

Editorial

Comments on the 2016 ESC Guidelines for the Management of Atrial Fibrillation



Comentarios a la guía ESC 2016 sobre el diagnóstico y tratamiento de la fibrilación auricular

SEC Working Group for the 2016 ESC Guidelines for the Management of Atrial Fibrillation, Expert Reviewers for the 2016 ESC Guidelines for the Management of Atrial Fibrillation, and the SEC Guidelines Committee^{o,}*

Article history:

Available online 27 December 2016

INTRODUCTION

In line with the methodology recommended by the Guidelines Committee of the Spanish Society of Cardiology,¹ the present article discusses the innovations and most controversial aspects of the recent guidelines for atrial fibrillation (AF).² Notably, of 154 recommendations, only 23 (15%) have a level of evidence A and 80 (52%) a level of evidence B, confirming the need for further clinical research into this condition.

Some of the most novel or relevant aspects of the guidelines are summarized in [Table](#), in conjunction with some critical comments.

EPIDEMIOLOGY

The guidelines report interesting data on the high incidence and prevalence of AF: 1 in every 4 middle-aged adults in Europe and the United States will develop AF during their lifetime. The estimated prevalence of AF in individuals older than 20 years is 3%, in line with data from the Spanish OFRECE study,³ which showed an AF prevalence of 4.4% in the general population older than 40 years.

PATHOPHYSIOLOGICAL AND GENETIC ASPECTS THAT GUIDE THE MANAGEMENT OF ATRIAL FIBRILLATION

The hypothesis that there are different types of AF with distinct pathophysiological bases is somewhat daring. Although the etiological factors can differ, the pathophysiological consequences are probably similar, and there is no evidence for the hypothesized “distinct pathophysiological mechanisms” and “different types of AF”, except in very specific disease and clinical situations. The attempts of the guidelines to link distinct etiological factors with specific

pathophysiological mechanisms are somewhat speculative but nonetheless interesting because this approach might suggest future lines of research to better understand the pathophysiology of AF.

DIAGNOSIS AND TIMELY DETECTION OF ATRIAL FIBRILLATION

The use of pulse palpation or electrocardiography for any reason as part of opportunistic screening of at-risk patients can detect about 3% of patients older than 65 years with asymptomatic AF. Asymptomatic AF episodes can also be detected in patients with implanted devices, which can record atrial high rate episodes (AHREs). Such episodes have been associated with a higher risk of embolic events, and it is hypothesized that anticoagulants might effectively prevent stroke. Implantable devices should be interrogated to identify AHREs, and patients with AHRE should undergo AF screening and embolic risk stratification.

A considerable percentage of strokes (about 6.5%) might be due to undetected AF episodes. The prevalence of asymptomatic AF is even higher in selected populations with cryptogenic stroke. There is no clear consensus on the optimal monitoring method or whether it needs to be invasive or not. Continuous monitoring is recommended for 72 hours after an ischemic stroke (class of recommendation I, level of evidence B) and, subsequently, ambulatory monitoring with noninvasive systems or implantable loop recorders for all patients who have had an ischemic stroke (IIa B).

CLASSIFICATION OF ATRIAL FIBRILLATION

The new guidelines classify AF episodes that are cardioverted within 7 days as paroxysmal; in previous guidelines, all episodes requiring cardioversion were considered persistent, even those lasting less than 7 days. This criteria change might be confusing and it remains to be seen whether these definitions will also be adopted by the guidelines of other scientific societies. A new type of AF is introduced—long-standing paroxysmal—but is insufficiently explained.

The classification of AF based on etiology no longer seems to be relevant from the therapeutic perspective.

The classification is now based on AHRE symptoms, with class 2 subdivided into 2a—mild symptoms—and 2b—severe symptoms. Thus, patients in class 2b could benefit from adequate rhythm control.

SEE RELATED ARTICLE:

<http://dx.doi.org/10.1016/j.rec.2016.11.032>, *Rev Esp Cardiol.* 2017;70:50.e1-e84.

^oThe names of all of the authors of this article are listed in the [Appendix](#).

