Guidelines.[9] Also, the United Kingdom's National Institute for Health and Clinical Excellence (NICE) and the ACCF, AHA, and HRS intend to completely rewrite their AF Guidelines in the near future.

Clinical outcomes research in AF continues at a fast pace. Also, considerably more clinical experience has been gathered in the fields of anticoagulation, atrial appendage occlusion, antiarrhythmic drug use for cardioversion and rhythm control, and left atrial ablation.[10] These five areas form the bulk of the revisions to our recommendations.

Screening for atrial fibrillation

Diagnosing AF before the first complications occur is a recognized priority for the prevention of strokes.[11] Recent data collected in patients with implanted devices,[12] and by Holter electrocardiograms (ECGs) in epidemiological studies,[13] reinforce the assumption that even short episodes of 'silent' AF convey an increased risk for stroke. We therefore recommend that, in patients aged 65 years or over, opportunistic screening for AF by pulse palpation, followed by recording of an ECG to verify diagnosis, should be considered for the early detection of AF.[14,15]

Recommendation for screening of AF

Recommendations	Class[a]	Level[b]	Ref[c]
Opportunistic screening for AF in patients ≥65 years of age using pulse-taking followed by an ECG is recommended to allow timely detection of AF.	I	B	14, 15

AF = atrial fibrillation; ECG = electrocardiogram.
[a]Class of recommendation.
[b]Level of evidence.
[c]References.

Key point

- In patients 65 years or older, opportunistic screening by pulse palpation, followed by an ECG in those with an irregular pulse, is important to detect AF prior to the first stroke.

3. Stroke and bleeding risk assessment

It is conventional to divide AF into cases which are described as "valvular or "non-valvular". No satisfactory or uniform definition of these terms exists. In this guideline, the term valvular AF is used to imply that AF is related to rheumatic valvular disease (predominantly mitral stenosis) or prosthetic heart valves.

Since the publication of the 2010 ESC Guidelines, additional evidence has strengthened the use of the risk factor-based approach to stroke risk stratification proposed in that guideline, with more focus on the identification of 'truly low-risk' patients who do not need any antithrombotic therapy, and more evidence on the use of novel oral anticoagulant drugs (NOACs; see below) as alternatives to dose-adjusted vitamin K antagonist (VKA) therapy [e.g. warfarin, international normalized ratio (INR) 2.0–3.0].[16]

Stroke risk is a continuum and the predictive value of artificially categorizing AF patients into low, moderate, and high-risk strata only has modest predictive value for identifying the 'high-risk' category of patients who would subsequently suffer strokes.[17] Until recently, the only oral anticoagulant (OAC) available was the VKA class of drugs (e.g. warfarin) and, despite its limitations, many physicians still prescribed VKA therapy in broadly similar proportions, irrespective of the categorization into low/moderate/high-risk strata; if a VKA was not used, aspirin was often prescribed instead.[18,19]

The evidence for effective stroke prevention with aspirin in AF is weak, with a potential for harm,[20–22] as data indicate that the risk of major bleeding or intracranial haemorrhage (ICH) with aspirin is not significantly different to that of OAC, especially in the elderly.[2,23–25] Given the availability of NOACs, the use of antiplatelet therapy (such as aspirin–clopidogrel combination therapy, or—less effectively—aspirin monotherapy) for stroke prevention in AF should be limited to the few patients who refuse any form of OAC. Aspirin–clopidogrel combination therapy has additional efficacy, compared with aspirin monotherapy, but at additional risk for major bleeding.[26] Thus, aspirin monotherapy should be confined to those who refuse any OAC and cannot tolerate aspirin–clopidogrel combination therapy due, for example, to excessive bleeding risk. There is no evidence for the decrease in total or cardiovascular mortality with aspirin (or antiplatelet drugs) in the AF population. Even in non-AF populations, aspirin prophylaxis in people without prior cardiovascular disease does not lead to reductions in either cardiovascular or cancer mortality and the benefits in non-fatal myocardial infarctiion are further offset by clinically important bleeding events.[27]

Thus, this guideline strongly recommends a practice shift towards greater focus on identification of 'truly low-risk' patients with AF (i.e. 'age <65 and lone AF', who do not need any antithrombotic therapy), instead of trying to focus on identifying 'high-risk' patients.

To achieve this, it is necessary to be more inclusive (rather than exclusive) of common stroke risk factors as part of any comprehensive stroke risk assessment. Indeed, patients with AF who have stroke risk factor(s) ≥1 are recommended to receive effective stroke prevention therapy, which is essentially OAC with either well-controlled VKA therapy [INR 2–3, with a high percentage of time in the therapeutic range (TTR), for example, at least 70%][28] or one of the NOACs.

Whilst the $CHADS_2$ [Congestive heart failure, Hypertension, Age ≥75, Diabetes, Stroke (doubled)] score is simple,[29] most now agree that it does not include many common stroke risk factors and its limitations have been highlighted.[30,31] The $CHADS_2$ score was also derived from risk factors identified in datasets of the non-VKA–treated patients in the historical trials of stroke prevention in AF conducted two decades ago. In these trials, fewer than 10% of the patients screened were included, and many stroke risk factors were inconsistently defined or were not systematically recorded.[17] For example, vascular disease (not included in the $CHADS_2$ score) is an independent risk factor for stroke in AF and significantly improves the predictive ability of $CHADS_2$.[32–34] The risk of stroke also increases from age ≥65 years, with even greater risk at age 75 years or older.[32,35,36]

Table 3 Risk factors for ischaemic stroke/TIA/systemic embolism in patients with AF: the Swedish Cohort Atrial Fibrillation study (adapted from Friberg *et al.*[25])

	Multivariate hazard ratios (95% CI)
Age (years) <65 65–74 ≥75	 1.0 (Reference) 2.97 (2.54–3.48) 5.28 (4.57–6.09)
Female sex	1.17 (1.11–1.22)
Previous ischaemic stroke	2.81 (2.68–2.95)
Intracranial bleeding	1.49 (1.33–1.67)
Vascular disease (any) • Myocardial infarction • Previous CABG • Peripheral artery disease	1.14 (1.06–1.23) 1.09 (1.03–1.15) 1.19 (1.06–1.33) 1.22 (1.12–1.32)
Hypertension	1.17 (1.11–1.22)
Heart failure (history)	0.98 (0.93–1.03)
Diabetes mellitus	1.19 (1.13–1.26)
Thyroid disease Thyrotoxicosis	1.00 (0.92–1.09) 1.03 (0.83–1.28)

AF = atrial fibrillation; CABG = coronary artery bypass graft; CI = confidence interval; TIA = transient ischaemic attack.
Whilst TIAs *per se* are less robust as an endpoint, a confirmed diagnosis would confer a risk similar to a stroke or systemic embolism. Multivariate analysis, based on 90 490 patients without anticoagulant treatment during follow-up.

Many patients classified as 'low-risk' using $CHADS_2$ (score = 0) have stroke rates >1.5%/year,[29,36] and a $CHADS_2$ score of 0 does not reliably identify AF patients who are 'truly low-risk'.[37,38]

The 2010 ESC Guidelines on AF[1] de-emphasized the use of the artificial low-, moderate-, and high-risk strata and recommended a risk factor-based approach defining 'major' and 'clinically relevant non-major' risk factors, which can be expressed as an acronym, CHA_2DS_2-VASc (Congestive heart failure/left ventricular dysfunction, Hypertension, Age ≥75 [doubled], Diabetes, Stroke [doubled] – Vascular disease, Age 65–74, and Sex category [female]).[39]

Given that guidelines should be applicable to most AF patients for most of the time and for most situations in everyday clinical practice, the ESC Guideline stroke risk assessment approach covers most of the AF patients seen and considers the common stroke risk factors in such patients. Antithrombotic therapy is not recommended in patients with AF (irrespective of gender) who are 'aged <65 and lone AF (i.e. truly 'low-risk'), as the latter have very low absolute event rates.

The CHA_2DS_2-VASc score is inclusive of the most common stroke risk factors in everyday clinical practice.[39–41] Contrary to older, conflicting (and weak) data, thyroid disease (or hyperthyroidism) is not considered to be an independent stroke risk factor on multivariable analysis (*Table 3*).[25] A history of 'any heart failure' *per se* is not consistently defined as a risk factor,[25,40] and the 'C' in CHA_2DS_2-VASc refers to documented moderate-to-severe systolic dysfunction [i.e. heart failure with reduced ejection fraction (HF-REF)][42,43] or patients with recent decompensated heart failure requiring hospitalization, irrespective of ejection fraction [i.e. both HF-REF and heart failure with preserved ejection fraction (HF-PEF)].[43] Female gender independently increases the risk of stroke overall (*Table 3*),[40,44,45] unless the criterion of 'age <65 and lone AF' is clearly fulfilled, whereby female gender does not independently increase stroke risk.[33,44] Moreover, stroke rates in these patients ('age <65 and lone AF') are so low in both males and females that antithrombotic therapy is not recommended. Thus, female patients with gender alone as a single risk factor (still a CHA_2DS_2-VASc score of 1) would not need anticoagulation if they clearly fulfil the criteria of 'age < 65 and lone AF', as confirmed in recent studies.[33,44]

The CHA_2DS_2-VASc score has since been validated in multiple cohorts;[17] the accumulated evidence shows that CHA_2DS_2-VASc is better at identifying 'truly low-risk' patients with AF[37,38,46,47] and is as good as, and possibly better than, scores such as $CHADS_2$ in identifying patients who develop stroke and thromboembolism.[25,36,48] Amongst patients with $CHADS_2$ score = 0, the 1-year event rates can range between 0.84% (CHA_2DS_2-VASc score = 0), 1.75% (CHA_2DS_2-VASc score = 1), 2.69% (CHA_2DS_2-VASc score = 2), and 3.2% (CHA_2DS_2-VASc score = 3).[38] Also, CHA_2DS_2-VASc refines stroke risk assessment in 'low-risk' AF patients after ablation.[49]

AF patients with severe renal failure are at high risk for stroke, but are also at increased risk for death, coronary events and serious bleeding. These patients have not been adequately studied and have been excluded from clinical trials, and their risk assessment is complex.[50] There is also the caveat that renal function may not remain static, especially in elderly AF patients with multiple comorbidities and concomitant drug therapies.

Decision-making for thromboprophylaxis needs to balance the risk of stroke against the risk of major bleeding, especially ICH, which is the most feared complication of anticoagulation therapy and confers a high risk of death and disability.[51] Until recently, bleeding risk assessment tools were based on complex formulae, with certain risk factors weighted in different ways and/or derived from cohorts of anticoagulated patients, rather than specifically from AF patients.[52] Of the available bleeding risk scores, only three have been derived and validated in AF populations: $HEMORR_2HAGES$ [Hepatic or renal disease, Ethanol abuse, Malignancy, Older (age ≥75 years), Reduced platelet count or function, Rebleeding risk, Hypertension (uncontrolled), Anaemia, Genetic factors, Excessive fall risk, and Stroke],[53] HAS-BLED [Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (e.g. age >65, frailty, etc.), Drugs/alcohol concomitantly],[54] and ATRIA (AnTicoagulation and Risk factors In Atrial fibrillation).[55]

The 2010 ESC Guidelines on AF,[1] Canadian Cardiovascular Society Guidelines (recently updated).[9,56] and the consensus document on bleeding in AF, prepared by the European Heart Rhythm Association (EHRA) and the ESC Working Group on Thrombosis,[52] all recommended use of the simple bleeding risk assessment score, HAS-BLED, rather than the more complicated

HEMORR$_2$HAGES score, or the less practical ATRIA score. The HAS-BLED score has better predictive value than that of ATRIA and, importantly, highlights risk factors that can be actively managed to reduce the bleeding risk.[57,58] The HAS-BLED score has been validated in several independent cohorts,[25,54,59–61] and correlates well with ICH risk. It is noteworthy that the ICH (and major bleeding) rate in patients on aspirin, for a given HAS-BLED score, was similar to that for those taking warfarin.[25]

Thus, a formal bleeding risk assessment is recommended for all patients with AF, and in patients with a HAS-BLED score $\geq$3, caution and regular review are appropriate, as well as efforts to correct the potentially reversible risk factors for bleeding. The HAS-BLED score *per se* should not be used to exclude patients from OAC therapy but allows clinicians to make an informed assessment of bleeding risk (rather than relying on guesswork) and, importantly, makes them think of the correctable risk factors for bleeding: for example, uncontrolled blood pressure, concomitant use of aspirin/non-steroidal anti-inflammatory drugs (NSAIDs), labile INRs, etc. Use of the CHA$_2$DS$_2$-VASc and HAS-BLED scores to aid practical decision-making for thromboprophylaxis in non-valvular AF has recently been reviewed.[62]

In the net clinical benefit analysis—balancing ischaemic stroke against intracranial bleeding—by Olesen *et al.*,[21] those patients with a high HAS-BLED score had an even greater net clinical benefit with warfarin, given that the higher-risk individuals would have a much greater absolute reduction in stroke risk with warfarin, which would outweigh the small absolute increase in major bleeding events. Similar observations were reported in a much larger dataset by Friberg *et al.*,[63] where the adjusted net clinical benefit favoured anticoagulation for almost all AF patients, with the exception of patients at very low risk of ischaemic stroke, with a CHA$_2$DS$_2$-VASc score of 0 and moderate–high bleeding risk. In the two large independent datasets,[21,63] the CHA$_2$DS$_2$-VASc score was able to identify those patients who had some disadvantage from anticoagulant treatment with warfarin. Notably, the CHADS$_2$ score was less discriminatory for 'truly low-risk' patients, where all AF patients, irrespective of CHADS$_2$ score, appeared to benefit from anticoagulation use.[63]

Additional evidence emphasizes that stroke prevention with a VKA is effective where the individual mean time in therapeutic range (TTR) is good; for example >70%.[28,64–67] Thus, where a VKA is used, efforts to improve quality of INR control are needed in order to achieve high TTRs.

4. Novel oral anticoagulants

The NOACs for stroke prevention in AF fall into two classes: the oral direct thrombin inhibitors (e.g. dabigatran) and oral direct factor Xa inhibitors (e.g. rivaroxaban, apixaban, etc.).[68] In contrast to VKAs, which block the formation of multiple active vitamin K-dependent coagulation factors (factors II, VII, IX, and X), these drugs block the activity of one single step in coagulation. Another oral factor Xa inhibitor with an ongoing, large phase III trial is edoxaban; this will probably be reported in 2013.[69]

4.1 Dabigatran etexilate

The RE-LY (Randomized Evaluation of Long-term anticoagulant therapY with dabigatran etexilate) trial was a prospective, randomized, open-label, phase III trial comparing two blinded doses of dabigatran etexilate [110 mg b.i.d. (D110) or 150 mg b.i.d. (D150)] with open-label adjusted-dose warfarin, aiming for an INR of 2.0–3.0 (*Table 4*).[70,71] For the primary efficacy endpoint of stroke and systemic embolism, D150 was superior to warfarin, with no significant difference in the primary safety endpoint of major bleeding. D110 was non-inferior to warfarin, with 20% fewer major bleeds. Rates of haemorrhagic stroke and ICH were lower with both doses of dabigatran, but gastrointestinal bleeding was significantly increased with D150. There was a non-significant numerical increase (of 28%) in myocardial infarction (MI) with both dabigatran doses.[71,72] There was a significant reduction in ischaemic stroke, as well as a borderline reduction in all-cause mortality with D150 ($P = 0.051$) and a significant reduction in vascular mortality ($P = 0.04$). The rates of discontinuation were higher with D150 (20.7%) and D110 (21.2%), compared with 16.6% with warfarin at 2 years. A *post-hoc* analysis has reported a significant age interaction, whereby patients aged >75 years had rates of major bleeding similar to warfarin with D110, with a trend towards more bleeding with D150; however, ICH was lower with both doses of dabigatran. The efficacy and safety of dabigatran was consistent across all CHADS$_2$ risk strata.[73] Previous VKA exposure does not influence the benefits of dabigatran at either dose, compared with warfarin.[74]

The concerns over the small increase in MI with dabigatran have prompted a detailed analysis where there was no excess of new angina hospitalizations or revascularization with dabigatran-treated patients, with a vascular mortality and a net clinical benefit in favour of dabigatran.[72] A meta-analysis of seven dabigatran studies (AF, venous thromboembolism, etc.) in over 30 000 patients showed a significant 33% increase in MI, but an 11% reduction in all-cause mortality, when dabigatran was compared to warfarin.[75] However, this may reflect a better protective effect of warfarin against MI.[76]

Based on the results of RE-LY, dabigatran etexilate has been approved by both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), as well as in many countries worldwide, for prevention of stroke and systemic embolism. The EMA indication is for patients with non-valvular AF with at least one risk factor, namely: previous stroke, transient ischaemic attack (TIA) or systemic embolism; LVEF <40%; symptomatic heart failure; and age $\geq$75 years or age $\geq$65 years with one of the following: diabetes, coronary artery disease or hypertension. The FDA has approved the 150 mg b.i.d. dose, and the 75 mg b.i.d. dose in severe renal impairment, while the EMA has approved both the 110 mg b.i.d. and 150 mg b.i.d. doses.

4.2 Rivaroxaban

The double-blind ROCKET-AF[3] trial randomized 14 264 high-risk patients with AF to either (i) treatment with rivaroxaban 20 mg o.d. [15 mg daily for those with estimated creatinine clearance (CrCl) 30–49 mL/min] or (ii) warfarin (*Table 4*). The population

was at considerably higher risk for stroke than in other NOAC AF trials, and the mean TTR was 55% (median 58%), which was lower than in other randomized trials. Rivaroxaban was non-inferior to warfarin for the primary endpoint of stroke and systemic embolism, and the per-protocol on-treatment analysis achieved statistical superiority [relative risk reduction (RRR) 21%, $P = 0.015$] but, using the more conventional intention-to-treat analysis, rivaroxaban was not superior ($P = 0.12$). There was no reduction in rates of mortality or ischaemic stroke, but a significant reduction in haemorrhagic stroke and intracranial haemorrhage. The primary safety endpoint was the composite of major- and clinically relevant non-major bleeding, which was not significantly different between rivaroxaban and warfarin but, with rivaroxaban, there was a significant reduction in fatal bleeding, as well as an increase in gastrointestinal bleeds and bleeds requiring transfusion. Premature discontinuation of treatment was more common with rivaroxaban (23.9%) than with warfarin (22.4%).

Rivaroxaban has been approved for stroke prevention in non-valvular AF by both the FDA and the EMA, and in many countries worldwide.

4.3 Apixaban

The AVERROES trial[2] randomized 5599 AF patients, who were not suitable candidates for—or were unwilling to take—VKA treatment, to double-blind, double-dummy treatment with either apixaban [5 mg b.i.d. with a dose adjustment to 2.5 mg b.i.d. in patients ≥80 years, weight ≤60kg or with a serum creatinine ≥1.5 mg/dL (133 μmol/L)] or aspirin (81–324 mg/day, with 91% taking ≤162 mg/day). After a mean follow-up of 1.1 years, the trial was stopped early, due to a significant 55% reduction in the primary endpoint of stroke or systemic embolism with apixaban compared with aspirin, with no significant difference in rates of major bleeding or ICH between apixaban and aspirin. Apixaban was slightly better tolerated, with rates of permanent discontinuation of study treatments being 20.5% per year in the aspirin group, vs. 17.9% per year in the apixaban group at 2 years ($P = 0.03$).

The ARISTOTLE trial[4] was a randomized, double-blind, double-dummy, phase III trial comparing apixaban [5 mg b.i.d. with a dose adjustment to 2.5 mg b.i.d. in patients ≥80 years, weight ≤60kg or with a serum creatinine ≥1.5 mg/dL (133 μmol/L)] with dose-adjusted warfarin aiming for an INR of 2.0–3.0 in 18 201 patients with non-valvular AF (*Table 4*). There was a significant reduction in the primary efficacy outcome of stroke or systemic embolism by 21% with apixaban compared with warfarin, with a 31% reduction in major bleeding and a significant 11% reduction in all-cause mortality (but not cardiovascular mortality). Rates of haemorrhagic stroke and ICH—but not of ischaemic stroke—were significantly lower in patients treated with apixaban than with warfarin. Gastrointestinal bleeding was similar between the treatment arms. Apixaban was better tolerated than warfarin, with slightly fewer early discontinuations (25.3% *vs.* 27.5%). Apixaban has not yet gained regulatory approval from the EMA or FDA. It is included in these guidelines because it may be approved shortly after the publication.