*Corresponding author: Departamento de Cardiología, Hospital Universitario 12 de Octubre, Avda. de Córdoba s/n, 28041 Madrid, Spain.

E-mail address: farribas@secardiologia.es (F. Arribas).

Table
New and Important Aspects

Recommendation		Comment
For patients with TIA or ischemic stroke, screening for AF should be performed using short-term ECG followed by continuous electrocardiographic monitoring for at least 72 hours	I B	
Pacemakers and ICDs should be regularly interrogated to identify AHREs. Patients with AHRE should also be monitored using ECG to document AF before its treatment is initiated	I B	Identification of AHRE justifies screening studies for AF and embolic risk stratification
For patients with stroke, physicians should consider additional continuous electrocardiographic monitoring using noninvasive ECG monitors or loop recorders to document silent AF	IIa B	Particularly applicable to cryptogenic stroke
Definition of paroxysmal AF: self-limiting, typically within 48 hours. Some paroxysmal AF episodes can last up to 7 days. AF episodes that are cardioverted within 7 days are considered paroxysmal		Appropriate reorganization, although the recommendation may generate temporary confusion and obligate reinterpretation of previous studies
Weight loss should be considered in obese patients with AF, as well as treatment of other risk factors to reduce AF burden and symptoms	IIa B	
Obstructive sleep apnea treatment should be optimized to reduce AF recurrence and improve the effects of its treatment	IIa B	
Integrated management with a structured approach should be considered for all patients with AF to improve adherence to guideline recommendations and reduce hospitalizations and mortality	IIa B	Complicated implementation. Lack of evidence for the recommendation
For patients of both sexes with AF with no other stroke risk factors, anticoagulant or antiplatelet therapy is not recommended to prevent stroke	III B, harm	
Anticoagulant therapy should be considered to prevent thromboembolisms in male patients with AF and a CHA ₂ DS ₂ -VASc score of 1, bearing in mind patients' individual characteristics and preferences	IIa B	
Anticoagulant therapy should be considered to prevent thromboembolisms in female patients with AF and a CHA ₂ DS ₂ -VASc score of 2, bearing in mind patients' individual characteristics and preferences	IIa B	
To improve stroke and bleeding risk estimation in patients with AF, measurement should be considered of levels of biomarkers, such as high-sensitivity troponin and natriuretic peptide	IIb B	Not clearly shown to reflect thromboembolic or bleeding risk
When patients receive VKA therapy, the TTR should be as high as possible and regularly checked	I A	Lack of definition of TTR level. Recommendable use of the SAME-TT ₂ R ₂ scale
When oral anticoagulation is initiated in patients with AF who are candidates for NOAC therapy (apixaban, dabigatran, edoxaban, or rivaroxaban), this treatment is preferable to a VKA	I A	
Patients with AF receiving VKA therapy should be considered for a NOAC if the TTR is poorly controlled despite good adherence or if it is preferred by the patient, as long as there are no NOAC contraindications (eg, a prosthetic valve)	IIb A	The recommendation level has been decreased without a clear reason
Antiplatelet monotherapy is not recommended for stroke prevention in patients with AF, independently of stroke risk	III A, harm	
Combination oral anticoagulants and antiplatelet agents increase bleeding risk and should be avoided in patients with AF with no other indication for platelet inhibition	III B, harm	
LAA occlusion can be considered to prevent stroke in patients with AF and contraindications to long-term anticoagulant therapy (eg, patients who have had potentially fatal bleeding without a reversible cause)	IIb B	Class of recommendation inexplicably low
Anticoagulation with heparin or LMWH is not recommended in patients with AF immediately after an ischemic stroke	III A, harm	
NOAC therapy is recommended in patients with AF and previous stroke instead of VKAs or aspirin	I B	
Combined treatment with an OAC and antiplatelet agent is not recommended after a TIA or stroke	III B, harm	
For patients who have had a stroke, aspirin should be considered for secondary stroke prevention until initiation or resumption of oral anticoagulation	IIa B	Slight disagreement due to bleeding risk
Beta-blockers, digoxin, diltiazem, or verapamil are recommended for heart rate control in patients with AF and LVEF ≥ 40%	IB	Removal of the recommendation to avoid digitalis in patients with paroxysmal AF. The use of digitalis drugs as isolated blocking agents is strengthened, without a solid rationale
Catheter ablation of AF should be considered as first-line treatment to prevent AF recurrence and improve symptoms in selected patients with paroxysmal AF as an alternative to antiarrhythmic drug therapy, considering the risks, benefits, and preferences of the patient	IIa B	
When physicians are planning catheter ablation of AF, they should consider maintaining oral anticoagulation with a VKA (IIa B) or NOAC (IIa C) during the procedure to maintain adequate anticoagulation	IIb B/C	
Catheter ablation should try to isolate the pulmonary veins via radiofrequency or cryoballoon ablation	IIa B	
Ablation of the AF should be considered to avoid pacemaker implantation in patients with AF-related bradycardia	IIa C	