4.4 Practical considerations[a]

The NOACs so far tested in clinical trials have all shown non-inferiority compared with VKAs, with better safety, consistently limiting the number of ICH. On this basis, this guideline now recommends them as broadly preferable to VKA in the vast majority of patients with non-valvular AF, when used as studied in the clinical trials performed so far. Since there is still limited experience with these agents, strict adherence to approved indications and careful post-marketing surveillance are strongly recommended.

In the absence of head-to-head trials, it is inappropriate to be definitive on which of the NOACs is best, given the heterogeneity of the different trials.[77] Indirect comparison analyses do not suggest profound differences in efficacy endpoints between the NOACs, but major bleeding appears lower with dabigatran 110mg b.i.d. and apixaban.[77] Patient characteristics, drug tolerability, and cost may be important considerations.[28] Some cost-effectiveness data for dabigatran have been published in various healthcare settings, and dabigatran appears to be cost-effective for most patients,[78–81] except in those with very well-controlled INRs. Also, there remain concerns over the applicability of data for the NOACs to very elderly patients with multiple comorbidities, polypharmacy, compliance issues etc., who are often managed by primary care physicians. None of the novel OACs has a specific antidote; dabigatran and apixaban have twice daily dose regimens, and some drug interactions are evident. Patients with severe renal impairment were excluded from the trials and, specifically, dabigatran has a high renal clearance.

The net clinical benefit of VKAs, balancing ischaemic stroke against ICH in patients with non-valvular AF, has been modelled on to stroke and bleeding rates from the Danish nationwide cohort study for dabigatran, rivaroxaban, and apixaban, on the basis of recent clinical trial outcome data for these NOACs.[82] At a CHA_2DS_2-VASc score of 1, apixaban and both doses of dabigatran (110 mg b.i.d. and 150 mg b.i.d.) had a positive net clinical benefit while, in patients with CHA_2DS_2-VASc score ≥2, all three NOACs were superior to warfarin, with a positive net clinical benefit, irrespective of bleeding risk.

When switching from a VKA to a NOAC, the INR should be allowed to fall to about 2.0 (there are NOAC-specific and transatlantic differences detailed in the Summaries of Product Characteristics/Package Inserts, but the principle is to judge the waning effect of warfarin against the increasing anticoagulant effect of the NOAC) before starting the NOAC, all of which have rapid onset of anticoagulation effect. When changing from a NOAC to a VKA, the VKA should be started after a period that depends on renal function as, for example, with dabigatran, where overlap with VKA for 2–3 days is necessary, as VKAs would take a few days to achieve therapeutic anticoagulation.

Compliance and adherence to treatment is crucial, especially since these drugs have a relatively short half-life, such that patients would be left without any anticoagulation protection if more than one dose were missed. All of these drugs have a degree of renal

[a] (Note: Given the multiple considerations on how to safely use NOAC in daily clinical practice in different clinical scenarios, EHRA has prepared additional educational material and a regularly updated website specifically addressing this.)

Table 4 Summary of the clinical trials involving novel anticoagulants vs. warfarin for stroke prevention in non-valvular AF

	Dabigatran (RE-LY)[70,71]			Rivaroxaban (ROCKET-AF)[3]		Apixaban (ARISTOTLE)[4]	
Drug characteristics							
Mechanism	Oral direct thrombin inhibitor			Oral direct factor Xa inhibitor		Oral direct factor Xa inhibitor	
Bioavailability, %	6			60–80		50	
Time to peak levels, h	3			3		3	
Half-life, h	12–17			5–13		9–14	
Excretion	80% renal			2/3 liver, 1/3 renal		25% renal, 75% faecal	
Dose	150 mg b.i.d.			20 mg o.d.		5 mg b.i.d.	
Dose in renal impairment	110 mg b.i.d.			15 mg o.d. (if CrCl 30-49 mL/min)		2.5 mg b.i.d.	
Special considerations	Intestinal absorption is pH-dependent and is reduced in patients taking proton pump inhibitors			Higher levels expected in patients with renal or hepatic failure			
	Increased risk of bleeding in patients taking verapamil/amiodarone/quinidine/ketoconazole			Activity lower in fasted patients so should be taken after food			
Study characteristics							
Study design	Randomized, open-label			Randomized, double-blind		Randomized, double-blind	
Number of patients	18 111			14 264		18 201	
Follow-up period, years	2			1.9		1.8	
Randomized groups	Dose-adjusted warfarin vs. blinded doses of dabigatran (150 mg b.i.d., 110 mg b.i.d.)			Dose-adjusted warfarin vs. rivaroxaban 20 mg o.d.		Dose-adjusted warfarin vs. apixaban 5 mg b.i.d.	
Baseline patient characteristics							
Age, years	71.5 ± 8.7 (mean ± SD)			73 (65–78) [median (interquartile range)]		70 (63–76) [median (interquartile range)]	
Male sex, %	63.6			61.3		64.5	
$CHADS_2$ (mean)	2.1			3.5		2.1	
Outcomes (% per year)							
	Warfarin	Dabigatran 150	Dabigatran 110	Warfarin	Rivaroxaban	Warfarin	Apixaban
	(*n* = 6022)	(*n* = 6076)	(*n* = 6015)	(*n* = 7133)	(*n* = 7131)	(*n* = 9081)	(*n* = 9120)
		(RR, 95% CI; *P* value)	(RR, 95% CI; *P* value)		(HR, 95% CI; *P* value)		(HR, 95% CI; *P* value)
Stroke/systemic embolism	1.69	1.11 (0.66, 0.53–0.82; *P* for superiority <0.001)	1.53 (0.91, 0.74–1.11; *P* for non-inferiority <0.001)	2.4	2.1 (0.88, 0.75–1.03; *P* for non-inferiority <0.001, *P* for superiority = 0.12) (ITT)	1.6	1.27 (0.79, 0.66–0.95; *P* <0.001 for non-inferiority, *P* = 0.01 for superiority)
Ischaemic stroke	1.2	0.92 (0.76, 0.60–0.98; *P* = 0.03)	1.34 (1.11, 0.89–1.40; *P* = 0.35)	1.42	1.34 (0.94; 0.75–1.17; *P* = 0.581)	1.05	0.97 (0.92, 0.74–1.13; *P* = 0.42)
Haemorrhagic stroke	0.38	0.10 (0.26, 0.14–0.49; *P* <0.001)	0.12 (0.31, 0.17–0.56; *P* <0.001)	0.44	0.26 (0.59; 0.37–0.93; *P* =0.024)	0.47	0.24 (0.51, 0.35–0.75; *P* <0.001)
Major bleeding	3.36	3.11 (0.93, 0.81–1.07; *P* = 0.31)	2.71 (0.80, 0.69–0.93; *P* = 0.003)	3.4	3.6 (*P* = 0.58)	3.09	2.13 (0.69, 0.60–0.80; *P* <0.001)
Intracranial bleeding	0.74	0.30 (0.40, 0.27–0.60; *P* <0.001)	0.23 (0.31, 0.20–0.47; *P* <0.001)	0.7	0.5 (0.67; 0.47–0.93; *P* = 0.02)	0.80	0.33 (0.42, 0.30–0.58; *P* <0.001)
Extracranial bleeding	2.67	2.84 (1.07, 0.92–1.25; *P* = 0.38)	2.51 (0.94, 0.80–1.10; *P* = 0.45)	–	–	–	–

(*continued*)

Table 4 *Continued*

	Dabigatran (RE-LY)[70,71]			Rivaroxaban (ROCKET-AF)[3]		Apixaban (ARISTOTLE)[4]	
Outcomes (% per year)							
Gastrointestinal bleeding	1.02	1.51 (1.50, 1.19–1.89; *P* <0.001)	1.12 (1.10, 0.86–1.41; *P* = 0.43)	2.2	3.2 (*P* <0.001)	0.86	0.76 (0.89, 0.70–1.15; *P* = 0.37)
Myocardial infarction	0.64	0.81 (1.27, 0.94-1.71; *P* = 0.12)	0.82 (1.29, 096-1.75; *P* = 0.09)	1.1	0.9 (0.81; 0.63–1.06; *P* = 0.12)	0.61	0.53 (0.88, 0.66–1.17; *P* = 0.37)
Death from any cause	4.13	3.64 (0.88, 0.77–1.00; *P* = 0.051)	3.75 (0.91, 0.80–1.03; *P* = 0.13)	2.2	1.9 (0.85; 0.70–1.02; *P* = 0.07)	3.94	3.52 (0.89, 0.80–0.99; *P* = 0.047)
% Discontinuation at the end of follow-up	10.2	15.5	14.5	22.2	23.7	27.5	25.3
% Discontinuation/year	5.1	7.8	7.3	11.7	12.5	15.3	14.1

AF = atrial fibrillation; b.i.d. = bis in die (twice daily); $CHADS_2$ = congestive heart failure, hypertension, age ≥75, diabetes, stroke/TIA [doubled]; CI = confidence interval; CrCl = creatinine clearance; HR = hazard ratio; ITT = intention-to-treat; o.d. = once daily; RR = relative risk; SD = standard deviation; TIA = transient ischaemic attack; VKA = vitamin K antagonist.

excretion, especially dabigatran. Thus, assessment of renal function (by CrCl) is mandatory for all NOACs, but especially for patients taking dabigatran. Indeed, renal function should be assessed annually in patients with normal (CrCl ≥80 mL/min) or mild (CrCl 50–79 mL/min) renal impairment, and perhaps 2–3 times per year in patients with moderate (i.e. creatinine clearance 30–49 mL/min) renal impairment. Dabigatran may also cause dyspepsia, which may perhaps be ameliorated by taking the drug with food or the use of a proton pump inhibitor.

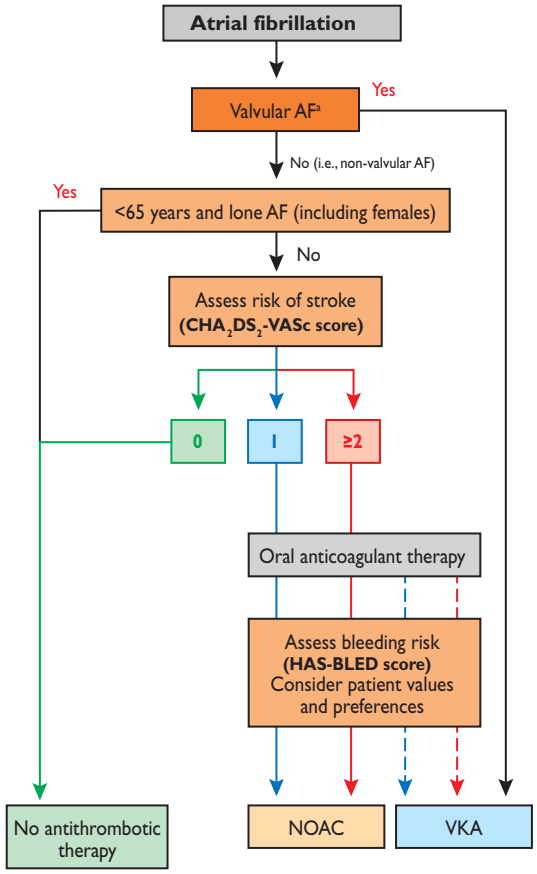
The NOACs do not require dose adjustment on the basis of a specific coagulation test (in contrast to the INR for VKAs). There are non-specific coagulation tests that can be used to check for the presence of an anticoagulation effect (rather than anticoagulation intensity *per se*).[28,83] These should not be used for dose adjustment). For dabigatran, the ecarin clotting time and thrombin clotting time are useful tests, and directly reflect thrombin inhibition;[84] however, an activated partial thromboplastin time (aPTT) can also be used (especially in an emergency setting), although the correlation is not linear, particularly at higher concentrations.[84,85] Rivaroxaban prolongs the prothrombin time (PT) and this might be used as a rough estimate of an anticoagulation effect.[86] A better estimate for an anticoagulant effect for the oral Factor Xa inhibitors is an anti-Xa assay.[86,87]

These novel drugs do not have specific antidotes and management of bleeding is thus largely supportive, given that these drugs have a relatively short (5 to 17 hours) half-life.[85,88] One small study suggested normalization of coagulation tests with non-activated prothrombin complex concentrate (Cofact®, Sanquin Blood Supply, Amsterdam, the Netherlands) administered to healthy and relatively young individuals taking rivaroxaban, but no effect was seen with dabigatran.[89] Another study found that low-dose FEIBA® (Baxter AG, Vienna, Austria) reversed the anticoagulant activity of rivaroxaban and dabigatran.[90] However, the lack of normalization of coagulation tests does not necessarily correlate with the absence of an anti-haemorrhagic effect, as shown in animal models.[84]

Perioperative management is another important consideration.[88,91] Given the rapid onset and offset of action of dabigatran etexilate, no bridging therapy with low molecular weight heparin (LMWH) is required for the majority of interventions, although this is dependent upon balancing the risks of stroke/thromboembolism vs. bleeding (where the HAS-BLED score has been shown to be useful).[92] Following surgery, NOACs can be restarted as soon as effective haemostasis has been achieved. The NOAC effect will be evident within a few hours after the first dose.

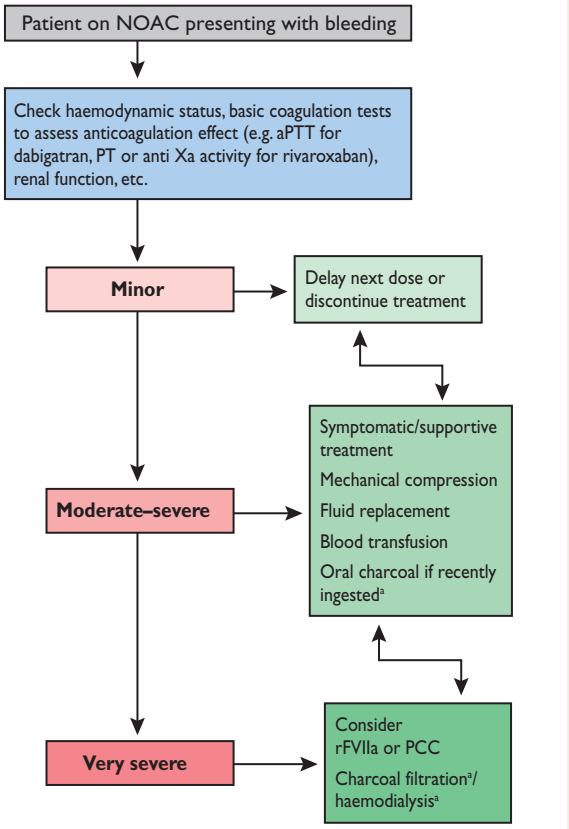
The available data suggest that elective cardioversion can be safely performed on dabigatran,[93] with the requirement for 3 weeks of therapeutic anticoagulation pre-cardioversion, the cardioversion performed, and anticoagulation continued for a minimum of 4 weeks post-cardioversion. Event rates were not different between conventional and trans-oesophageal echocardiogram-guided cardioversion; however, drug compliance is crucial for the anticoagulation period peri-cardioversion as, unlike the INR for VKAs, there is no easy means to assess therapeutic anticoagulation. In patients with stroke risk factors or at high risk of recurrence, OAC should be continued long-term, whether with a VKA or a NOAC. No published data on cardioversion with rivaroxaban or apixaban are yet available.

There are currently no controlled data on the risk–benefit profile of catheter ablation on uninterrupted NOACs. Ablation of a patient whilst still taking uninterrupted NOACs may carry a small theoretical risk, given the lack of a reversal agent, should a major bleeding complication arise. Data from limited case series suggest that appropriate post-ablation management with dabigatran is associated with a low risk of embolic or bleeding complications,[94] although brief interruption of dabigatran use is associated with more thromboembolic and bleeding complications.[95]



Antiplatelet therapy with aspirin plus clopidogrel, or—less effectively—aspirin only, should be considered in patients who refuse any OAC, or cannot tolerate anticoagulants for reasons unrelated to bleeding. If there are contraindications to OAC or antiplatelet therapy, left atrial appendage occlusion, closure or excision may be considered.
Colour: CHA_2DS_2-VASc; green = 0, blue = 1, red ≥2.
Line: solid = best option; dashed = alternative option.
AF = atrial fibrillation; CHA_2DS_2-VASc = see text; HAS-BLED = see text;
NOAC = novel oral anticoagulant; OAC = oral anticoagulant;
VKA = vitamin K antagonist.
[a]Includes rheumatic valvular disease and prosthetic valves.

Figure 1 Choice of anticoagulant.



aPTT = activated partial thromboplastin time; NOAC = novel oral anticoagulant; PCC = prothrombin complex concentrate; PT = prothrombin time; rFVIIa = activated recombinant factor VII.
[a]With dabigatran.

Figure 2 Management of bleeding in patients taking novel oral anticoagulants.

Patients taking the NOACs may present with an acute coronary syndrome (ACS) and/or undergo percutaneous coronary intervention (PCI). Concomitant use of antiplatelet therapy with the NOACs significantly increases bleeding risk,[96] as is the case with combining any OAC with antiplatelet therapy. In AF patients at risk of stroke, and irrespective of HAS-BLED score, OAC still confers benefit (reduced mortality and major adverse cardiac events) but with more bleeds.[97] In the absence of robust data, in AF patients with an ACS or PCI/stenting, recommendations based on expert consensus on the management of such patients should be followed, as found within the 2010 ESC Guidelines or current European or North American consensus documents.[98–100] Thus, a period of triple therapy is needed (OAC plus aspirin plus clopidogrel), followed by the combination OAC plus single antiplatelet drug and, after one year, management can be with OAC alone in stable patients, where OAC can be adjusted-dose VKA therapy or probably a NOAC. Notably, the only trial where clopidogrel use was not contraindicated was RE-LY, so the data on triple therapy with a NOAC (when given at stroke prevention doses in AF patients) are limited.

A patient taking dabigatran may present with an ACS and, given the non-significant but small numerical increase in MI events with dabigatran compared with warfarin,[71,72] the concerned clinician may consider the use of a VKA or an alternative NOAC (e.g. rivaroxaban or apixaban). There is little evidence to support this, as the relative effects of dabigatran vs. warfarin on myocardial ischaemic events were consistent in patients with or without a baseline history of MI or coronary artery disease. Although twice-daily low-dose rivaroxaban (2.5 mg or 5 mg b.i.d.) has been used with some benefit in ACS,[101] there are no data on ACS relating to the dose of rivaroxaban used for anticoagulation in AF (20 mg o.d.). Apixaban, used in the stroke prevention dose (5 mg b.i.d.) in the ACS setting in combination with aspirin plus clopidogrel, was associated with no reduction in cardiovascular events but an excess of major bleeding.[102] Patients with AF and stable vascular disease (i.e. no acute events or revascularization for >12 months, whether coronary or peripheral artery disease) can be

Recommendations for prevention of thromboembolism in non-valvular AF

Recommendations	Class[a]	Level[b]	Ref[c]
Recommendations for prevention of thromboembolism in non-valvular AF—general			
Antithrombotic therapy to prevent thromboembolism is recommended for all patients with AF, except in those patients (both male and female) who are at low risk (aged <65 years and lone AF), or with contraindications.	I	A	21, 63, 104, 105, 106
The choice of antithrombotic therapy should be based upon the absolute risks of stroke/thromboembolism and bleeding and the net clinical benefit for a given patient.	I	A	21, 63, 105
The CHA_2DS_2-VASc score is recommended as a means of assessing stroke risk in non-valvular AF.	I	A	25, 36 ,39
In patients with a CHA_2DS_2-VASc score of 0 (i.e., aged <65 years with lone AF) who are at low risk, with none of the risk factors, no antithrombotic therapy is recommended.	I	B	21, 36, 82
In patients with a CHA_2DS_2-VASc score ≥2, OAC therapy with: • adjusted-dose VKA (INR 2–3); or • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)[d] … is recommended, unless contraindicated.	I	A	3, 4, 70, 82
In patients with a CHA_2DS_2-VASc score of 1, OAC therapy with • adjusted-dose VKA (INR 2–3); or • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)[d] …. should be considered, based upon an assessment of the risk of bleeding complications and patient preferences.	IIa	A	33, 44
Female patients who are aged <65 and have lone AF (but still have a CHA_2DS_2-VASc score of 1 by virtue of their gender) are low risk and no antithrombotic therapy should be considered.	IIa	B	33, 44
When patients refuse the use of any OAC (whether VKAs or NOACs), antiplatelet therapy should be considered, using combination therapy with aspirin 75–100 mg plus clopidogrel 75 mg daily (where there is a low risk of bleeding) or—less effectively—aspirin 75–325 mg daily.	IIa	B	21, 26, 51, 109
Recommendations for prevention of thromboembolism in non-valvular AF—NOACs			
When adjusted-dose VKA (INR 2–3) cannot be used in a patient with AF where an OAC is recommended, due to difficulties in keeping within therapeutic anticoagulation, experiencing side effects of VKAs, or inability to attend or undertake INR monitoring, one of the NOACs, either: • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)[d] … is recommended.	I	B	2, 28, 65, 107
Where OAC is recommended, one of the NOACs, either: • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)[d] … should be considered rather than adjusted-dose VKA (INR 2–3) for most patients with non-valvular AF, based on their net clinical benefit.	IIa	A	3, 4, 70, 82
Where dabigatran is prescribed, a dose of 150 mg b.i.d. should be considered for most patients in preference to 110 mg b.i.d., with the latter dose recommended in: • elderly patients, age ≥ 80 • concomitant use of interacting drugs (e.g. verapamil) • high bleeding risk (HAS-BLED score ≥3) • moderate renal impairment (CrCl 30–49 mL/min).	IIa	B	85, 96
Where rivaroxaban is being considered, a dose of 20 mg o.d. should be considered for most patients in preference to 15 mg o.d., with the latter dose recommended in: • high bleeding risk (HAS-BLED score ≥3) • moderate renal impairment (CrCl 30–49 mL/min).	IIa	C	3, 108
Baseline and subsequent regular assessment of renal function (by CrCl) is recommended in patients following initiation of any NOAC, which should be done annually but more frequently in those with moderate renal impairment where CrCl should be assessed 2–3 times per year.	IIa	B	85
NOACs (dabigatran, rivaroxaban, and apixaban) are not recommended in patients with severe renal impairment (CrCl <30 mL/min).	III	A	3, 24, 70

managed with OAC alone, whether as adjusted dose VKA therapy or, probably, a NOAC. In such stable patients, there is no need for concomitant aspirin, which could increase the risk of serious haemorrhage, including intracranial haemorrhage.

Patients taking the NOACs may also present with an acute ischaemic stroke. If the aPTT is prolonged in a patient taking dabigatran (or the PT with rivaroxaban), it should be assumed that the patient is anticoagulated, and thrombolysis should not be administered.[103] Given that dabigatran 150 mg b.i.d. did result in a significant reduction in both ischaemic *and* haemorrhagic stroke, should the acute ischaemic stroke occur whilst the patient is taking rivaroxaban or apixaban (neither of which

Recommendations for prevention of thromboembolism in non-valvular AF (*Continued*)

Recommendations	Class[a]	Level[b]	Ref[c]
Recommendations for prevention of thromboembolism in non-valvular AF—bleeding			
Assessment of the risk of bleeding is recommended when prescribing antithrombotic therapy (whether with VKA, NOAC, aspirin/clopidogrel, or aspirin).	I	A	25, 54, 59, 60
The HAS-BLED score should be considered as a calculation to assess bleeding risk, whereby a score ≥3 indicates 'high risk' and some caution and regular review is needed, following the initiation of antithrombotic therapy, whether with OAC or antiplatelet therapy (LoE = A). Correctable risk factors for bleeding [e.g. uncontrolled blood pressure, labile INRs if the patient was on a VKA, concomitant drugs (aspirin, NSAIDs, etc.), alcohol, etc.] should be addressed (LoE = B). Use of the HAS-BLED score should be used to identify modifiable bleeding risks that need to be addressed, but should not be used on its own to exclude patients from OAC therapy (LoE = B).	IIa	A B	25, 54, 60
The risk of major bleeding with antiplatelet therapy (with aspirin–clopidogrel combination therapy and – especially in the elderly – also with aspirin monotherapy) should be considered as being similar to OAC.	IIa	B	18, 21, 23, 24, 26, 35
Recommendations for prevention of thromboembolism in non-valvular AF—peri-cardioversion			
For patients with AF of ≥48 h duration, or when the duration of AF is unknown, OAC therapy (e.g. VKA with INR 2-3 or dabigatran) is recommended for ≥3 weeks prior to and for ≥4 weeks after cardioversion, regardless of the method (electrical or oral/i.v. pharmacological).	I	B	93
In patients with risk factors for stroke or AF recurrence, OAC therapy, whether with dose-adjusted VKA (INR 2-3) or a NOAC, should be continued lifelong irrespective of the apparent maintenance of sinus rhythm following cardioversion.	I	B	110

AF = atrial fibrillation; b.i.d. = bis in die (twice daily); CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74, sex category (female); CrCl = creatinine clearance; HAS-BLED = hypertension, abnormal renal/liver function (1 point each), stroke, bleeding tendency or predisposition, labile INR if on warfarin, elderly (e.g., age >65), drugs (aspirin, NSAIDs, etc.)/alcohol concomitantly (1 point each); INR = international normalized ratio; i.v. = intravenous; OAC = oral anticoagulant; NOAC = novel oral anticoagulant; NSAID = non-steroidal anti-inflammatory drug; VKA = vitamin K antagonist.
[a]Class of recommendation.
[b]Level of evidence.
[c]References.
[d]Apixaban (pending approval EMA and FDA approval): prescribing information is awaited.

significantly reduced ischaemic stroke, compared with warfarin, in their respective trials), the clinician may consider the use of dabigatran 150 mg b.i.d. instead. Algorithms illustrating the choice of antithrombotic therapy and the management of bleeding in patients on NOACs in patients with AF are shown in *Figures 1* and *2*. Although NOACs may be preferred on the basis of clinical trial data clinicians should remain aware that clinical experience with these agents is still limited and that care, vigilance and further information on their effectiveness in clinical practice are needed.

Key points

- The efficacy of stroke prevention with aspirin is weak, with a potential for harm, since the risk of major bleeding (and ICH) with aspirin is not significantly different to that of OAC, especially in the elderly.
- The use of antiplatelet therapy (as aspirin–clopidogrel combination therapy or—less effectively—aspirin monotherapy for those who cannot tolerate aspirin–clopidogrel combination therapy) for stroke prevention in AF should be limited to the few patients who refuse any form of OAC.
- The CHA_2DS_2-VASc score is better at identifying 'truly low-risk' patients with AF and is as good as—and possibly better than—scores such as $CHADS_2$ in identifying patients who develop stroke and thromboembolism.
- The HAS-BLED score allows clinicians to make an informed assessment of bleeding risk and, importantly, makes them think of the correctable risk factors for bleeding. In patients with a HAS-BLED score ≥3, caution and regular review are recommended, as well as efforts to correct the potentially reversible risk factors for bleeding. A high HAS-BLED score *per se* should not be used to exclude patients from OAC therapy.
- The NOACs offer better efficacy, safety, and convenience compared with OAC with VKAs. Thus, where an OAC is recommended, one of the NOACs—either a direct thrombin inhibitor (dabigatran) or an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)—should be considered instead of adjusted-dose VKA (INR 2–3) for most patients with AF.
- There is insufficient evidence to recommend one NOAC over another, although some patient characteristics, drug compliance and tolerability, and cost may be important considerations in the choice of agent.

5. Left atrial appendage closure

5.1 Rationale and techniques for left atrial appendage closure

The left atrial appendage (LAA) is considered the main (but not the only) site of thrombus formation inducing ischaemic stroke

in patients suffering from AF. Trans-oesophageal echocardiography detects most thrombi in the LAA and low stroke rates are reported in patients in whom the LAA has been surgically removed (although these patients were also reverted to sinus rhythm by various surgical techniques).[111,112] Indeed, surgical excision or stapling of the LAA is widely performed as a concomitant procedure during open heart surgery. More recently, minimally invasive epicardial techniques and interventional trans-septal techniques have been developed for occlusion of the LAA orifice to reduce the stroke risk.[113–115] These devices/procedures may provide an alternative to OAC for AF patients at high risk for stroke but with contraindications for chronic OAC and, if the efficiency of LAA closure can be conclusively shown, to potentially replace long-term OAC.

5.2 Results of left atrial appendage closure

Although clinically applied for decades, there is no conclusive evidence that surgical LAA excision or occlusion reduces stroke risk in AF patients, due to a lack of large, controlled trials with systematic follow-up.[113] Furthermore, there are data to suggest that not all strokes in AF patients are cardio-embolic or due to AF, and the LAA is probably not the only left atrial region where thrombi can potentially originate. This suggests that there may be a need for antithrombotic therapy in AF patients, even after removal or closure of the LAA.[116]

Data from retrospective or observational studies in different patient populations have shown inconsistent results of surgical LAA excision or occlusion.[117] In addition, no conclusive data are available on the best surgical technique for performing LAA closure. Risks of surgical LAA excision include major bleeding and incomplete LAA occlusion with residual stroke risk.[117]

Non-randomized observational studies, involving relatively small numbers of patients, have shown the feasibility of percutaneous LAA occlusion. Currently, two self-expanding devices, the WATCHMAN (Boston Scientific, Natick, MA, USA) and the Amplatzer Cardiac Plug (St. Jude Medical, St Paul, MN, USA), that are transseptally placed in the LAA, are available for clinical use in Europe, while their evaluation in controlled trials is still in process.

The WATCHMAN LAA system for embolic PROTECTion in patients with Atrial Fibrillation (PROTECT AF) trial randomized 707 eligible patients either to percutaneous closure of the LAA, using the WATCHMAN device, or to OAC (INR range 2–3; control; $n = 244$).[115] Patients randomized to LAA occlusion were treated with OAC for 45 days after the procedure, followed by dual platelet inhibition for six months and aspirin alone as chronic therapy. The primary efficacy event rate (composite endpoint of stroke, cardiovascular death, and systemic embolism) in the LAA occlusion group was non-inferior to patients treated with OAC. There was a high rate of adverse events in the intervention group, mainly due to peri-procedural complications. Many of the adverse events in the intervention group occurred early in the trial, indicative of an operator learning curve. The Continued Access to PROTECT AF (CAP) registry is following patient outcomes beyond the end of enrolment and demonstrates a "learning curve effect" with reduced complication rates after the end of the trial.[118] A second randomized trial, PREVAIL (Prospective Randomized EVAluation of the Watchman LAA closure device In patients with atrial fibrillation vs. Long-term warfarin therapy), is currently enrolling patients.

In a feasibility and safety study, LAA occlusion with the Amplatzer Cardiac Plug was attempted in 137 of 143 patients, and was successfully performed in 132 (96%).[114] Serious complications occurred in 10 (7.0%) patients. A randomized prospective study with the device is currently under way (Amplatzer Cardiac Plug Trial).

Although the concept of LAA closure seems reasonable, the evidence of efficacy and safety is currently insufficient to recommend these approaches for any patients other than those in whom long-term OAC is contraindicated. However, in the absence of controlled clinical data this recommendation is based on expert consensus only. Additional, adequately powered, randomized studies in patients with high stroke risk and long-term follow-up, comparing interventional/percutaneous/surgical LAA closure with OAC therapy including NOAC drugs, are needed for adequate assessment of such techniques. The need for lifelong aspirin treatment after placement of LAA closure devices, and the significant bleeding risk with aspirin,[2] may weigh against preference for interventional LAA occlusion. At present, interventional LAA closure is not indicated simply as an alternative to OAC therapy to reduce stroke risk.

Recommendations for LAA closure/occlusion/excision

Recommendations	Class[a]	Level[b]	Ref[c]
Interventional, percutaneous LAA closure may be considered in patients with a high stroke risk and contraindications for long-term oral anticoagulation.	IIb	B	115, 118
Surgical excision of the LAA may be considered in patients undergoing open heart surgery.	IIb	C	

LAA = left atrial appendage.
[a]Class of recommendation.
[b]Level of evidence.
[c]References.

Key point

- Interventional percutaneous occlusion/closure of the LAA has a role in patients with thromboembolic risk who cannot be managed in the long-term using any form of OAC.

6. Cardioversion with pharmacological agents

Since the publication of the 2010 ESC Guidelines, a new intravenous antiarrhythmic agent, vernakalant, has been approved for pharmacological cardioversion of AF of ≤7 days, or ≤3 days for patients after cardiac surgery. This update only includes recommendations that have been modified since 2010.

Vernakalant acts preferentially in the atria by blocking several ion channels, resulting in prolongation of atrial refractoriness and rate-dependent slowing of atrial conduction, but has little impact on currents involved in ventricular repolarisation. Vernakalant has a rapid onset of action and a mean elimination half-life of 3–5 hours.

6.1 Clinical evidence for vernakalant

The efficacy of vernakalant was investigated in one dose-finding study, three medium-sized randomized placebo-controlled phase III clinical studies, one randomized clinical trial with amiodarone as an active comparator, and a phase IV open-label study (*Table 5*).[119–124] In phase III and IV studies, vernakalant was administered as a 10-min infusion of 3 mg/kg and, if AF persisted after 15 minutes, a second infusion of 2 mg/kg was given. Patients enrolled in the vernakalant studies were primarily men (68%), with a mean age of 63 years, with approximately half of the patients over 65 years.

In the Atrial arrhythmia Conversion Trials (ACT), vernakalant was significantly more effective than placebo in converting AF of ≤7 days (51.7% and 51.2% compared with 4% and 3.6%, respectively).[120,121] The median time to conversion was 8–11 minutes, with the majority of patients (75 –82%) converting after the first dose.[125]

In direct comparison, vernakalant was significantly superior to intravenous amiodarone in restoration of sinus rhythm within 90 min (51.7% vs. 5.2%; $P < 0.0001$) and within 4 hours after infusion (54.4% vs. 22.6%; $P < 0.0001$).[124] Meta-analysis of the efficacy of vernakalant showed that patients were 8.4 times more likely to convert to sinus rhythm within 90 minutes after vernakalant infusion, than on placebo or amiodarone (95% CI 4.4–16.3), without excess risk of serious adverse events (risk ratio 0.91; 95% CI 0.6–1.36).[126] In another meta-analysis vernakalant compared favourably with older antiarrhythmic agents for rapid cardioversion (within 2 hours).[127]

Vernakalant retained its efficacy in subgroups of patients with associated cardiovascular pathologies such as ischaemic heart disease and hypertension. Specifically, in 274 patients with ischaemic heart disease (41% with previous MI) included in all studies, the placebo-subtracted efficacy of vernakalant was 45.7%, compared with 47.3% in those without ischaemic heart disease, with no excess in adverse events such as hypotension, bradycardia, and ventricular arrhythmias.[128] However, there was a trend towards a reduced benefit in patients with heart failure.[125] Over 95% of patients who converted to sinus rhythm after receiving vernakalant injection remained in sinus rhythm at 24 hours. In the pooled ACT I and -III trials, 76% of patients in the vernakalant group received concomitant rate-control treatment with beta-blockers, calcium antagonists or digoxin, and 24% were receiving antiarrhythmic drug therapy. There was no difference in adverse events.

Vernakalant cardioverted 47% of patients enrolled in ACT II with postoperative AF after cardiac surgery, compared with 14% who converted spontaneously on placebo, with a median time to conversion of 12 min.[122] Vernakalant was ineffective in converting AF of more than 7 days duration or typical atrial flutter.[121,123,129] Conversion of AF to atrial flutter was observed in 8.6–12.7% of patients treated with vernakalant, one-third of whom subsequently converted to sinus rhythm.[120,121]

6.2 Safety of vernakalant

The most common side effects of vernakalant were taste alterations (~30%), sneezing (16%), paraesthesiae (10%), and nausea (9%), which usually resolved within 5–15 minutes.[125] Serious adverse events were reported at similar rates for vernakalant and placebo (4.1% vs. 3.9%). Transient hypotension occurred in about 5–7% of patients treated with vernakalant, with the blood pressure returning to baseline after approximately 15–20 minutes. Hypotension within the first 2 hours was most common in patients with heart failure (16.1%), leading to discontinuation of treatment in 2.9%.[130] Bradycardia was more common with vernakalant than placebo but seldom led to drug discontinuation (0.5%). There was no excess in ventricular arrhythmia events compared with placebo (5.3% vs. 6.3% at 2 hours and 12.5% vs. 16.5% at 24 hours after the start of treatment) and no drug-related *torsades de pointes*[120,121,125] However, in patients with heart failure, non-sustained ventricular arrhythmias (usually ventricular triplets and salvos) occurred more often on treatment (7.3% vs. 1.6% on placebo). The QTc interval was typically prolonged by 20–25 ms and the QRS complex was increased by about 8 ms after infusion of vernakalant.

The drug is contraindicated in patients with hypotension (systolic blood pressure <100 mmHg), ACS within 30 days, NYHA class III and IV heart failure, severe aortic stenosis, and QT interval prolongation (uncorrected QT >440 ms), and should be used with caution in

Recommendations for pharmacological cardioversion of recent-onset AF

Recommendations	Class[a]	Level[b]	Ref[c]
When pharmacological cardioversion is preferred and there is no or minimal structural heart disease, intravenous flecainide, propafenone, ibutilide, or vernakalant are recommended.	I	A	120, 121, 123, 124, 126, 127, 131–134
In patients with AF ≤7 days and moderate structural heart disease [but without hypotension <100 mm Hg, NYHA class III or IV heart failure, recent (<30 days) ACS, or severe aortic stenosis], intravenous vernakalant may be considered. Vernakalant should be used with caution in patients with NYHA class I–II heart failure.	IIb	B	120, 121, 124, 128
Intravenous vernakalant may be considered for cardioversion of postoperative AF ≤3 days in patients after cardiac surgery.	IIb	B	122

ACS = acute coronary syndrome; AF = atrial fibrillation; LoE = level of evidence; NYHA = New York Heart Association.
[a]Class of recommendation.
[b]Level of evidence.
[c]References.