AF, atrial fibrillation; AHRE, atrial high rate episode; ICD, implantable cardioverter defibrillator; LAA, left atrial appendage; LMWH, low-molecular-weight heparin; LVEF, left ventricular ejection fraction; NOAC, new oral anticoagulant; TIA, transient ischemic attack; TTR, time in therapeutic range; VKA, vitamin K antagonist.

DETECTION AND MANAGEMENT OF RISK FACTORS AND CONCOMITANT CARDIOVASCULAR DISEASES

The guidelines highlight the risk factors and comorbidities associated with AF and quantify their effect on AF risk. In addition to the usual risk factors, particular emphasis is given to obesity, alcohol consumption, smoking, and regular vigorous exercise.

Some drugs used in the treatment of AF in heart failure patients decrease AF risk (angiotensin-converting enzyme inhibitors, beta-blockers [BBs], and eplerenone), but not others (angiotensin II receptor blockers and neprilysin inhibitors). To reduce recurrence, weight loss is recommended (IIa B) for obese patients, whether via AF ablation or other strategies. For patients with chronic obstructive pulmonary disease, hypoxemia and acidosis correction is recommended in acute episodes (IIa C), as well as obstructive sleep apnea treatment (IIa B). A useful addition would be discussion of the relationship of reduced alcohol consumption and vigorous exercise with AF risk reduction.

A novel recommendation is to abandon the term “nonvalvular AF” and to refer to the specific underlying condition. Although up to 30% of patients with AF have some type of valve involvement, only mechanical heart valve prostheses or rheumatic mitral stenosis impact stroke risk.

INTEGRATED MANAGEMENT OF PATIENTS WITH ATRIAL FIBRILLATION

The guidelines propose (IIa B) the establishment of specific integrated multidisciplinary management programs for patients with AF to increase adherence to the guidelines' recommendations and improve prognosis. This recommendation is supported by 2 randomized studies that compared this strategy with usual care in tertiary centers, although one of these studies found only a marginal benefit. Various observational studies have also found fewer events with these programs. Although this strategy probably improves the prognosis and treatment of patients with AF, we believe that the current evidence is insufficient.

STROKE PREVENTION

A controversial aspect is the use of biomarkers (high-sensitivity troponin and N-terminal pro-B-type natriuretic peptide) to stratify thromboembolic risk, although the recommendation is IIb B. The diagnostic and prognostic usefulness of these biomarkers has been shown in other cardiovascular diseases but confirmation is required of their additional prognostic value in clinical risk scales. The studies contributing to the inclusion of these biomarkers in the guidelines were performed in patients enrolled in large trials comparing vitamin K antagonists (VKAs) with new oral anticoagulants (NOACs). Accordingly, the role of biomarkers is controversial because all patients were anticoagulated. Their use in low-risk patients has not been validated and their role in patients without anticoagulation remains to be studied.

The guidelines strengthen the usefulness of the CHA₂DS₂-VASc score for predicting thromboembolic risk. Anticoagulation is not recommended in patients with a CHA₂DS₂-VASc score of 0, even women (III B). However, anticoagulation is assigned a IIa B recommendation in men and women with a single stroke risk factor and a I A recommendation for men with 2 or more risk factors and women with at least 3. Thus, the female sex is no longer considered an independent risk factor when the anticoagulation indication is being assessed. Men with 1 point and women with 2 points are combined in a special section and the recommendation is for an individual risk evaluation. A recent meta-analysis⁴ showed that the embolic risk with a CHA₂DS₂-VASc score of 1 is below the estimated net-benefit threshold for VKAs

(1.7% per year), whereas the net-benefit threshold would be lower for NOACs (0.9% per year).