Table 5 Summary of clinical studies of vernakalant in AF/flutter

Study	Design	Number of patients	Underlying heart disease	AF duration	Time to conversion (median), minutes	Conversion to sinus rhythm vs. placebo or control (primary endpoint[a])	Other efficacy outcomes
CRAFT[119]	Double-blind, dose-ranging, placebo-controlled, phase II	56 Vernakalant 2 + 3 mg/kg: *n* = 18; Vernakalant 0.5 + 1 mg/kg: *n* = 18 Placebo: *n* = 20	Hypertension, 57%; diabetes, 23%	AF 3–72 h (mean, 11.5–19.5 h)	14	61% (vernakalant 2 + 3 mg) vs. 5%, *P* <0.001	Conversion rate for vernakalant 0.5 + 1 mg/kg: 11%
ACT I[120]	Double-blind, placebo-controlled, phase III	336 Vernakalant: *n* = 221 Placebo: *n* = 115	Hypertension, 42.5%; ischaemic heart disease, 20.2%; myocardial infarction, 9.8%; heart failure, 14.9%; diabetes, 8%	AF 3 h–45 days (median, 41.8–59.1 h) AF 3 h–7 days (median, 28.2–28.4 h): *n* = 220 AF 8–45 days (median, 19.4–25.5 days): *n* = 116	11	51.7% vs. 4%, *P* <0.001	76% converted after a single dose. Conversion rates for patients with AF ≤48 h: 62.1% vs. 4.9%, *P* <0.001; with AF >7 days: 7.9% vs. 0%, *P* = 0.09
ACT II[122]	Double-blind, placebo-controlled, phase III	160 Vernakalant: *n* = 106 Placebo: *n* = 54	CABG, 67%; valvular surgery, 23.6%; combined, 9.3%. Hypertension, 69.5%; ischaemic heart disease, 80%; heart failure, 31.6%	AF 3–72 h between 24 h and 7 days after cardiac surgery Atrial flutter: *n* = 10	12	47% vs. 14%, *P* <0.001	75% converted after a single dose. Patients with flutter converted: 0/6 vs. 1/4
ACT III[121]	Double-blind, placebo-controlled, phase III	265 Vernakalant: *n* = 134 Placebo: *n* = 131	Hypertension, 43.9%; ischaemic heart disease, 11.8%; myocardial infarction, 6.5%; heart failure, 19.8%; diabetes, 8.4%	AF 3 h–45 days AF 3 h–7 days: *n* = 172 AF 8–45 days: *n* = 70 Atrial flutter: *n* = 23	8	51.2% vs. 3.6%, *P* <0.001	81.8% converted after a single dose. Conversion rates for patients with AF >7 days: 9% vs. 3%, *P* = 0.33; with flutter: 7.1% (1/14) vs. 0% (0/9)
ACT IV[123]	Open-label, phase IV	167	Hypertension, 44%; ischaemic heart disease, 8%; heart failure, 11%	AF 3 h–45 days (median, 38.5 h) AF 3 h–7 days: *n* = 170 AF 8–45 days: *n* = 69	14	50.9%	Conversion rates for patients with AF ≤48 h: 57.9%; with AF >7 days: 11.6%
AVRO[124]	Double-blind, active-controlled (i.v. amiodarone), phase III	232 Vernakalant: *n* = 116 Amiodarone: *n* = 116	Hypertension, 71.6%; ischaemic heart disease, 22.4%; myocardial infarction, 8.2%; heart failure, 19.8%, (NYHA I, 45.7%, NYHA II, 54.3%); valvular heart disease, 6.9%	AF 3–48 h (median, 17.7 h)	11	51.7% vs. 5.2%, *P* <0.0001	Reduction in symptoms at 2 h reported by 53.4% patients in the vernakalant group vs. 32.8% in the amiodarone group, *P* = 0.0012
Scene 2[129]	Double-blind, controlled, phase II/III	54 Vernakalant: *n* = 39 Placebo: *n* = 15	–	Atrial flutter 3 h–45 days (mean, 98–178 h)	–	3% vs. 0%, *P* = 0.45	–

ACT = Atria arrhythmia Conversion Trial; AF = atrial fibrillation; AVRO = A prospective, randomized, double-blind, Active-controlled, superiority study of Vernakalant vs. amiodarone in Recent Onset atrial fibrillation; CRAFT = Controlled Randomized Atrial Fibrillation Trial; NYHA = New York Heart Association.
In the dose-finding CRAFT study, two doses of vernakalant were used: 0.5 mg/kg 10-min bolus followed by 1 mg/kg bolus or 2 mg/kg 10-min bolus followed by 3 mg/kg bolus if AF was present 30 min after the first infusion. In the subsequent ACT I–IV, AVRO, and Scene 2 studies, a 10-min infusion of 3 mg/kg was given followed by a 2 mg/kg bolus if AF did not terminate within 15 min after the first infusion.
[a]The primary endpoint in the ACT I–IV and Scene 2 studies was the proportion of patients with AF of 3 h–7 days duration or atrial flutter, respectively, who converted to sinus rhythm within 90 min of drug initiation; the primary endpoint in the CRAFT study was the proportion of patients with AF of 3 h–72 h duration who converted to sinus rhythm during infusion or within 30 min after the last infusion; the primary endpoint in the AVRO study was the proportion of patients with AF of 3–48 h duration who converted to sinus rhythm within 90 min of drug initiation.
No reports of *torsades de pointes* within 24 hours of treatment; three cases of *torsades de pointes* at 32 h, 16, and 17 days, respectively, after vernakalant infusion (drug-unrelated). One other trial (ACT V) was terminated prematurely after one death associated with vernakalant infusion. No details are available.

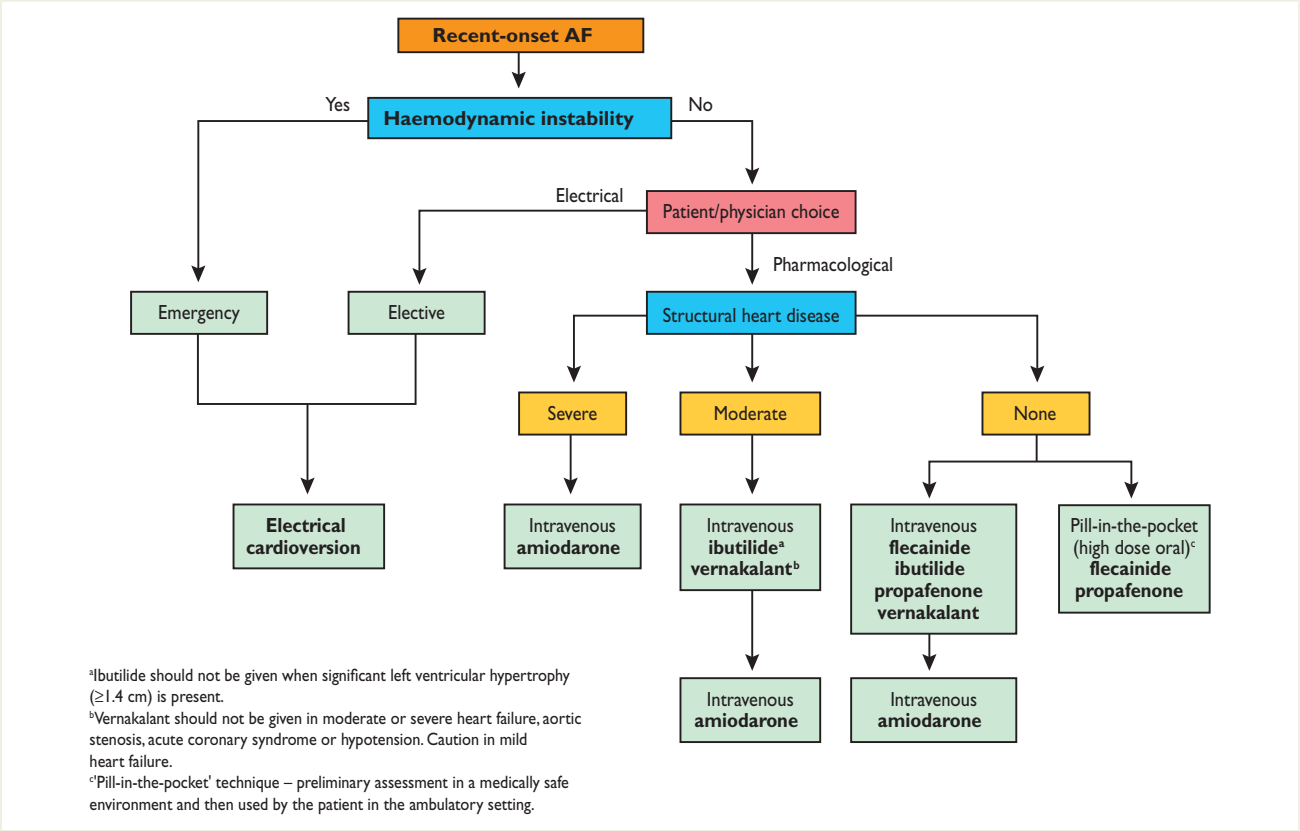


Figure 3 Indications for electrical and pharmacological cardioversion, and choice of antiarrhythmic drugs for pharmacological cardioversion in patients with recent-onset AF.

patients with NYHA I or II heart failure because of increased risk of hypotension. At present, vernakalant should be avoided in patients with reduced LVEF (≤35%) because of limited experience.

The integration of vernakalant into the general schema for pharmacological and electrical cardioversion is shown in *Figure 3*.

Key Points

- Vernakalant is effective in cardioversion of patients with AF ≤7 days or AF ≤3 days after cardiac surgery and provides a rapid antiarrhythmic effect with approximately 50% of patients converting within 90 minutes after the start of treatment and a median time to conversion of 8–14 minutes.
- Vernakalant is administered as a 10-minute infusion of 3 mg/kg and, if AF persists after 15 minutes, a second infusion of 2 mg/kg can be given.
- Vernakalant has a satisfactory safety profile in patients with minimal-to-moderate heart disease, including ischaemic heart disease, but should be used with caution in haemodynamically stable patients with NYHA class I and II heart failure, because of increased risk of hypotension and non-sustained ventricular arrhythmias in these patients.
- Vernakalant is contraindicated in patients with hypotension <100 mmHg, recent (<30 days) acute coronary syndrome, NYHA class III and IV heart failure, severe aortic stenosis, and QT interval prolongation (uncorrected QT >440 ms).

7. Oral antiarrhythmic drug therapy

7.1 Upstream therapy

In the last several years, a number of trials investigating upstream therapy for prevention of AF have been reported.[135,136] All of the recent placebo-controlled, double-blind trials with angiotensin-receptor blockers (ARBs) and the majority of trials with polyunsaturated fatty acids failed to show convincing results.[136–140] There is now very little reason to consider the use of such therapy for the prevention of AF recurrence in patients with little or no underlying heart disease. It may still be justified to co-prescribe an ARB or an angiotensin-converting enzyme inhibitor with an antiarrhythmic drug to increase the likelihood of maintaining sinus rhythm after cardioversion.[136]

7.2 Principles of antiarrhythmic drug therapy

Oral antiarrhythmic drug therapy can be considered for the treatment of recurrent (paroxysmal and persistent) AF. Several meta-analyses and systematic reviews have confirmed antiarrhythmic efficacy whilst raising signals of concern related to adverse events and mortality.[141–144] For this reason, it is important to emphasise that antiarrhythmic drug therapy should only be offered to control resistant symptoms due to recurrent AF and that a safety-

Table 6 Summary of clinical studies of dronedarone in AF

Study	Patients (n)	Patient characteristics	Dose of dronedarone	Placebo controlled	Primary endpoint	Follow-up (months)	Outcome	Comments
DAFNE[152]	199	Post cardioversion	400 mg b.i.d. 600 mg b.i.d. 800 mg b.i.d.	Yes	Time to first AF recurrence	6	Dronedarone 400 mg b.i.d. significantly prolonged median time to first AF recurrence vs. placebo: 60 vs. 5.3 days ($P = 0.026$); RRR 55% (95% CI 28–72%; $P = 0.001$)	Higher doses were ineffective and were associated with discontinuation rates of 7.6% and 22.6%; conversion rates were 5.8%, 8.2%, and 14.8% vs. 3.1% on placebo
EURIDIS[153]	615	Paroxysmal or persistent AF (post cardioversion)	400 mg b.i.d.	Yes	Time to first AF recurrence	12	Median time to first AF recurrence was 41 days on dronedarone vs. 96 days on placebo ($P = 0.01$)	Ventricular rates during AF recurrence were significantly lower on dronedarone
ADONIS[153]	630	Paroxysmal or persistent AF (post cardioversion)	400 mg b.i.d.	Yes	Time to first AF recurrence	12	Median time to first AF recurrence was 59 days on dronedarone vs. 158 days on placebo ($P = 0.002$)	Dronedarone reduced ventricular rates during AF recurrence vs. placebo
ERATO[154]	630	Permanent AF with ventricular rates >80 b.p.m. on rate-controlling therapy	400 mg b.i.d.	Yes	Mean 24-h ventricular rate at 2 weeks	6	Ventricular rates were 12 b.p.m. lower on dronedarone vs. placebo	Peak heart rates during exercise were 24 b.p.m. lower on dronedarone vs. placebo
ANDROMEDA[149]	67 (1000 planned)	Congestive heart failure; EF <0.35%	400 mg b.i.d.	Yes	All-cause mortality	Median, 2	Stopped early because of increased mortality in the dronedarone arm: total mortality $n = 25$ in dronedarone group, $n = 12$ in placebo group; cardiovascular mortality $n = 24$ in dronedarone group, 9 in placebo group	
ATHENA[148]	4628	Paroxysmal or persistent AF with risk factors	400 mg b.i.d.	Yes	All-cause mortality and hospitalizations for cardiac causes	21 ± 5	Dronedarone reduced the primary endpoint vs. placebo by 24% ($P < 0.001$)	CV hospitalizations, CV mortality and hospitalizations for AF and for ACS reduced
DIONYSOS[155]	504	Persistent AF	400 mg b.i.d.	Amiodarone	AF recurrence or premature study drug discontinuation	6	Amiodarone superior to dronedarone ($P < 0.001$)	
PALLAS[5]	3236 (10 800 planned)	Permanent AF with CV risk factors	400 mg b.i.d.	Yes	1. Co-primary = composite of stroke, MI, SE, CV death 2. Co-primary = composite of first unplanned CV hospitalization or death	Median, 3.5	Stopped early because of excess events in the dronedarone group: total mortality $n = 25$ in dronedarone group, $n = 13$ in placebo group; cardiovascular mortality $n = 21$ in dronedarone group, $n = 10$ in placebo group	Only 64 of planned 844 outcome events occurred

ACS = acute coronary syndrome; ADONIS = American-Australian-African trial with DronedarONe In atrial fibrillation or flutter for the maintenance of Sinus rhythm; AF = atrial fibrillation; ANDROMEDA = ANtiarrhythmic trial with DROnedarone in Moderate to severe heart failure Evaluating morbidity DecreASe; ATHENA = A placebo-controlled, doubleblind, parallel arm Trial to assess the efficacy of dronedarone 400 mg b.i.d. for the prevention of cardiovascular Hospitalization or death from any cause in patiENts with Atrial fibrillation/atrial flutter; b.i.d. = bis in die (twice daily); b.p.m. = beats per minute; CI = confidence interval; CV = cardiovascular; DAFNE = Dronedarone Atrial FibrillatioN study after Electrical cardioversion; DIONYSOS = Randomized Double blind trIal to evaluate efficacy and safety of drOnedarone (400 mg b.i.d.) vs. amiodaroNe (600 mg q.d. for 28 daYS, then 200 mg q.d. thereafter) for at least 6 mOnths for the maintenance of Sinus rhythm in patients with atrial fibrillation; EF = ejection fraction; ERATO = Efficacy and safety of dRonedArone for The cOntrol of ventricular rate during atrial fibrillation; EURIDIS = EURopean trial In atrial fibrillation or flutter patients receiving Dronedarone for the maIntenance of Sinus rhythm; MI = myocardial infarction; RRR = relative risk reduction; SE = systemic embolism.

first principle should prevail. In this regard, the finding that persistent episodes of AF can be reduced or delayed by short-term (4 weeks post cardioversion) antiarrhythmic therapy may allow shorter treatment durations.

Antiarrhythmic drug therapy for AF has generally been given as long-term therapy. A recently published trial, the Flec-SL (Flecainide Short Long) trial[145] randomized 635 patients (mean age 64 years, 64% male, 97% preserved left ventricular ejection fraction, 6% coronary artery disease, mean left atrial diameter 47 mm) to (i) no antiarrhythmic drug therapy (81 patients), (ii) long-term therapy (263 patients), or (iii) to short-term antiarrhythmic drug therapy limited to four weeks after cardioversion (261 patients). The trial tested the hypothesis that short-term therapy was non-inferior to long-term therapy. Patients were followed for six months by daily telemetric ECG recording for the primary outcome of persistent AF or death. The trial demonstrated that short-term therapy conveyed a slightly inferior—but still effective—antiarrhythmic action, estimated at 80% of the effect of long-term therapy six months after cardioversion. One prior trial compared episodic amiodarone treatment to continuous treatment, assessing a composite primary outcome containing efficacy and safety events. In that trial, episodic amiodarone was not nearly as effective as continuous amiodarone.[146] Based on that trial and on the pharmacokinetics of amiodarone, especially its long half-life, amiodarone does not seem to be suitable for short-term antiarrhythmic drug therapy.[147] Taken as a whole, the available information suggests that short-term antiarrhythmic drug therapy after cardioversion should not be the default type of treatment and should not be considered with amiodarone, but may be useful in patients who are either at high risk for drug-induced adverse effects or for patients with infrequent recurrences of AF.

7.3 Update on dronedarone

Dronedarone is a benzofuran derivative, structurally related to amiodarone, which has recently been approved for the treatment of paroxysmal or persistent AF. Dronedarone is a 'multichannel blocker' that inhibits sodium and potassium channels, shows a non-competitive antiadrenergic activity, and has calcium antagonist properties. The drug is more effective in maintaining sinus rhythm than placebo but inferior to amiodarone in that respect (*Table 6*). In the ATHENA (A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg b.i.d. for the prevention of cardiovascular Hospitalization or death from any cause in patiENts with Atrial fibrillation/atrial flutter),[148] a large outcome trial in patients at moderate risk for cardiovascular events, who had paroxysmal or persistent AF, dronedarone was associated with a significant reduction in cardiovascular outcome events, including the composite of unplanned cardiovascular hospitalizations and all-cause mortality. Other analyses demonstrated a significant reduction in arrhythmic mortality, cardiovascular mortality (including arrhythmic mortality), and stroke (*Table 6*).

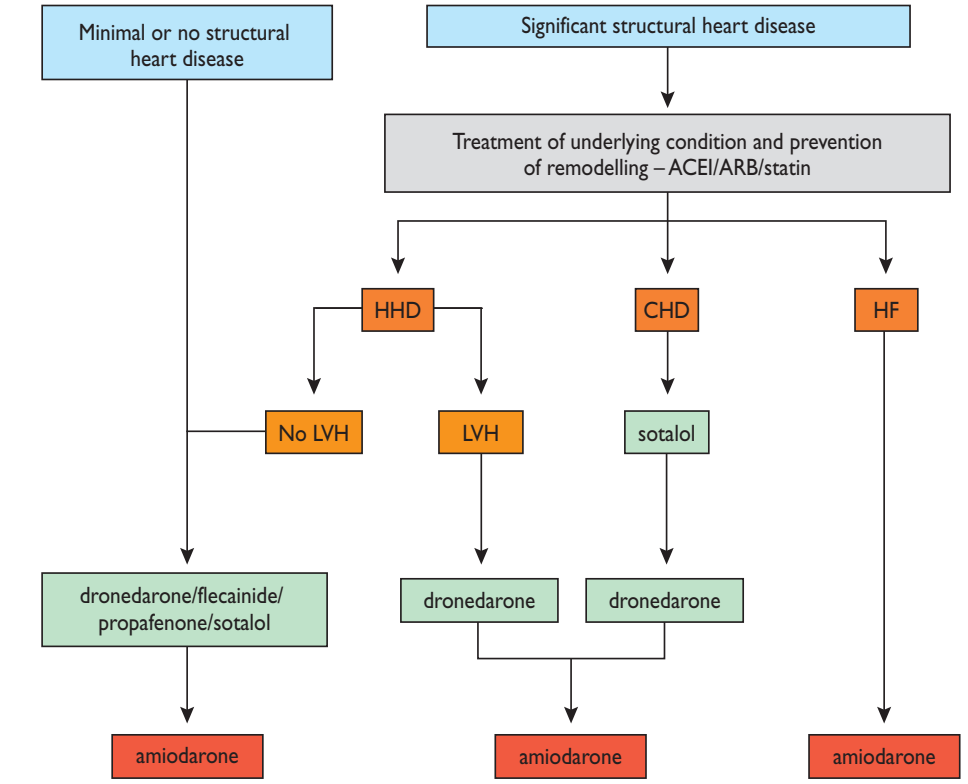
A similar but unexpected reduction in outcome events was also seen in a small population of patients that remained in AF throughout the trial. A large randomized trial to compare dronedarone against placebo in patients with permanent AF was therefore undertaken. The results were recently reported of the PALLAS (Permanent Atrial fibriLLAtion outcome Study) trial,[5] in which patients with permanent AF (defined for inclusion in the trial as >6 months) and cardiovascular risk factors were randomized to receive dronedarone 400 mg b.i.d. or matching placebo on top of best medical therapy (*Table 6*).

The trial planned to enrol 10 800 patients but was stopped prematurely by the Data Monitoring Committee after enrolment of 3236 patients, due to an increase in cardiovascular events—including cardiovascular mortality—in the dronedarone arm, compared with the control group. The first co-primary study outcome (composite of stroke, MI, systemic embolism, and cardiovascular death) was observed in 43 patients receiving dronedarone and 19 receiving placebo [hazard ratio (HR) 2.29; 95% CI, 1.34–3.94; $P = 0.002$]. The secondary co-primary study outcome (first unplanned cardiovascular hospitalization or death) occurred in 127 patients receiving dronedarone and 67 patients on placebo (HR 1.95, 95% CI 1.45–2.62; $P < 0.001$). There were 21 deaths from cardiovascular causes in the dronedarone group and 10 in the placebo group (HR 2.11; 95% CI 1.00–4.49; $P = 0.046$), including sudden death, probably from an arrhythmia in 13 patients and four patients, respectively (HR 3.26; 95% CI 1.06–10.00; $P = 0.03$). Stroke occurred in 23 patients in the dronedarone group and 10 in the placebo group (HR 2.32; 95% CI 1.11–4.88; $P = 0.02$). Hospitalization for heart failure occurred in 43 patients in the dronedarone group and 24 in the placebo group (HR 1.81; 95% CI 1.10–2.99; $P = 0.02$).

The reasons why the PALLAS results differed so much from ATHENA are not entirely clear. PALLAS patients had greater cardiovascular disease burden and obviously had permanent AF. There are no other antiarrhythmic drug trials in permanent AF; hence the results of PALLAS cannot be compared with other studies. From a methodological point of view, PALLAS had only collected 64 of the planned 844 primary study endpoints before it was terminated. Moreover, mortality in the placebo group of PALLAS was lower than that in the dronedarone group in ATHENA, despite more cardiovascular disease burden in the former study.

As a consequence of the PALLAS trial, patients with permanent AF should not be treated with dronedarone, particularly those with a significant cardiovascular disease burden. The drug can still be used in patients with paroxysmal or persistent AF after cardioversion. The revised European Summary of Product Characteristics for the drug advises that dronedarone management be supervised by a 'specialist', i.e. hospital or office-based staff familiar with the use of antiarrhythmic drugs, and it is clear that it should not be initiated in general or family practice. Subsequent monitoring should also include input from an appropriate specialist. Currently there is European regulatory approval for the use of dronedarone for the maintenance of sinus rhythm after cardioversion. Cardioversion may be spontaneous or induced and the patient may or may not be taking dronedarone at the time of cardioversion. A recurrence of AF that persists requires that the physician and patient choose whether to achieve sinus rhythm (e.g. by electrical cardioversion), in which case therapy with dronedarone may be maintained, or to leave the patient in AF, which *de facto* becomes 'permanent' in nature, in which case treatment with dronedarone should be stopped.

In the most recent EMA update on dronedarone, the drug was contraindicated in patients with unstable haemodynamic conditions, with a history of (or current) heart failure or left ventricular



ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; HHD = hypertensive heart disease; CHD = coronary heart disease; HF = heart failure; LVH = left ventricular hypertrophy, NYHA = New York Heart Association. Antiarrhythmic agents are listed in alphabetical order within each treatment box.

Figure 4 Choice of antiarrhythmic drug according to underlying pathology.

dysfunction. For patients in NYHA functional class III or IV, there is evidence from the ANDROMEDA (ANtiarrhythmic trial with DROnedarone in Moderate-to-severe congestive heart failure Evaluating morbidity DecreAse (ANDROMEDA) trial that these patients may derive harm from dronedarone therapy.[149] On the other hand, in patients with NYHA class I or II heart failure, or with HF-PEF, there is no clear scientific evidence for harmful effects of the drug. There was no clear signal from the subgroup analysis of PALLAS that the extent of heart failure (NYHA class) or degree of left ventricular systolic dysfunction (left ventricular ejection fraction) was relevant to any PALLAS endpoint, including heart failure hospitalizations or events. On the other hand, PALLAS recruited a high proportion of patients with a history of heart failure and various degrees of cardiac decompensation, except for NYHA class IV. Heart failure events in PALLAS were more common in patients with underlying coronary artery disease, but the statistical validity of this subgroup analysis is uncertain. Use of dronedarone as an antiarrhythmic agent in patients with recurrent AF and less severe heart failure (NYHA class I–II) is not appropriate unless there is no suitable alternative.

There was a signal in the PALLAS trial that dronedarone was associated with increased sudden mortality in patients on concomitant digoxin therapy; hence the combined use of these two drugs is discouraged. No proarrhythmia has been documented with the use of dronedarone in any trial and there are few or any reports of *torsades de pointes* or ventricular tachycardia in the post-approval adverse event reporting. Therefore, it seems unnecessary to remove this option for the treatment of hypertension with left ventricular hypertrophy, where the risk from antiarrhythmic drugs is thought to be related to *torsades de pointes*.

Recommendations for oral antiarrhythmic agents

Recommendations	Class[a]	Level[b]	Ref[c]
Dronedarone is recommended in patients with recurrent AF as a moderately effective antiarrhythmic agent for the maintenance of sinus rhythm.	I	A	142, 144, 153
Short-term (4 weeks) antiarrhythmic therapy after cardioversion may be considered in selected patients e.g. those at risk for therapy-associated complications.	IIb	B	145
Dronedarone is not recommended in patients with permanent AF.	III	B	5

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

Dronedarone has been associated with severe hepatotoxicity in a few instances. Hence, monitoring of liver function tests is advisable in patients on long-term dronedarone treatment. Since dronedarone is a P-glycoprotein inhibitor, it increases plasma concentrations of dabigatran; therefore concomitant use of the two drugs has to be avoided.

The current choice of antiarrhythmic drugs related to underlying pathophysiology is illustrated in *Figure 4*.

Key points

- Rhythm-control therapy, whether by antiarrhythmic drugs or by catheter ablation, is indicated to relieve symptoms associated with AF.
- Antiarrhythmic drugs should not be used for rate control in patients with permanent AF, unless appropriate rate control agents fail.
- In selected patients, limiting antiarrhythmic drug therapy to four weeks after cardioversion may help to improve safety.
- In a given patient, the choice of an antiarrhythmic drug should be driven by the perceived safety of the drug. This is more important than perceived efficacy.
- Dronedarone is appropriate for maintaining sinus rhythm in patients with paroxysmal or persistent AF.
- Dronedarone should not be given to patients with moderate or severe heart failure, and should be avoided in patients with less-severe heart failure, if appropriate alternatives exist.

8. Catheter ablation of atrial fibrillation

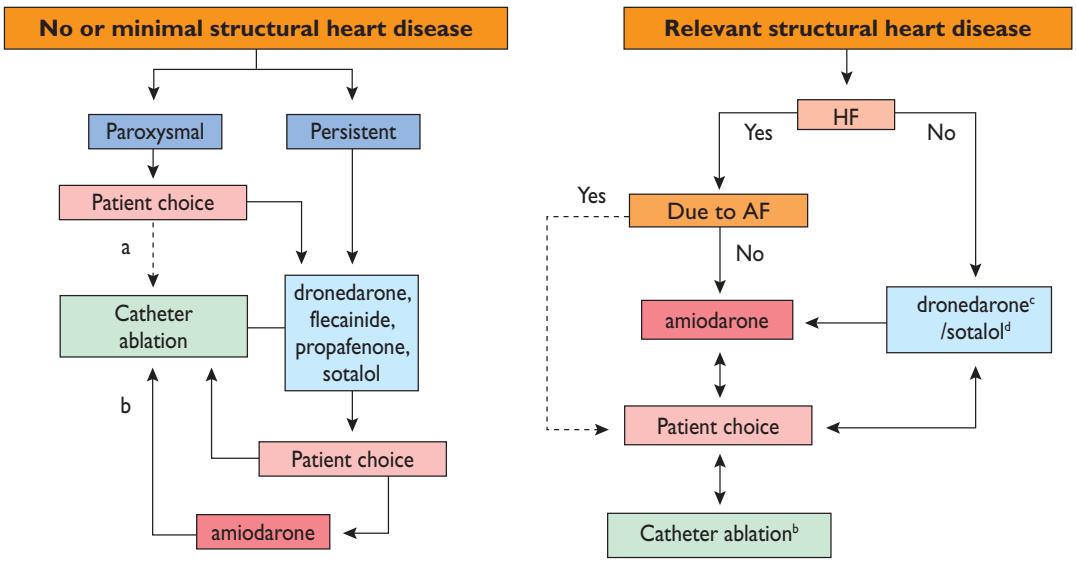
8.1 New evidence for catheter ablation

Since the publication of the ESC AF Guidelines in 2010, several new sets of data have become available. The randomized MANTRA-PAF (Medical ANtiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation)[156] trial compared catheter ablation of AF to antiarrhythmic drug therapy as a first-line rhythm control intervention in 294 patients. At 24-month follow-up, significantly more patients in the ablation group were free from any AF and symptomatic AF. Quality of life was significantly better in the ablation group at 12 and 24 months. However, total AF burden was not significantly different between both groups. Similar information has emerged from the results of the RAAFT II (Radiofrequency Ablation for Atrial Fibrillation Trial).[158]

These data further support the 2010 recommendation that it is reasonable to recommend catheter ablation as first-line therapy for AF rhythm control in selected patients, i.e. those with paroxysmal AF preferring interventional treatment with a low risk profile for procedure-associated complications.[158] Other reports also substantiate—albeit usually in single-centre, non-randomized data sets—that catheter ablation is more effective than antiarrhythmic drug therapy for the maintenance of sinus rhythm in patients with AF, mostly in patients without marked structural heart disease, with a low CHA_2DS_2-VASc score and with paroxysmal AF. All of these data support the statement in the guidelines that catheter ablation of AF is more effective than antiarrhythmic drug therapy in maintaining sinus rhythm.

The FAST (atrial Fibrillation catheter Ablation vs. Surgical ablation Treatment) trial compared the outcome of catheter ablation and surgical ablation in a relatively small patient population in a randomized study design. Rhythm outcome was better after surgical ablation. However, the complication rate after surgical ablation was significantly higher compared with catheter ablation.[159] Another recent trial highlighted that technical difficulties, especially with respect to transmural lines, apply to surgical approaches to AF ablation.[160]

While catheter ablation is more effective than antiarrhythmic drug therapy in maintaining sinus rhythm, the number of AF



AF = atrial fibrillation; HF = heart failure. [a]Usually pulmonary vein isolation is appropriate. [b]More extensive left atrial ablation may be needed. [c]Caution with coronary heart disease. [d]Not recommended with left ventricular hypertrophy. Heart failure due to AF = tachycardiomyopathy.

Figure 5 Antiarrhythmic drugs and/or left atrial ablation for rhythm control in AF.

recurrences during the long-term follow-up seems to be significant. Several recent reports demonstrate that late recurrences of AF are common, even when suitable patients with 'lone' or 'almost lone' AF undergo catheter ablation in experienced centres.[161–163] The most important predictor for such late recurrence appears to be early recurrence of AF after the ablation procedure,[164–167] indicating that persistence of early recurrence is much more frequent than true late recurrence. Nonetheless a low rate of recurrences, which may be due to progression of atrial damage, continues to add up to relevant, long-term recurrence rates.[168] Virtually all studies of catheter ablation of AF rely on isolation of the pulmonary vein as the target of the procedure. Whether full isolation of the pulmonary veins is needed to achieve the therapeutic effect is currently being studied.

While effective, catheter ablation of AF conveys a relevant risk of major complications.[169] This is illustrated by the recent publication of the pilot survey of AF ablation within the EURObservational Research Programme.[170] In this survey, which reported the outcome of more than 1000 ablation procedures carried out in high-volume centres throughout Europe, acute severe complication rates were 0.6% for stroke, 1.3% for tamponade, 1.3% for peripheral vascular complications, and around 2% for pericarditis. Similar complication rates have been reported from a large US ablation centre and, already available at the release of the 2010 ESC Guidelines, in the Worldwide AF Survey.[171,172] As all of this information comes from voluntary registries and has an inherent tendency to bias for experienced centres; true complication rates may be higher. In a very recent medical database analysis in 4156 patients who underwent their initial ablation between 2005 and 2008, the complication rate was 5% and the rate of all-cause hospitalization in the first year after catheter ablation was 38.5%.[173] Furthermore, several reports suggest that silent cerebral infarctions, detectable by cerebral magnetic resonance imaging, may be induced by catheter ablation procedures.[174–176]

According to several studies, the incidence of silent cerebral infarction varies significantly among different ablation technologies, ranging from approximately 4% to 35%.[174,175,177] The reasons for these differences are not fully understood, but seem to be augmented by the use of specific ablation technologies. Although the clinical significance of silent cerebral infarction is unclear, these risks need to be carefully considered when selecting an ablation tool or technology. There is a clear and unmet need to develop safer technologies for AF ablation.[177,174] Single-centre data series suggest that male patients with a low risk for stroke (CHA_2DS_2-VASc score of 0 or 1) are less likely to suffer from such complications than are older patients, women, and patients at increased risk for stroke.[171]

It will take some years before large outcome trials of ablation-based rhythm control therapy will have reported the primary results.[178,179] Until then, risk associated with AF ablation needs to be carefully weighed against the individual symptomatic benefit.

8.2 Catheter ablation in patients with heart failure

AF with concomitant HF-REF remains a challenging combination when rhythm control therapy is needed. The revised recommendations for antiarrhythmic drug therapy leave amiodarone as the only available antiarrhythmic agent in this setting (*Figure 4*). Many patients are rendered asymptomatic or mildly symptomatic (EHRA I or II) by such therapy, especially when heart failure and heart rate are well controlled. In patients who suffer from symptomatic AF recurrences on amiodarone therapy, catheter ablation remains as the sole choice for escalated rhythm control therapy. The main principles of rhythm control therapy apply to this group of patients as well, specifically that rhythm control therapy is indicated to improve AF-related symptoms (EHRA score II–IV), and that OAC therapy should be maintained, as the arrhythmia is likely to recur. It should be emphasized that the likelihood of maintaining sinus rhythm after catheter ablation is lower and the procedure-related risks may be higher in heart failure patients. In addition, correct assessment of AF-related symptoms may be more difficult with overlapping heart failure symptoms, emphasizing the need for an individual and informed decision for catheter ablation in patients with heart failure. In selected patients suffering from heart failure and treated in highly experienced centres, catheter ablation of AF may confer an improvement in left ventricular function. These recommendations are summarized in *Figure 5*.

8.3 Anticoagulant therapy peri-ablation

There is consensus that OAC is helpful to prevent thromboembolic complications around ablation procedures.[180] This applies both to patients who have an indication for long-term OAC therapy and to patients without stroke risk factors, highlighting the fact that ablation somehow increases stroke risk around the time of the procedure.

Since the 2010 Guidelines on AF, there have been several reports to suggest that catheter ablation of AF may be performed with fewer complications when OAC therapy is continued (usually VKA, with INR 2.0-3.0),[181–184] including one report on the outcome of ablation-induced cardiac tamponade in patients with and without continuous anticoagulation during the procedure.[185] These reports conclude that continuous OAC is safe during ablation procedures, in line with previous recommendations for coronary revascularization procedures.[95,98] Continuation of OAC therapy is also recommended in the recent HRS/EHRA/APHRS consensus statement on AF ablation, as an alternative to a bridging approach with heparin, for patients on OAC with VKA prior to catheter ablation.[186] Experience with NOACs is limited. Initial reports, albeit using non-standardized protocols for the use of NOACs peri-ablation, suggest that the stroke risk may be slightly increased, which is counter-intuitive in light of the effects of NOAC in prevention of stroke in the general AF setting.[95] While the exact relative risk of uninterrupted OAC with NOACs peri-ablation is not known, there is a known risk for bleeding events when switching or bridging of anticoagulants is applied.[52,186] For patients taken off OAC before the ablation procedure, initiation of anticoagulation with NOAC shortly after the ablation procedure seems to be reasonable. This approach would also avoid any bridging with heparin.

At present, for patients on OAC with VKA, we therefore recommend undertaking catheter ablation of AF on continuous anticoagulation. Anticoagulant therapy should be kept at low therapeutic levels (such as an INR of 2 to 2.5) throughout ablation.

Such a regimen may help to reduce peri-procedural strokes, possibly including silent cerebral infarcts. As already recommended in the 2010 Guidelines,[1] continuation of long-term OAC therapy post-ablation is recommended in all patients with a CHA_2DS_2-VASc score of ≥ 2, irrespective of apparent procedural success.

8.4 Safety first

There is much evolving technology that may help to reduce the risk of peri-procedural complications during AF ablation.[174,187] As stated before, improving safety of catheter ablation should be a primary goal in the further development of this therapy.[178] However, pathophysiological considerations suggest that rhythm control therapy may be best performed early after the initial diagnosis, as this time period may provide a 'window of opportunity' for effective rhythm control therapy[178,187,188]. This concept clearly requires testing in controlled trials.

8.5 New considerations for AF catheter ablation

In the 2010 ESC Guidelines, catheter ablation of symptomatic paroxysmal AF after failed antiarrhythmic drug therapy was graded as a class IIa LoE A indication. Considering the results of randomized studies on catheter ablation of AF vs. antiarrhythmic drug therapy and recent publications from randomized and non-randomized trials,[156,158,189,190] it is reasonable to upgrade this recommendation to class I, provided that the ablation is carried out by skilled operators. This is in line with the 2011 focused update from the ACCF/AHA and HRS, and the 2012 expert consensus statement on catheter and surgical ablation, co-authored by the EHRA.[6,186] For patients with highly symptomatic paroxysmal AF with a low-risk profile for catheter ablation, primary catheter ablation should be considered.[156,190,191]

These recommendations are restricted to: (i) highly experienced centres/investigators; (ii) appropriate patient selection; (iii) careful evaluation of treatment alternatives and (iv) patient preference. For patients with drug-refractory persistent and long-standing persistent AF, there is no change in recommendations. Currently there is no evidence to recommend catheter ablation of AF in asymptomatic patients.

Key points

- Catheter ablation is recommended as an alternative to antiarrhythmic drug therapy for patients with symptomatic recurrent paroxysmal AF on antiarrhythmic drug therapy, provided the procedure is performed by an experienced operator.
- Continuation of oral VKA therapy can be considered throughout the ablation procedure but robust data for NOACs are lacking.
- In selected patients with paroxysmal AF and no structural heart disease left atrial ablation is reasonable as first-line therapy.

Recommendations for left atrial ablation

Recommendations	Class[a]	Level[b]	Ref[c]
Catheter ablation of symptomatic paroxysmal AF is recommended 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	192, 193
Catheter ablation of AF should target isolation of the pulmonary veins.	IIa	A	170, 172, 192, 194
Catheter ablation of AF should be considered as first-line therapy in selected patients with symptomatic paroxysmal AF as an alternative to antiarrhythmic drug therapy, considering patient choice, benefit, and risk.	IIa	B	156–158
When catheter ablation of AF is planned, continuation of oral anticoagulation with a VKA should be considered during the procedure, maintaining an INR close to 2.0.	IIa	B	170, 181–184
When AF recurs within the first 6 weeks after catheter ablation, a watch-and-wait rhythm control therapy should be considered.	IIa	B	195

AF = atrial fibrillation; INR = international normalized ratio.
[a]Class of recommendation.
[b]Level of evidence.
[c]References.

9. Concluding remarks

This document is an update to the 2010 ESC Guidelines on the management of AF. It is not intended as a comprehensive new guideline and there are many other areas where small revisions to the 2010 Guidelines might be useful. These must await a further update or new guideline. Where relevant, flow charts and tables have been upgraded. This focused update will stand alone as a publication and will not be fully incorporated into a single publication together with the original Guidelines. A Pocket Guideline will be issued with all the recommendations, flow charts, and tables fully integrated.

The CME text '2012 Focused update of the ESC Guidelines on the management of a trial fibrillation' is accredited by the European Board for Accreditation in Cardiology (EBAC). EBAC works according to the quality standards of the European Accreditation Council for Continuing Medical Education (EACCME), which is an institution of the European Union of Medical Specialists (UEMS). In compliance with EBAC/EACCME Guidelines, all authors participating in this programme have disclosed any potential conflicts of interest that might cause a bias in the article. The Organizing Committee is responsible for ensuring that all potential conflicts of interest relevant to the programme are declared to the participants prior to the CME activities.

CME questions for this article are available at: European Heart Journal http://www.oxforde-learning.com/eurheartj and European Society of Cardiology http://www.escardio.org/guidelines.