A list of modifiable risk factors for bleeding is proposed but no bleeding risk scale is explicitly recommended. Estimation of bleeding risk was a landmark in the treatment of patients with AF. The HAS-BLED score identifies modifiable risk factors for bleeding, such as the use of antiplatelet agents, uncontrolled hypertension, and poor control of VKA therapy. New bleeding risk scales, such as ATRIA, ORBIT, and ABC,^{5,6} have replaced the HAS-BLED score with a table of bleeding risk factors grouped into modifiable, potentially modifiable, and nonmodifiable. Another surprising change is the inclusion of biomarkers that are not used in daily clinical practice, such as GDF-15.

VKAs are the sole therapeutic option for patients with rheumatic mitral valve disease or a mechanical heart valve prosthesis. The guidelines note the importance of adequate VKA therapy in anticoagulation control, estimated by the time in therapeutic range (TTR). These antagonists continue to have a I A recommendation when the TTR is adequate. Notably, no cutoff point has been established for the TTR in this section or in the recommendation box. In recent years, a new score, the SAME-TT₂R₂, has been shown to be useful in identifying patients failing to achieve optimal anticoagulation control.⁷ This scale has been validated in a Spanish population.⁸ Its use would increase the percentage of patients considered suitable for these drugs who are not predicted to achieve stable anticoagulation—exceeding 40% of patients in different series—and would also avoid the 6-month transition period for VKAs mandated by current Spanish regulations.⁹

A clear preference is expressed for NOACs over VKAs for nonvalvular AF (I A recommendation). However, it seems illogical to reduce the recommendation for a change to a NOAC when inadequate control of the international normalized ratio (INR) is achieved with VKAs: this recommendation was I B in 2012 and is now IIb A. In addition, the bleeding risk associated with NOACs is similar to that of aspirin¹⁰ and they show a greater ability to reduce embolic events.¹¹

A conclusive recommendation is made to avoid the use of aspirin to prevent stroke, independently of patients' embolic risk (III A). The use of antithrombotics is also discouraged if there is no specific indication for antiplatelet therapy.

The guidelines incorporate edoxaban and present a “per-protocol on-treatment analysis”, which favors the drug. We believe that it would have been pertinent to discuss the main analysis in more detail. Table 13 shows discrepancies in dosage with the summary of product characteristics of edoxaban. The authors of the guideline have expressly chosen the criteria used in the clinical studies, given the international setting of the guidelines and possible differences in labeling between countries.

Two interesting differences with previous guidelines are the clear declaration of the safety of anticoagulation with NOACs in patients with mild-to-moderate chronic kidney disease and the recommendation to monitor renal function to enable anticoagulant dose modification and risk redefinition.

We must remember that no important clinical trial has validated the utility of acenocoumarol, the most widely used VKA in Spain. Acenocoumarol has a plasma half-life of 8 to 11 hours, similar to that of NOACs. Warfarin has a more prolonged half-life, which stabilizes the anticoagulation level.

Spain is not likely to be able to apply these recommendations on the use of NOACs, largely due to a lack of public funding.

Due to the results of a meta-analysis, surgical closure of the atrial appendage has gone from being supported by expert consensus opinion to having a level of evidence B. Similarly, the guidelines add the possibility of atrial appendage exclusion with thoracoscopy with the same recommendation level. However, despite the reduced embolic risk, the guidelines recommend that oral anticoagulation therapy be maintained after surgical exclusion of the atrial

appendage. Percutaneous occlusion of the atrial appendage as an alternative due to contraindication to oral anticoagulation continues to be only a IIb B recommendation, despite recent evidence showing a high success rate and low complication rate (< 5%) with this procedure.