References

1. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH; ESC Committee for Practice Guidelines, Vahanian A, Auricchio A, Bax J, Ceconi C, Dean V, Filippatos G, Funck-Brentano C, Hobbs R, Kearney P, McDonagh T, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Vardas PE, Widimsky. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Europace* 2010;**12**:1360–1420.
2. Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, Flaker G, Avezum A, Hohnloser SH, Diaz R, Talajic M, Zhu J, Pais P, Budaj A, Parkhomenko A, Jansky P, Commerford P, Tan RS, Sim KH, Lewis BS, Van Mieghem W, Lip GY, Kim JH, Lanas-Zanetti F, Gonzalez-Hermosillo A, Dans AL, Munawar M, O'Donnell M, Lawrence J, Lewis G, Afzal R, Yusuf S; AVERROES Steering Committee and Investigators. Apixaban in patients with atrial fibrillation. *N Engl J Med* 2011;**364**:806–817.
3. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM; ROCKET AF Investigators. Rivaroxaban vs. warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;**365**:883–891.
4. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L; ARISTOTLE Committees and Investigators. Apixaban vs. warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;**365**:981–992.
5. Connolly SJ, Camm AJ, Halperin JL, Joyner C, Alings M, Amerena J, Atar D, Avezum Á, Blomström P, Borggrefe M, Budaj A, Chen SA, Ching CK, Commerford P, Dans A, Davy JM, Delacrétaz E, Di Pasquale G, Diaz R, Dorian P, Flaker G, Golitsyn S, Gonzalez-Hermosillo A, Granger CB, Heidbüchel H, Kautzner J, Kim JS, Lanas F, Lewis BS, Merino JL, Morillo C, Murin J, Narasimhan C, Paolasso E, Parkhomenko A, Peters NS, Sim KH, Stiles MK, Tanomsup S, Toivonen L, Tomcsányi J, Torp-Pedersen C, Tse HF, Vardas P, Vinereanu D, Xavier D, Zhu J, Zhu JR, Baret-Cormel L, Weinling E, Staiger C, Yusuf S, Chrolavicius S, Afzal R, Hohnloser SH; PALLAS Investigators. Dronedarone in high-risk permanent atrial fibrillation. *N Engl J Med* 2011;**365**:2268–2276.
6. Wann LS, Curtis AB, January CT, Ellenbogen KA, Lowe JE, Estes NA 3rd, Page RL, Ezekowitz MD, Slotwiner DJ, Jackman WM, Stevenson WG, Tracy CM; 2011 Writing Group Members, Fuster V, Rydén LE, Cannom DS, Le Heuzey JY, Crijns HJ, Lowe JE, Curtis AB, Olsson SB, Ellenbogen KA, Prystowsky EN, Halperin JL, Tamargo JL, Kay GN, Wann LS; 2006 Writing Committee Members, Jacobs AK, Anderson JL, Albert N, Hochman JS, Buller CE, Kushner FG, Creager MA, Ohman EM, Ettinger SM, Stevenson WG, Guyton RA, Tarkington LG, Halperin JL, Yancy CW; ACCF/AHA Task Force Members. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (Updating the 2006 Guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2011;**123**:104–123.
7. Wann LS, Curtis AB, Ellenbogen KA, Estes NA 3rd, Ezekowitz MD, Jackman WM, January CT, Lowe JE, Page RL, Slotwiner DJ, Stevenson WG, Tracy CM, Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Kay GN, Le Heuzey JY, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann LS, Jacobs AK, Anderson JL, Albert N, Creager MA, Ettinger SM, Guyton RA, Halperin JL, Hochman JS, Kushner FG, Ohman EM, Stevenson WG, Yancy CW; American College of Cardiology Foundation/American Heart Association Task Force. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (update on dabigatran). A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2011;**123**:1144–1150.
8. You JJ, Singer DE, Howard PA, Lane DA, Eckman MH, Fang MC, Hylek EM, Schulman S, Go AS, Hughes M, Spencer FA, Manning WJ, Halperin JL, Lip GY; American College of Chest Physicians. Antithrombotic therapy for atrial fibrillation: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;**141**:e531S–e575S.
9. Skanes AC, Healey JS, Cairns JA, Dorian P, Gillis AM, McMurtry MS, Mitchell LB, Verma A, Nattel S; Canadian Cardiovascular Society Atrial Fibrillation Guidelines Committee. Focused 2012 Update of the Canadian Cardiovascular Society Atrial fibrillation Guidelines: recommendations for stroke prevention and rate/rhythm control. *Can J Cardiol* 2012;**28**:125–136.
10. Lip GY, Tse HF, Lane DA. Atrial fibrillation. *Lancet* 2012;**379**:648–61.
11. Kirchhof P, Lip GY, Van Gelder IC, Bax J, Hylek E, Kaab S, Schotten U, Wegscheider K, Boriani G, Brandes A, Ezekowitz M, Diener H, Haegeli L, Heidbuchel H, Lane D, Mont L, Willems S, Dorian P, Aunes-Jansson M, Blomstrom-Lundqvist C, Borentain M, Breitenstein S, Brueckmann M, Cater N, Clemens A, Dobrev D, Dubner S, Edvardsson NG, Friberg L, Goette A, Gulizia M, Hatala R, Horwood J, Szumowski L, Kappenberger L, Kautzner J, Leute A, Lobban T, Meyer R, Millerhagen J, Morgan J, Muenzel F, Nabauer M, Baertels C, Oeff M, Paar D, Polifka J, Ravens U, Rosin L, Stegink W, Steinbeck G, Vardas P, Vincent A, Walter M, Breithardt G, Camm AJ. Comprehensive risk reduction in patients with atrial fibrillation: Emerging diagnostic and therapeutic options. Executive summary of the report from the 3rd AFNET/EHRA consensus conference. *Europace* 2012;**14**:8–27.
12. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, Lau CP, Fain E, Yang S, Bailleul C, Morillo CA, Carlson M, Themeles E, Kaufman ES, Hohnloser SH; ASSERT Investigators. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med* 2012;**366**:120–129.
13. Binici Z, Intzilakis T, Nielsen OW, Kober L, Sajadieh A. Excessive supraventricular ectopic activity and increased risk of atrial fibrillation and stroke. *Circulation* 2010;**121**:1904–1911.
14. Fitzmaurice DA, Hobbs FD, Jowett S, Mant J, Murray ET, Holder R, Raftery JP, Bryan S, Davies M, Lip GY, Allan TF. Screening vs. routine practice in detection of atrial fibrillation in patients aged 65 or over: cluster randomised controlled trial. *Br Med J* 2007;**335**:383.
15. Hobbs FD, Fitzmaurice DA, Mant J, Murray E, Jowett S, Bryan S, Raferty J, Davies M, Lip G. A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) vs. routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study. *Health Technol Assess* 2005;**9**:iii–iv, ix–x, 1–74.
16. Lip G. What is the most effective and safest delivery of thromboprophylaxis in atrial fibrillation? *J R Coll Physicians Edinb* 2012;**42**(Suppl 18):35–44.
17. Lip GY. Stroke in atrial fibrillation: epidemiology and thromboprophylaxis. *J Thromb Haemost* 2011;**9** Suppl 1:344–351.
18. Wilke T, Groth A, Mueller S, Pfannkuche M, Verheyen F, Linder R, Maywald U, Kohlmann T, Feng YS, Breithardt G, Bauersachs R. Oral anticoagulation use by patients with atrial fibrillation in Germany. Adherence to guidelines, causes of anticoagulation under-use and its clinical outcomes, based on claims-data of 183,448 patients. *Thromb Haemost* 2012;**107**:1053–1065.
19. K Kirchhof P, Nabauer M, Gerth A, Limbourg T, Lewalter T, Goette A, Wegscheider K, Treszl A, Meinertz T, Oeff M, Ravens U, Breithardt G, Steinbeck G; AFNET registry investigators. Impact of the type of centre on management of AF patients: surprising evidence for differences in antithrombotic therapy decisions. *Thromb Haemost* 2011;**105**:1010–1023.
20. Lip GY. The role of aspirin for stroke prevention in atrial fibrillation. *Nat Rev Cardiol* 2011;**8**:602–606.
21. Olesen JB, Lip GY, Lindhardsen J, Lane DA, Ahlehoff O, Hansen ML, Raunsø J, Tolstrup JS, Hansen PR, Gislason GH, Torp-Pedersen C. Risks of thromboembolism and bleeding with thromboprophylaxis in patients with atrial fibrillation: a net clinical benefit analysis using a 'real world' nationwide cohort study. *Thromb Haemost* 2011;**106**:739–749.
22. Ogilvie IM, Welner SA, Cowell W, Lip GY. Ischaemic stroke and bleeding rates in 'real-world' atrial fibrillation patients. *Thromb Haemost* 2011;**106**:34–44.
23. Mant J, Hobbs FD, Fletcher K, Roalfe A, Fitzmaurice D, Lip GY, Murray E; BAFTA investigators; Midland Research Practices Network (MidReC). Warfarin vs.

aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet* 2007;**370**:493–503.
24. Rash A, Downes T, Portner R, Yeo WW, Morgan N, Channer KS. A randomised controlled trial of warfarin vs. aspirin for stroke prevention in octogenarians with atrial fibrillation (WASPO). *Age Ageing* 2007;**36**:151–156.
25. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation Cohort study. *Eur Heart J* 2012;**33**:1500–1510.
26. Connolly SJ, Pogue J, Hart RG, Hohnloser SH, Pfeffer M, Chrolavicius S, Yusuf S. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med* 2009;**360**:2066–2078.
27. Seshasai SR, Wijesuriya S, Sivakumaran R, Nethercott S, Erqou S, Sattar N, Ray KK. Effect of aspirin on vascular and nonvascular outcomes: meta-analysis of randomized controlled trials. *Arch Intern Med* 2012;**172**:209–216.
28. De Caterina R, Husted S, Wallentin L, Andreotti F, Arnesen H, Bachmann F, Baigent C, Huber K, Jespersen J, Kristensen SD, Lip GY, Morais J, Rasmussen LH, Siegbahn A, Verheugt FW, Weitz JI; Coordinating Committee. New oral anticoagulants in atrial fibrillation and acute coronary syndromes: ESC Working Group on Thrombosis—Task Force on Anticoagulants in Heart Disease position paper. *J Am Coll Cardiol* 2012;**59**:1413–1425.
29. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001;**285**:2864–2870.
30. Karthikeyan G, Eikelboom JW. The CHADS2 score for stroke risk stratification in atrial fibrillation—friend or foe? *Thromb Haemost* 2010;**104**:45–48.
31. Keogh C, Wallace E, Dillon C, Dimitrov BD, Fahey T. Validation of the CHADS2 clinical prediction rule to predict ischaemic stroke. A systematic review and meta-analysis. *Thromb Haemost* 2011;**106**:528–538.
32. Lin LY, Lee CH, Yu CC, Tsai CT, Lai LP, Hwang JJ, Chen PC, Lin JL. Risk factors and incidence of ischemic stroke in Taiwanese with nonvalvular atrial fibrillation—a nationwide database analysis. *Atherosclerosis* 2011;**217**:292–295.
33. Olesen JB, Fauchier L, Lane DA, Taillandier S, Lip GY. Risk factors for stroke and thromboembolism in relation to age among patients with atrial fibrillation: the Loire Valley Atrial Fibrillation Project. *Chest* 2012;**141**:147–153.
34. Olesen JB, Lip GY, Lane DA, Køber L, Hansen ML, Karasoy D, Hansen CM, Gislason GH, Torp-Pedersen C. Vascular disease and stroke risk in atrial fibrillation: a nationwide cohort study. *Am J Med* 2012;**125**:826.e13–23.
35. van Walraven C, Hart RG, Connolly S, Austin PC, Mant J, Hobbs FD, Koudstaal PJ, Petersen P, Perez-Gomez F, Knottnerus JA, Boode B, Ezekowitz MD, Singer DE. Effect of age on stroke prevention therapy in patients with atrial fibrillation. *Stroke* 2009;**40**:1410–1416.
36. Olesen JB, Lip GY, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, Selmer C, Ahlehoff O, Olsen AM, Gislason GH, Torp-Pedersen C. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. *Br Med J* 2011;**342**.
37. Potpara TS, Polovina MM, Licina MM, Marinkovic JM, Prostran MS, Lip GY. Reliable identification of 'truly low' thromboembolic risk in patients initially diagnosed with 'lone' atrial fibrillation: the Belgrade Atrial Fibrillation Study. *Circ Arrhythm Electrophysiol* 2012;**5**:319–326.
38. Olesen JB, Torp-Pedersen C, Hansen ML, Lip G. The value of the CHA_2DS_2-VASc score for refining stroke risk stratification in patients with atrial fibrillation with a $CHADS_2$ score 0–1: a nationwide cohort study. *Thromb Haemost* 2012;**107**:1172–1179.
39. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on Atrial Fibrillation. *Chest* 2010;**137**:263–272.
40. Stroke Risk in Atrial Fibrillation Working Group. Independent predictors of stroke in patients with atrial fibrillation: a systematic review. *Neurology* 2007;**69**:546–554.
41. Hughes M, Lip GY. Stroke and thromboembolism in atrial fibrillation: a systematic review of stroke risk factors, risk stratification schema and cost effectiveness data. *Thromb Haemost* 2008;**99**:295–304.
42. AF-Investigators. Echocardiographic predictors of stroke in patients with atrial fibrillation: a prospective study of 1066 patients from 3 clinical trials. *Arch Intern Med* 1998;**158**:1316–1320.
43. Banerjee A, Taillandier S, Olesen JB, Lane DA, Lallemand B, Lip GY, Fauchier L. Ejection fraction and outcomes in patients with atrial fibrillation and heart failure: the Loire Valley Atrial Fibrillation Project. *Eur J Heart Fail* 2012;**14**:295–301.
44. Friberg L, Benson L, Rosenqvist M, Lip GY. Assessment of female sex as a risk factor in atrial fibrillation in Sweden: nationwide retrospective cohort study. *BMJ* 2012;**344**:e3522.
45. Avgil Tsadok M, Jackevicius CA, Rahme E, Humphries KH, Behlouli H, Pilote L. Sex differences in stroke risk among older patients with recently diagnosed atrial fibrillation. *JAMA* 2012;**307**:1952–1958.
46. Van Staa TP, Setakis E, Di Tanna GL, Lane DA, Lip GY. A comparison of risk stratification schemes for stroke in 79,884 atrial fibrillation patients in general practice. *J Thromb Haemost* 2011;**9**:39–48.
47. Abu-Assi E, Otero-Raviña F, Allut Vidal G, Coutado Méndez A, Vaamonde Mosquera L, Sánchez Loureiro M, Caneda Villar MC, Fernández Villaverde JM, Maestro Saavedra FJ, González-Juanatey JR; on behalf of Grupo Barbanza researchers. Comparison of the reliability and validity of four contemporary risk stratification schemes to predict thromboembolism in non-anticoagulated patients with atrial fibrillation. *Int J Cardiol.* Published online ahead of print 19 November 2011.
48. Boriani G, Botto GL, Padeletti L, Santini M, Capucci A, Gulizia M, Ricci R, Biffi M, De Santo T, Corbucci G, Lip GY; Italian AT-500 Registry Investigators. Improving stroke risk stratification using the $CHADS_2$ and CHA_2DS_2-VASc risk scores in patients with paroxysmal atrial fibrillation by continuous arrhythmia burden monitoring. *Stroke* 2011;**42**:1768–1770.
49. Chao TF, Lin YJ, Tsao HM, Tsai CF, Lin WS, Chang SL, Lo LW, Hu YF, Tuan TC, Suenari K, Li CH, Hartono B, Chang HY, Ambrose K, Wu TJ, Chen SA. CHADS(2) and CHA(2)DS(2)-VASc scores in the prediction of clinical outcomes in patients with atrial fibrillation after catheter ablation. *J Am Coll Cardiol* 2011;**58**:2380–2385.
50. Marinigh R, Lane DA, Lip GY. Severe renal impairment and stroke prevention in atrial fibrillation: implications for thromboprophylaxis and bleeding risk. *J Am Coll Cardiol* 2011;**57**:1339–1348.
51. Connolly SJ, Eikelboom JW, Ng J, Hirsh J, Yusuf S, Pogue J, de Caterina R, Hohnloser S, Hart RG; ACTIVE (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events) Steering Committee and Investigators. Net clinical benefit of adding clopidogrel to aspirin therapy in patients with atrial fibrillation for whom vitamin K antagonists are unsuitable. *Ann Intern Med* 2011;**155**:579–586.
52. Lip GY, Andreotti F, Fauchier L, Huber K, Hylek E, Knight E, Lane DA, Levi M, Marin F, Palareti G, Kirchhof. Bleeding risk assessment, management in atrial fibrillation patients. Executive Summary of a Position Document from the European Heart Rhythm Association [EHRA], endorsed by the European Society of Cardiology [ESC] Working Group on Thrombosis. *Europace* 2011;**13**:723–746.
53. Gage BF, Yan Y, Milligan PE, Waterman AD, Culverhouse R, Rich MW, Radford MJ. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). *Am Heart J* 2006;**151**:713–719.
54. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010;**138**:1093–1100.
55. Fang MC, Go AS, Chang Y, Borowsky LH, Pomernacki NK, Udaltsova N, DE. A new risk scheme to predict warfarin-associated hemorrhage: The ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study. *J Am Coll Cardiol* 2011;**58**:395–401.
56. Cairns JA, Connolly S, McMurtry S, Stephenson M, Talajic M. Canadian Cardiovascular Society atrial fibrillation Guidelines 2010: prevention of stroke and systemic thromboembolism in atrial fibrillation and flutter. *Can J Cardiol* 2011;**27**:74–90.
57. Roldan V, Marin F, Manzaro-Fernandez S, Gallego P, Valdes M, Vincente V, Lip GY. Predictive value of the HAS-BLED and ATRIA bleeding scores for the risk of serious bleeding in a 'real world' anticoagulated atrial fibrillation population. *Chest.* Published online ahead of print 21 June 2012. doi:10.1378/chest.12-0608.
58. Apostolakis S, Lane DA, Guo Y, Buller HR, Lip GYH. Performance of the $HEMORR_2HAGES$, ATRIA and HAS-BLED bleeding risk prediction scores in anticoagulated patients with atrial fibrillation: The AMADEUS study. *J Am Coll Cardiol* 2012;**60**:861–867.
59. Lip GY, Frison L, Halperin JL, Lane DA. Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: the HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol concomitantly) score. *J Am Coll Cardiol* 2011;**57**:173–180.
60. Olesen JB, Lip GY, Hansen PR, Lindhardsen J, Ahlehoff O, Andersson C, Weeke P, Hansen ML, Gislason GH, Torp-Pedersen C. Bleeding risk in 'real world' patients with atrial fibrillation: comparison of two established bleeding prediction schemes in a nationwide cohort. *J Thromb Haemost* 2011;**9**:1460–1467.
61. Gallego P, Roldán V, Torregrosa JM, Gálvez J, Valdés M, Vicente V, Marín F, Lip GY. Relation of the HAS-BLED bleeding risk score to major bleeding,

cardiovascular events and mortality in anticoagulated patients with atrial fibrillation. *Circ Arrhythm Electrophysiol* 2012;**5**:312–318.
62. Lane DA, Lip GYH. Use of the CHA_2DS_2-VASc and HAS-BLED scores to aid decision making for thromboprophylaxis in non-valvular atrial fibrillation. *Circulation* 2012;**126**:860–865.
63. Friberg L, Rosenqvist M, Lip G. Net clinical benefit of warfarin in patients with atrial fibrillation: A report from the Swedish Atrial Fibrillation cohort study. *Circulation* 2012;**125**:2298–2307.
64. Connolly SJ, Pogue J, Eikelboom J, Flaker G, Commerford P, Franzosi MG, Healey JS, Yusuf S; ACTIVE W Investigators. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. *Circulation* 2008;**118**:2029–2037.
65. Gallagher AM, Setakis E, Plumb JM, Clemens A, van Staa TP. Risks of stroke and mortality associated with suboptimal anticoagulation in atrial fibrillation patients. *Thromb Haemost* 2011;**106**:968–977.
66. Wallentin L, Yusuf S, Ezekowitz MD, Alings M, Flather M, Franzosi MG, Pais P, Dans A, Eikelboom J, Oldgren J, Pogue J, Reilly PA, Yang S, Connolly SJ; RE-LY investigators. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. *Lancet* 2010;**376**:975–983.
67. Morgan CL, McEwan P, Tukiendorf A, Robinson PA, Clemens A, Plumb JM. Warfarin treatment in patients with atrial fibrillation: observing outcomes associated with varying levels of INR control. *Thromb Res* 2009;**124**:37–41.
68. Ahrens I, Lip GY, Peter K. New oral anticoagulant drugs in cardiovascular disease. *Thromb Haemost* 2010;**104**:49–60.
69. Ruff CT, Giugliano RP, Antman EM, Crugnale SE, Bocanegra T, Mercuri M, Hanyok J, Patel I, Shi M, Salazar D, McCabe CH, Braunwald E. Evaluation of the novel factor Xa inhibitor edoxaban compared with warfarin in patients with atrial fibrillation: design and rationale for the Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation-Thrombolysis In Myocardial Infarction study 48 (ENGAGE AF-TIMI 48). *Am Heart J* 2010;**160**:635–641.
70. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; RE-LY Steering Committee and Investigators. Dabigatran vs. warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;**361**:1139–1151.
71. Connolly SJ, Ezekowitz MD, Yusuf S, Reilly PA, Wallentin L. Newly identified events in the RE-LY trial. *N Engl J Med* 2010;**363**:1875–1876.
72. Hohnloser SH, Oldgren J, Yang S, Wallentin L, Ezekowitz M, Reilly P, Eikelboom J, Brueckmann M, Yusuf S, Connolly SJ. Myocardial ischemic events in patients with atrial fibrillation treated with dabigatran or warfarin in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial. *Circulation* 2012;**125**:669–676.
73. Oldgren J, Alings M, Darius H, Diener HC, Eikelboom J, Ezekowitz MD, Kamensky G, Reilly PA, Yang S, Yusuf S, Wallentin L, Connolly SJ; RE-LY Investigators. Risks for stroke, bleeding, and death in patients with atrial fibrillation receiving dabigatran or warfarin in relation to the $CHADS_2$ score: a subgroup analysis of the RE-LY trial. *Ann Intern Med* 2011;**155**:660–667.
74. Ezekowitz MD, Wallentin L, Connolly SJ, Parekh A, Chernick MR, Pogue J, Aikens TH, Yang S, Reilly PA, Lip GY, Yusuf S; RE-LY Steering Committee and Investigators. Dabigatran and warfarin in vitamin K antagonist-naive and -experienced cohorts with atrial fibrillation. *Circulation* 2010;**122**:2246–2253.
75. Uchino K, Hernandez AV. Dabigatran association with higher risk of acute coronary events: meta-analysis of noninferiority randomized controlled trials. *Arch Intern Med* 2012;**172**:397–402.
76. Lip GY, Lane DA. Does warfarin for stroke thromboprophylaxis protect against MI in atrial fibrillation patients? *Am J Med* 2010;**123**:785–789.
77. Lip GYH, Larsen TB, Skjoth F, Rasmussen LH. Indirect comparisons of new oral anticoagulant drugs for efficacy and safety when used for stroke prevention in atrial fibrillation. *J Am Coll Cardiol* 2012;**60**:738–746.
78. Freeman JV, Zhu RP, Owens DK, Garber AM, Hutton DW, Go AS, Wang PJ, Turakhia MP. Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in atrial fibrillation. *Ann Intern Med* 2011;**154**:1–11.
79. Sorensen SV, Kansal AR, Connolly S, Peng S, Linnehan J, Bradley-Kennedy C, Plumb JM. Cost-effectiveness of dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation: a Canadian payer perspective. *Thromb Haemost* 2011;**105**:908–919.
80. Pink J, Lane S, Pirmohamed M, Hughes DA. Dabigatran etexilate vs. warfarin in management of non-valvular atrial fibrillation in UK context: quantitative benefit-harm and economic analyses. *BMJ* 2011;**343**:d6333.
81. Shah SV, Gage BF. Cost-effectiveness of dabigatran for stroke prophylaxis in atrial fibrillation. *Circulation* 2011;**123**:2562–2570.
82. Banerjee A, Lane DA, Torp-Pedersen C, Lip GY. Net clinical benefit of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) vs. no treatment in a 'real world' atrial fibrillation population: a modelling analysis based on a nationwide cohort study. *Thromb Haemost* 2012;**107**:584–589.
83. Douxfils J, Mullier F, Robert S, Chatelain C, Chatelain B, Dogne JM. Impact of dabigatran on a large panel of routine or specific coagulation assays. Laboratory recommendations for monitoring of dabigatran etexilate. *Thromb Haemost* 2012;**107**:985–997.
84. van Ryn J, Stangier J, Haertter S, Liesenfeld KH, Wienen W, Feuring M, Clemens A. Dabigatran etexilate—a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. *Thromb Haemost* 2010;**103**:1116–1127.
85. Huisman MV, Lip GY, Diener HC, Brueckmann M, van Ryn J, Clemens A. Dabigatran etexilate for stroke prevention in patients with atrial fibrillation: resolving uncertainties in routine practice. *Thromb Haemost* 2012;**107**:838–847.
86. Tripodi A. Measuring the anticoagulant effect of direct factor Xa inhibitors. Is the anti-Xa assay preferable to the prothrombin time test? *Thromb Haemost* 2011;**105**:735–736.
87. Barrett YC, Wang Z, Frost C, Shenker A. Clinical laboratory measurement of direct factor Xa inhibitors: anti-Xa assay is preferable to prothrombin time assay. *Thromb Haemost* 2010;**104**:1263–1271.
88. Pengo V, Crippa L, Falanga A, Finazzi G, Marongiu F, Palareti G, Poli D, Testa S, Tiraferri E, Tosetto A, Tripodi A, Manotti C; Italian Federation of Thrombosis Centers. Questions and answers on the use of dabigatran and perspectives on the use of other new oral anticoagulants in patients with atrial fibrillation. A consensus document of the Italian Federation of Thrombosis Centers (FCSA). *Thromb Haemost* 2011;**106**:868–876.
89. Eerenberg ES, Kamphuisen PW, Sijpkens MK, Meijers JC, Buller HR, Levi M. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. *Circulation* 2011;**124**:1573–1579.
90. Marlu R, Hodaj E, Paris A, Albaladejo P, Crackowski JL, Pernod G. Effect of non-specific reversal agents on anticoagulant activity of dabigatran , rivaroxaban. A randomised crossover ex vivo study in healthy volunteers. *Thromb Haemost* 2012;**108**:217–224.
91. Sié P, Samama CM, Godier A, Rosencher N, Steib A, Llau JV, van der Linden P, Pernod G, Lecompte T, Gouin-Thibault I, Albaladejo P; Working Group on Perioperative Haemostasis; French Study Group on Thrombosis and Haemostasis. Surgery and invasive procedures in patients on long-term treatment with direct oral anticoagulants: thrombin or factor-Xa inhibitors. Recommendations of the Working Group on Perioperative Haemostasis and the French Study Group on Thrombosis and Haemostasis. *Arch Cardiovasc Dis* 2011;**104**:669–676.
92. Omran H, Bauersachs R, Rubenacker S, Goss F, Hammerstingl C. The HAS-BLED score predicts bleedings during bridging of chronic oral anticoagulation. Results from the national multicentre BNK Online bRiDging REgistRy (BORDER). *Thromb Haemost* 2012;**108**:65–73.
93. Nagarakanti R, Ezekowitz MD, Oldgren J, Yang S, Chernick M, Aikens TH, Flaker G, Brugada J, Kamensky G, Parekh A, Reilly PA, Yusuf S, Connolly SJ. Dabigatran vs. warfarin in patients with atrial fibrillation: an analysis of patients undergoing cardioversion. *Circulation* 2011;**123**:131–136.
94. Winkle RA, Mead RH, Engel G, Kong MH, Patrawala RA. The use of dabigatran immediately after atrial fibrillation ablation. *J Cardiovasc Electrophysiol* 2011;**23**:264–268.
95. Lakkireddy D, Reddy YM, Di Biase L, Vanga SR, Santangeli P, Swarup V, Pimentel R, Mansour MC, D'Avila A, Sanchez JE, Burkhardt JD, Chalhoub F, Mohanty P, Coffey J, Shaik N, Monir G, Reddy VY, Ruskin J, Natale A. Feasibility and safety of dabigatran vs. warfarin for periprocedural anticoagulation in patients undergoing radiofrequency ablation for atrial Fibrillation results from a multicenter prospective registry. *J Am Coll Cardiol* 2012;**59**:1168–1174.
96. Eikelboom JW, Wallentin L, Connolly SJ, Ezekowitz M, Healey JS, Oldgren J, Yang S, Alings M, Kaatz S, Hohnloser SH, Diener HC, Franzosi MG, Huber K, Reilly P, Varrone J, Yusuf S. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. *Circulation* 2011;**123**:2363–2372.
97. Ruiz-Nodar JM, Marín F, Roldán V, Valencia J, Manzano-Fernández S, Caballero L, Hurtado JA, Sogorb F, Valdés M, Lip GY. Should we recommend oral anticoagulation therapy in patients with atrial fibrillation undergoing coronary artery stenting with a high HAS-BLED bleeding risk score? *Circ Cardiovasc Interv* 2012;**5**:459–466.
98. Lip GY, Huber K, Andreotti F, Arnesen H, Airaksinen JK, Cuisset T, Kirchhof P, Marín F; Consensus Document of European Society of Cardiology Working Group on Thrombosis. Antithrombotic management of atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing coronary stenting. *Eur Heart J* 2010;**31**:1311–1318.
99. Huber K, Airaksinen KJ, Cuisset T, Marin F, Rubboli A, Lip GY. Antithrombotic therapy in patients with atrial fibrillation undergoing coronary stenting:

similarities and dissimilarities between North America and Europe. *Thromb Haemost* 2011;**106**:569–571.
100. Faxon DP, Eikelboom JW, Berger PB, Holmes DR, Bhatt DL, Moliterno DJ, Becker RC, Angiolillo DJ. Consensus document: antithrombotic therapy in patients with atrial fibrillation undergoing coronary stenting. A North-American perspective. *Thromb Haemost* 2011;**106**:572–584.
101. Mega JL, Braunwald E, Wiviott SD, Bassand JP, Bhatt DL, Bode C, Burton P, Cohen M, Cook-Bruns N, Fox KA, Goto S, Murphy SA, Plotnikov AN, Schneider D, Sun X, Verheugt FW, Gibson CM; ATLAS ACS 2–TIMI 51 Investigators. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med* 2012;**366**:9–19.
102. Alexander JH, Lopes RD, James S, Kilaru R, He Y, Mohan P, Bhatt DL, Goodman S, Verheugt FW, Flather M, Huber K, Liaw D, Husted SE, Lopez-Sendon J, De Caterina R, Jansky P, Darius H, Vinereanu D, Cornel JH, Cools F, Atar D, Leiva-Pons JL, Keltai M, Ogawa H, Pais P, Parkhomenko A, Ruzyllo W, Diaz R, White H, Ruda M, Geraldes M, Lawrence J, Harrington RA, Wallentin L; APPRAISE-2 Investigators. Apixaban with antiplatelet therapy after acute coronary syndrome. *N Engl J Med* 2011;**365**:699–708.
103. Matute MC, Masjuan J, Egido JA, Fuentes B, Simal P, Díaz-Otero F, Reig G, Díez-Tejedor E, Gil-Nuñez A, Vivancos J, Alonso de Leciñana M. Safety and outcomes following thrombolytic treatment in stroke patients who had received prior treatment with anticoagulants. *Cerebrovasc Dis* 2012;**33**:231–239.
104. Potpara TS, Polovina MM, Licina MM, Marinkovic JM, Prostran MS, Lip GY. Reliable identification of 'truly low' thromboembolic risk in patients initially diagnosed with 'lone' atrial fibrillation: The Belgrade Atrial Fibrillation Study. *Circ Arrhythm Electrophysiol* 2012;**5**:319–326.
105. Singer DE, Chang Y, Fang MC, Borowsky LH, Pomernacki NK, Udaltsova N, Go AS. The net clinical benefit of warfarin anticoagulation in atrial fibrillation. *Ann Intern Med* 2009;**151**:297–305.
106. De Caterina R, Connolly SJ, Pogue J, Chrolavicius S, Budaj A, Morais J, Renda G, Yusuf S. Mortality predictors and effects of antithrombotic therapies in atrial fibrillation: insights from ACTIVE-W. *Eur Heart J* 2010;**31**:2133–2140.
107. Hylek EM, D'Antonio J, Evans-Molina C, Shea C, Henault LE, Regan S. Translating the results of randomized trials into clinical practice: the challenge of warfarin candidacy among hospitalized elderly patients with atrial fibrillation. *Stroke* 2006;**37**:1075–1080.
108. Fox KA, Piccini JP, Wojdyla D, Becker RC, Halperin JL, Nessel CC, Paolini JF, Hankey GJ, Mahaffey KW, Patel MR, Singer DE, Califf RM. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. *Eur Heart J* 2011;**32**:2387–2394.
109. Connolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, Chrolavicius S, Pfeffer M, Hohnloser S, Yusuf S. Clopidogrel plus aspirin vs. oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet* 2006;**367**:1903–1912.
110. Corley SD, Epstein AE, DiMarco JP, Domanski MJ, Geller N, Greene HL, Josephson RA, Kellen JC, Klein RC, Krahn AD, Mickel M, Mitchell LB, Nelson JD, Rosenberg Y, Schron E, Shemanski L, Waldo AL, Wyse DG; AFFIRM Investigators. Relationships between sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Study. *Circulation* 2004;**109**:1509–1513.
111. Klein AL, Grimm RA, Murray RD, Apperson-Hansen C, Asinger RW, Black IW, Davidoff R, Erbel R, Halperin JL, Orsinelli DA, Porter TR, Stoddard MF; Assessment of Cardioversion Using Transesophageal Echocardiography Investigators. Use of transesophageal echocardiography to guide cardioversion in patients with atrial fibrillation. *N Engl J Med* 2001;**344**:1411–1420.
112. Cox JL. Cardiac surgery for arrhythmias. *J Cardiovasc Electrophysiol* 2004;**15**:250–262.
113. Bayard YL, Omran H, Neuzil P, Thuesen L, Pichler M, Rowland E, Ramondo A, Ruzyllo W, Budts W, Montalescot G, Brugada P, Serruys PW, Vahanian A, Piéchaud JF, Bartorelli A, Marco J, Probst P, Kuck KH, Ostermayer SH, Büscheck F, Fischer E, Leetz M, Sievert H. PLAATO (Percutaneous Left Atrial Appendage Transcatheter Occlusion) for prevention of cardioembolic stroke in non-anticoagulation eligible atrial fibrillation patients: results from the European PLAATO study. *EuroIntervention* 2010;**6**:220–226.
114. Park JW, Bethencourt A, Sievert H, Santoro G, Meier B, Walsh K, Lopez-Minquez JR, Meerkin D, Valdés M, Ormerod O, Leithäuser B. Left atrial appendage closure with Amplatzer cardiac plug in atrial fibrillation: initial European experience. *Catheter Cardiovasc Interv* 2011;**77**:700–706.
115. Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, Mullin CM, Sick P. Percutaneous closure of the left atrial appendage vs. warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet* 2009;**374**:534–542.
116. Whitlock RP, Healey JS, Connolly SJ. Left atrial appendage occlusion does not eliminate the need for warfarin. *Circulation* 2009;**120**:1927–1932; discussion 32.
117. Dawson AG, Asopa S, Dunning J. Should patients undergoing cardiac surgery with atrial fibrillation have left atrial appendage exclusion? *Interact Cardiovasc Thorac Surg* 2010;**10**:306–311.
118. Reddy VY, Holmes D, Doshi SK, Neuzil P, Kar S. Safety of percutaneous left atrial appendage closure: results from the Watchman left atrial appendage system for embolic protection in patients with AF (PROTECT AF) clinical trial and the Continued Access Registry. *Circulation* 2011;**123**:417–424.
119. Roy D, Rowe BH, Stiell IG, Coutu B, Ip JH, Phaneuf D, Lee J, Vidaillet H, Dickinson G, Grant S, Ezrin AM, Beatch GN; CRAFT Investigators. A randomized, controlled trial of RSD1235, a novel anti-arrhythmic agent, in the treatment of recent onset atrial fibrillation. *J Am Coll Cardiol* 2004;**44**:2355–2361.
120. Roy D, Pratt CM, Torp-Pedersen C, Wyse DG, Toft E, Juul-Moller S, Nielsen T, Rasmussen SL, Stiell IG, Coutu B, Ip JH, Pritchett EL, Camm AJ; Atrial Arrhythmia Conversion Trial Investigators. Vernakalant hydrochloride for rapid conversion of atrial fibrillation: a phase 3, randomized, placebo-controlled trial. *Circulation* 2008;**117**:1518–1525.
121. Pratt CM, Roy D, Torp-Pedersen C, Wyse DG, Toft E, Juul-Moller S, Retyk E, Drenning DH; Atrial Arrhythmia Conversion Trial (ACT-III) Investigators. Usefulness of vernakalant hydrochloride injection for rapid conversion of atrial fibrillation. *Am J Cardiol* 2010;**106**:1277–1283.
122. Kowey PR, Dorian P, Mitchell LB, Pratt CM, Roy D, Schwartz PJ, Sadowski J, Sobczyk D, Bochenek A, Toft E; Atrial Arrhythmia Conversion Trial Investigators. Vernakalant hydrochloride for the rapid conversion of atrial fibrillation after cardiac surgery: a randomized, double-blind, placebo-controlled trial. *Circ Arrhythm Electrophysiol* 2009;**2**:652–659.
123. Stiell IG, Roos JS, Kavanagh KM, Dickinson G. A multicenter, open-label study of vernakalant for the conversion of atrial fibrillation to sinus rhythm. *Am Heart J* 2010;**159**:1095–1101.
124. Camm AJ, Capucci A, Hohnloser SH, Torp-Pedersen C, Van Gelder IC, Mangal B, Beatch G; AVRO Investigators. A randomized active-controlled study comparing the efficacy and safety of vernakalant to amiodarone in recent-onset atrial fibrillation. *J Am Coll Cardiol* 2011;**57**:313–321.
125. FDA. Briefing materials for the Cardiovascular and Renal Drugs Advisory Committee December 11, 2007. Kynapid (vernakalant hydrochloride injection) NDA 22–034. Astellas Pharma US, Inc.
126. Buccelletti F, Iacomini P, Botta G, Marsiliani D, Carroccia A, Gentiloni Silveri N, Franceschi F. Efficacy and safety of vernakalant in recent-onset atrial fibrillation after the European Medicines Agency approval: systematic review and meta-analysis. *J Clin Pharmacol* 2011.
127. Bash LD, Buono JL, Davies GM, Martin A, Fahrbach K, Phatak H, Avetisyan R, Mwamburi M. Systematic review and meta-analysis of the efficacy of cardioversion by vernakalant and comparators in patients with atrial fibrillation. *Cardiovasc Drugs Ther* 2012;**26**:167–179.
128. Torp-Pedersen C, Camm AJ, Butterfield NN, Dickinson G, Beatch GN. Vernakalant: conversion of atrial fibrillation in patients with ischemic heart disease. *Int J Cardiol*. Published online 21 November 2011. doi.org/10.1016/j.ijcard.2011.10.108.
129. Camm AJ, Toft E, Torp-Pedersen C, Vijayaraman P, Juul-Moller S, Ip J, Beatch GN, Dickinson G, Wyse DG; Scene 2 Investigators. Efficacy and safety of vernakalant in patients with atrial flutter: a randomized, double-blind, placebo-controlled trial. *Europace* 2012;**14**:804–809.
130. E.U. Summary of Product Characteristics, Brinavess, MSD, 2010. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001215/WC500097154.pdf. 2010.
131. Slavik RS, Tisdale JE, Borzak S. Pharmacologic conversion of atrial fibrillation: a systematic review of available evidence. Prog Cardiovasc Dis 2001;**44**:121–152.
132. Stambler BS, Wood MA, Ellenbogen KA, Perry KT, Wakefield LK, VanderLugt JT; Ibutilide Repeat Dose Study Investigators. Efficacy and safety of repeated intravenous doses of ibutilide for rapid conversion of atrial flutter or fibrillation. *Circulation* 1996;**94**:1613–2152.
133. Volgman AS, Carberry PA, Stambler B, Lewis WR, Dunn GH, Perry KT, Vanderlugt JT, Kowey PR. Conversion efficacy and safety of intravenous ibutilide compared with intravenous procainamide in patients with atrial flutter or fibrillation. *J Am Coll Cardiol* 1998;**31**:1414–1419.
134. Vos MA, Golitsyn SR, Stangl K, Ruda MY, Van Wijk LV, Harry JD, Perry KT, Touboul P, Steinbeck G, Wellens HJ; Ibutilide/Sotalol Comparator Study Group. Superiority of ibutilide (a new class III agent) over DL-sotalol in converting atrial flutter and atrial fibrillation. *Heart* 1998;**79**:568–575.
135. Savelieva I, Kakouros N, Kourliouros A, Camm AJ. Upstream therapies for management of atrial fibrillation: review of clinical evidence and implications for European Society of Cardiology Guidelines. Part I: primary prevention. *Europace* 2011;**13**:308–328.

136. Savelieva I, Kakouros N, Kourliouros A, Camm AJ. Upstream therapies for management of atrial fibrillation: review of clinical evidence and implications for European Society of Cardiology Guidelines. Part II: secondary prevention. *Europace* 2011;**13**:610–625.
137. Goette A, Schön N, Kirchhof P, Breithardt G, Fetsch T, Häusler KG, Klein HU, Steinbeck G, Wegscheider K, Meinertz T. Angiotensin II-Antagonist in Paroxysmal Atrial Fibrillation (ANTIPAF) Trial. *Circ Arrhythm Electrophysiol* 2012;**5**:43–51.
138. Yamashita T, Inoue H, Okumura K, Kodama I, Aizawa Y, Atarashi H, Ohe T, Ohtsu H, Kato T, Kamakura S, Kumagai K, Kurachi Y, Koretsune Y, Saikawa T, Sakurai M, Sato T, Sugi K, Nakaya H, Hirai M, Hirayama A, Fukatani M, Mitamura H, Yamazaki T, Watanabe E, Ogawa S; J-RHYTHM II Investigators. Randomized trial of angiotensin II-receptor blocker vs. dihydropiridine calcium channel blocker in the treatment of paroxysmal atrial fibrillation with hypertension (J-RHYTHM II study). *Europace* 2011;**13**:473–479.
139. Bianconi L, Calò L, Mennuni M, Santini L, Morosetti P, Azzolini P, Barbato G, Biscione F, Romano P, Santini M. *n*-3 polyunsaturated fatty acids for the prevention of arrhythmia recurrence after electrical cardioversion of chronic persistent atrial fibrillation: a randomized, double-blind, multicentre study. *Europace* 2011; **13**:174–181.
140. Kowey PR, Reiffel JA, Ellenbogen KA, Naccarelli GV, Pratt CM. Efficacy and safety of prescription omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation: a randomized controlled trial. *JAMA* 2010;**304**: 2363–2372.
141. Lafuente-Lafuente C, Mouly S, Longas-Tejero MA, Mahe I, Bergmann JF. Antiarrhythmic drugs for maintaining sinus rhythm after cardioversion of atrial fibrillation: a systematic review of randomized controlled trials. *Arch Intern Med* 2006; **166**:719–728.
142. Freemantle N, Lafuente-Lafuente C, Mitchell S, Eckert L, Reynolds M. Mixed treatment comparison of dronedarone, amiodarone, sotalol, flecainide, and propafenone, for the management of atrial fibrillation. *Europace* 2011;**13**:329–345.
143. Piccini JP, Hasselblad V, Peterson ED, Washam JB, Califf RM, Kong DF. Comparative efficacy of dronedarone and amiodarone for the maintenance of sinus rhythm in patients with atrial fibrillation. *J Am Coll Cardiol* 2009;**54**):1089–1095.
144. Sullivan SD, Orme ME, Morais E, Mitchell SA. Interventions for the treatment of atrial fibrillation: A systematic literature review and meta-analysis. *Int J Cardiol*. Published online 31 March 2012. doi.org/10.1016/j.ijcard.2012.03.070.
145. Kirchhof P, Andresen D, Bosch R, Borggrefe M, Meinertz T, Parade U, Ravens U, Samol A, Steinbeck G, Treszl A, Wegscheider K, Breithardt G. Short-term versus long-term antiarrhythmic drug treatment after cardioversion of atrial fibrillation (Flec-SL): a prospective, randomised, open-label, blinded endpoint assessment trial. *Lancet* 2012;**380**:238–246.
146. Ahmed S, Rienstra M, Crijns HJ, Links TP, Wiesfeld AC, Hillege HL, Bosker HA, Lok DJ, Van Veldhuisen DJ, Van Gelder IC; CONVERT Investigators. Continuous vs. episodic prophylactic treatment with amiodarone for the prevention of atrial fibrillation: a randomized trial. *JAMA* 2008;**300**:1784–1792.
147. Connolly SJ. Evidence-based analysis of amiodarone efficacy and safety. *Circulation* 1999;**100**:2025–2034.
148. Hohnloser SH, Crijns HJ, van Eickels M, Gaudin C, Page RL, Torp-Pedersen C, Connolly SJ; ATHENA Investigators. Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med* 2009;**360**:668–678.
149. Køber L, Torp-Pedersen C, McMurray JJ, Gøtzsche O, Lévy S, Crijns H, Amlie J, Carlsen J; Dronedarone Study Group. Increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med* 2008;**358**:2678–2687.
150. Duray GZ, Schmitt J, Hohnloser SH. Dronedarone therapy in atrial fibrillation: a summary of recent controlled trials. *J Cardiovasc Pharmacol Ther* 2010;**15**(Suppl 4):19S–23S.
151. Camm AJ, Savelieva I. Atrial fibrillation: the rate vs. rhythm management controversy. *J R Coll Physicians Edinb* 2012;**42**(Suppl 18):23–34.
152. Touboul P, Brugada J, Capucci A, Crijns HJ, Edvardsson N, Hohnloser SH. Dronedarone for prevention of atrial fibrillation: a dose-ranging study. *Eur Heart J* 2003;**24**:1481–1487.
153. Singh BN, Connolly SJ, Crijns HJ, Roy D, Kowey PR, Capucci A, Radzik D, Aliot EM, Hohnloser SH; EURIDIS and ADONIS Investigators. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. *N Engl J Med* 2007;**357**:987–999.
154. Davy JM, Herold M, Hoglund C, Timmermans A, Alings A, Radzik D, Van Kempen L. Dronedarone for the control of ventricular rate in permanent atrial fibrillation: the Efficacy and safety of dRonedArone for the cOntrol of ventricular rate during atrial fibrillation (ERATO) study. *Am Heart J* 2008;**156**:527 e1–e9.
155. Le Heuzey JY, De Ferrari GM, Radzik D, Santini M, Zhu J, Davy JM. A short-term, randomized, double-blind, parallel-group study to evaluate the efficacy and safety of dronedarone vs. amiodarone in patients with persistent atrial fibrillation: the DIONYSOS study. *J Cardiovasc Electrophysiol* 2010;**21**:597–605.
156. Cosedis Nielsen J, Johannessen A, Raatikainen P, Hindricks G, Walfridsson H, Kongstad O *et al.* A randomized comparison of radiofrequency ablation and antiarrhythmia drug therapy as first line treatment in paroxysmal atrial fibrillation. *N Engl J Med* 2012:in press.
157. Morillo C, Verma A, Kuck KH *et al.* Radiofrequency Ablation vs. Antiarrhythmic Drugs as First-Line Treatment of Symptomatic Atrial Fibrillation: (RAAFT 2): A randomized trial. *Heart Rhythm Society 2012 Scientific Sessions; May 11, 2012; Boston, MA. Abstract LB02-1*.
158. Wazni OM, Marrouche NF, Martin DO, Verma A, Bhargava M, Saliba W, Bash D, Schweikert R, Brachmann J, Gunther J, Gutleben K, Pisano E, Potenza D, Fanelli R, Raviele A, Themistoclakis S, Rossillo A, Bonso A, Natale A: Radiofrequency ablation vs antiarrhythmic drugs as firstline treatment of symptomatic atrial fibrillation: A randomized trial. *JAMA* 2005;**293**:2634–2640.
159. Boersma LV, Castella M, van Boven W, Berruezo A, Yilmaz A, Nadal M, Sandoval E, Calvo N, Brugada J, Kelder J, Wijffels M, Mont L. Atrial fibrillation catheter ablation vs. surgical ablation treatment (FAST): a 2-center randomized clinical trial. *Circulation* 2012;**125**:23–30.
160. 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.
161. Weerasooriya R, Khairy P, Litalien J, Macle L, Hocini M, Sacher F, Lellouche N, Knecht S, Wright M, Nault I, Miyazaki S, Scavee C, Clementy J, Haissaguerre M, Jais P. Catheter ablation for atrial fibrillation: are results maintained at 5 years of follow-up? *J Am Coll Cardiol* 2011;**57**:160–166.
162. Ouyang F, Tilz R, Chun J, Schmidt B, Wissner E, Zerm T, Neven K, Köktürk B, Konstantinidou M, Metzner A, Fuernkranz A, Kuck KH. Long-term results of catheter ablation in paroxysmal atrial fibrillation: lessons from a 5-year follow-up. *Circulation* 2010;**122**:2368–2377.
163. Tzou WS, Marchlinski FE, Zado ES, Lin D, Dixit S, Callans DJ, Cooper JM, Bala R, Garcia F, Hutchinson MD, Riley MP, Verdino R, Gerstenfeld EP. Long-term outcome after successful catheter ablation of atrial fibrillation. *Circ Arrhythm Electrophysiol* 2010;**3**:237–242.
164. Arya A, Hindricks G, Sommer P, Huo Y, Bollmann A, Gaspar T, Bode K, Husser D, Kottkamp H, Piorkowski C. Long-term results and the predictors of outcome of catheter ablation of atrial fibrillation using steerable sheath catheter navigation after single procedure in 674 patients. *Europace* 2010;**12**: 173–180.
165. Oral H, Knight BP, Ozaydin M, Tada H, Chugh A, Hassan S, Scharf C, Lai SW, Greenstein R, Pelosi F Jr, Strickberger SA, Morady F. Clinical significance of early recurrences of atrial fibrillation after pulmonary vein isolation. *J Am Coll Cardiol* 2002;**40**:100–104.
166. Lellouche N, Jaïs P, Nault I, Wright M, Bevilacqua M, Knecht S, Matsuo S, Lim KT, Sacher F, Deplagne A, Bordachar P, Hocini M, Haïssaguerre M. Early recurrences after atrial fibrillation ablation: prognostic value and effect of early reablation. *J Cardiovasc Electrophysiol* 2008;**19**:599–605.
167. Pokushalov E, Romanov A, Corbucci G, Bairamova S, Losik D, Turov A, Shirokova N, Karaskov A, Mittal S, Steinberg JS. Does atrial fibrillation burden measured by continuous monitoring during the blanking period predict the response to ablation at 12-month follow-up? *Heart Rhythm*. Published online ahead of print 23 March 2012. doi.org/10.1016/j.hrthm.2012.03.047.
168. Medi C, Sparks PB, Morton JB, Kistler PM, Halloran K, Rosso R, Vohra JK, Kumar S, Kalman JM. Pulmonary vein antral isolation for paroxysmal atrial fibrillation: results from long-term follow-up. *J Cardiovasc Electrophysiol* 2011;**22**: 137–141.
169. Lee G, Sparks PB, Morton JB, Kistler PM, Vohra JK, Medi C, Rosso R, Teh A, Halloran K, Kalman JM. Low risk of major complications associated with pulmonary vein antral isolation for atrial fibrillation: results of 500 consecutive ablation procedures in patients with low prevalence of structural heart disease from a single center. *J Cardiovasc Electrophysiol* 2011;**22**:163–168.
170. Arbelo E, Brugada J, Hindricks G, Maggioni A, Tavazzi L, Vardas P, Anselme F, Inama G, Jais P, Kalarus Z, Kautzner J, Lewalter T, Mairesse G, Perez-Villacastin J, Riahi S, Taborsky M, Theodorakis G, Trines S; on behalf of the Atrial Fibrillation Ablation Pilot Study Investigators. ESC-EURObservational research programme: the atrial fibrillation ablation pilot study, conducted by the European Heart Rhythm Association. *Europace* 2012;**14**:1094–1103.
171. Hoyt H, Bhonsale A, Chilukuri K, Alhumaid F, Needleman M, Edwards D, Govil A, Nazarian S, Cheng A, Henrikson CA, Sinha S, Marine JE, Berger R, Calkins H, Spragg DD. Complications arising from catheter ablation of atrial fibrillation: temporal trends and predictors. *Heart Rhythm* 2011;**8**:1869–1874.
172. Cappato R, Calkins H, Chen SA, Davies W, Iesaka Y, Kalman J, Kim YH, Klein G, Natale A, Packer D, Skanes A, Ambrogi F, Biganzoli E. Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. *Circ Arrhythm Electrophysiol* 2010;**3**:32–38.

173. Shah RU, Freeman JV, Shilane D, Wang PJ, Go AS, Hlatky MA. Procedural complications, rehospitalizations, and repeat procedures after catheter ablation for atrial fibrillation. *J Am Coll Cardiol* 2012;**59**:143–149.
174. Herrera Siklódy C, Deneke T, Hocini M, Lehrmann H, Shin DI, Miyazaki S, Henschke S, Fluegel P, Schiebeling-Römer J, Bansmann PM, Bourdias T, Dousset V, Haïssaguerre M, Arentz T. Incidence of asymptomatic intracranial embolic events after pulmonary vein isolation: comparison of different atrial fibrillation ablation technologies in a multicenter study. *J Am Coll Cardiol* 2011;**58**: 681–688.
175. Di Biase L, Burkhardt JD, Mohanty P, Sanchez J, Horton R, Gallinghouse GJ, Lakkireddy D, Verma A, Khaykin Y, Hongo R, Hao S, Beheiry S, Pelargonio G, Dello Russo A, Casella M, Santarelli P, Santangeli P, Wang P, Al-Ahmad A, Patel D, Themistoclakis S, Bonso A, Rossillo A, Corrado A, Raviele A, Cummings JE, Schweikert RA, Lewis WR, Natale A. Periprocedural stroke and management of major bleeding complications in patients undergoing catheter ablation of atrial fibrillation: the impact of periprocedural therapeutic international normalized ratio. *Circulation* 2010;**121**:2550–2556.
176. Haeusler KG, Kirchhof P, Endres M. Left atrial catheter ablation and ischemic stroke. *Stroke* 2012;**43**:265–270.
177. Gaita F, Leclercq JF, Schumacher B, Scaglione M, Toso E, Halimi F, Schade A, Froehner S, Ziegler V, Sergi D, Cesarani F, Blandino A. Incidence of silent cerebral thromboembolic lesions after atrial fibrillation ablation may change according to technology used: comparison of irrigated radiofrequency, multipolar nonirrigated catheter and cryoballoon. *J Cardiovasc Electrophysiol* 2011;**22**: 961–968.
178. Kirchhof P, Bax J, Blomstrom-Lundquist C, Calkins H, Camm AJ, Cappato R, Cosio F, Crijns H, Diener HC, Goette A, Israel CW, Kuck KH, Lip GY, Nattel S, Page RL, Ravens U, Schotten U, Steinbeck G, Vardas P, Waldo A, Wegscheider K, Willems S, Breithardt G. Early and comprehensive management of atrial fibrillation: proceedings from the 2nd AFNET/EHRA consensus conference on atrial fibrillation entitled 'research perspectives in atrial fibrillation'. *Europace* 2009;**11**:860–885.
179. Van Gelder IC, Haegeli LM, Brandes A, Heidbuchel H, Aliot E, Kautzner J, Szumowski L, Mont L, Morgan J, Willems S, Themistoclakis S, Gulizia M, Elvan A, Smit MD, Kirchhof P. Rationale and current perspective for early rhythm control therapy in atrial fibrillation. *Europace* 2011;**13**:1517–1525.
180. Schmidt M, Segerson NM, Marschang H, Akoum N, Rittger H, Clifford SM, Brachmann J, Daccarett M, Marrouche NF. Atrial fibrillation ablation in patients with therapeutic international normalized ratios. *Pacing Clin Electrophysiol* 2009; **32**:995–999.
181. Page SP, Siddiqui MS, Finlay M, Hunter RJ, Abrams DJ, Dhinoja M, Earley MJ, Sporton SC, Schilling RJ. Catheter ablation for atrial fibrillation on uninterrupted warfarin: can it be done without echo guidance? *J Cardiovasc Electrophysiol* 2011; **22**:265–270.
182. Gautam S, John RM, Stevenson WG, Jain R, Epstein LM, Tedrow U, Koplan BA, McClennen S, Michaud GF. Effect of therapeutic INR on activated clotting times, heparin dosage, and bleeding risk during ablation of atrial fibrillation. *J Cardiovasc Electrophysiol* 2011;**22**:248–254.
183. Gopinath D, Lewis WR, Di Biase L, Natale A. Pulmonary vein antrum isolation for atrial fibrillation on therapeutic coumadin: special considerations. *J Cardiovasc Electrophysiol* 2011;**22**:236–239.
184. Hakalahti A, Uusimaa P, Ylitalo K, Raatikainen MJ. Catheter ablation of atrial fibrillation in patients with therapeutic oral anticoagulation treatment. *Europace* 2011;**13**:640–645.
185. Latchamsetty R, Gautam S, Bhakta D, Chugh A, John RM, Epstein LM, Miller JM, Michaud GF, Oral H, Morady F, Jongnarangsin K. Management and outcomes of cardiac tamponade during atrial fibrillation ablation in the presence of therapeutic anticoagulation with warfarin. *Heart Rhythm* 2011;**8**:805–808.
186. Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA, Crijns HJ, Damiano RJ Jr, Davies DW, DiMarco J, Edgerton J, Ellenbogen K, Ezekowitz MD, Haines DE, Haissaguerre M, Hindricks G, Iesaka Y, Jackman W, Jalife J, Jais P, Kalman J, Keane D, Kim YH, Kirchhof P, Klein G, Kottkamp H, Kumagai K, Lindsay BD, Mansour M, Marchlinski FE, McCarthy PM, Mont JL, Morady F, Nademanee K, Nakagawa H, Natale A, Nattel S, Packer DL, Pappone C, Prystowsky E, Raviele A, Reddy V, Ruskin JN, Shemin RJ, Tsao HM, Wilber D. 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. *Europace* 2012; **14**:528–606.
187. Kirchhof P, Lip GY, Van Gelder IC, Bax J, Hylek E, Kaab S, Schotten U, Wegscheider K, Boriani G, Brandes A, Ezekowitz M, Diener H, Haegeli L, Heidbuchel H, Lane D, Mont L, Willems S, Dorian P, Aunes-Jansson M, Blomstrom-Lundqvist C, Borentain M, Breitenstein S, Brueckmann M, Cater N, Clemens A, Dobrev D, Dubner S, Edvardsson NG, Friberg L, Goette A, Gulizia M, Hatala R, Horwood J, Szumowski L, Kappenberger L, Kautzner J, Leute A, Lobban T, Meyer R, Millerhagen J, Morgan J, Muenzel F, Nabauer M, Baertels C, Oeff M, Paar D, Polifka J, Ravens U, Rosin L, Stegink W, Steinbeck G, Vardas P, Vincent A, Walter M, Breithardt G, Camm AJ. Comprehensive risk reduction in patients with atrial fibrillation: emerging diagnostic and therapeutic options–a report from the 3rd Atrial Fibrillation Competence NETwork/European Heart Rhythm Association consensus conference. *Europace* 2012;**14**:8–27.
188. Van Gelder IC, Haegeli LM, Brandes A, Heidbuchel H, Aliot E, Kautzner J, Szumowski L, Mont L, Morgan J, Willems S, Themistoclakis S, Gulizia M, Elvan A, Smit MD, Kirchhof P. Rationale and current perspective for early rhythm control therapy in atrial fibrillation. *Europace* 2011;**13**:1517–1525.
189. Pappone C, Vicedomini G, Augello G, Manguso F, Saviano M, Baldi M, Petretta A, Giannelli L, Calovic Z, Guluta V, Tavazzi L, Santinelli V. Radiofrequency catheter ablation and antiarrhythmic drug therapy: a prospective, randomized, 4-year follow-up trial: the APAF study. *Circ Arrhythm Electrophysiol* 2011;**4**:808–814.
190. Tanner H, Makowski K, Roten L, Seiler J, Schwick N, Müller C, Fuhrer J, Delacrétaz E. Complications arising from catheter ablation of atrial fibrillation: temporal trends and predictors. *Europace* 2011;**13**:646–653.
191. Wazni O, Wilkoff B, Saliba W. Catheter ablation for atrial fibrillation. *N Engl J Med* 2011;**365**:2296–2304.
192. Calkins H, Reynolds MR, Spector P, Sondhi M, Xu Y, Martin A, Williams CJ, Sledge I. Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation: two systematic literature reviews and meta-analyses. *Circ Arrhythm Electrophysiol* 2009;**2**:349–361.
193. Wilber DJ, Pappone C, Neuzil P, De Paola A, Marchlinski F, Natale A, Macle L, Daoud EG, Calkins H, Hall B, Reddy V, Augello G, Reynolds MR, Vinekar C, Liu CY, Berry SM, Berry DA; ThermoCool AF Trial Investigators. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. *JAMA* 2010;**303**: 333–340.
194. Haïssaguerre M, Jaïs P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, Le Métayer P, Clémenty J. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med* 1998; **339**:659–666.
195. Leong-Sit P, Roux JF, Zado E, Callans DJ, Garcia F, Lin D, Marchlinski FE, Bala R, Dixit S, Riley M, Hutchinson MD, Cooper J, Russo AM, Verdino R, Gerstenfeld EP. Antiarrhythmics after ablation of atrial fibrillation (5A Study): six-month follow-up study. *Circ Arrhythm Electrophysiol* 2011;**4**:11–14.