Secondary Stroke Prevention

Another new development is a special section containing a useful management scheme for anticoagulant resumption. Heparin is not recommended after a stroke or transient ischemic attack (III A) because it increases the risk of intracranial hemorrhage without reducing the risk of stroke. An interesting innovation is the preferred indication (I B) of NOACs over VKAs and aspirin and the contraindication of combined antiplatelet agents and anticoagulants in secondary prevention (III B). A possible weak point is that the flowchart is based on expert consensus.

The recommended use of fibrinolytics in anticoagulated patients with AF who have had a stroke is limited to patients under treatment with a VKA and with an INR < 1.7 or under treatment with dabigatran if the activated partial thromboplastin time is within the normal range and the last dose has not been administered within the last 48 hours. The safety and effectiveness of anticoagulation reversal for fibrinolysis are unknown.

Notably, aspirin can be considered after a stroke in patients with AF until (re)initiation of anticoagulant therapy is possible (IIa B). It seems that this recommendation fails to consider the bleeding risk of the drug (which is mentioned in various sections of the guidelines). Previous editions of North American guidelines for the prevention of recurrent stroke indicate that aspirin has a net clinical benefit.

An algorithm is proposed for the management of oral anticoagulant therapy after an intracranial hemorrhage. If anticoagulation is reinitiated, the anticoagulant should have a lower bleeding profile, although no specific agent is specified. Atrial appendage occlusion is recommended if anticoagulation is contraindicated (IIb C).

Finally, the established levels of evidence can be confusing regarding parenteral anticoagulation after a stroke (level A) and the preference for NOACs in this setting (level B), given the characteristics of the studies addressing these issues.

A specific section of the document summarizes the various factors increasing bleeding risk. This section includes a cutoff point for a labile INR, and the guidelines recommend that patients be switched to a NOAC when an adequate TTR ($\geq 70\%$) cannot be maintained. Falls and dementia do not increase intracranial hemorrhage risk. Interruptions to anticoagulant therapy for surgical operations and minor procedures should be avoided, as well as the use of bridging therapy because it increases bleeding risk. However, NOACs are not mentioned in this context.

A surprising recommendation is to use fresh frozen plasma in patients with a bleeding event and anticoagulated with VKAs. Most guidelines recommend the use of prothrombin complex concentrate, given the lack of efficacy of fresh frozen plasma and its difficult administration (requiring thawing and a large volume) and associated secondary effects.¹² Idarucizumab is recommended as an antidote to dabigatran, as recently shown.

One noteworthy contradiction: the guidelines mentions that the greater risk of gastrointestinal bleeding associated with dabigatran 150 mg, rivaroxaban 20 mg and edoxaban 60 mg vs VKAs, dabigatran 110 mg and apixaban 5 mg has not been reproduced in subsequent registries, but then explicitly recommend that these drugs not be used in patients with a high risk of gastrointestinal bleeding.

Regarding combination anticoagulant and antiplatelet therapy, the guidelines reproduce the latest expert consensus of the European Heart Rhythm Association (EHRA). Thrombotic and ischemic risks should be estimated and the clinical situation evaluated, particularly elective coronary stenting for acute coronary

syndrome. Triple antithrombotic therapy is recommended in most patients; the duration should be as short as possible (IIa B or IIa C) and followed by dual therapy (oral anticoagulation plus a single antiplatelet agent). When a NOAC is used, the consensus is to use the lowest effective dose to prevent stroke in AF. However, the combination of aspirin, clopidogrel, and low-dose rivaroxaban (2.5 mg twice daily) is not recommended for stroke prevention in patients with AF. The use of prasugrel or ticagrelor as part of triple therapy should be avoided unless there is a clear need for these agents (eg, for stent thrombosis in patients under treatment with aspirin plus clopidogrel).

RATE CONTROL THERAPY IN ATRIAL FIBRILLATION

No major changes have been made to these recommendations. For acute rate control, the guidelines continue to preferentially recommend BBs and nondihydropyridine calcium antagonists (CAs) over digitalis. For long-term rate control, the same strength of recommendation is given to these 3 types of drugs (I B); specific drug selection should be based on patient characteristics. The guidelines have removed the recommendation not to use digitalis drugs as the only agents for heart rate control in patients with paroxysmal AF. This advice contrasts with North American guidelines, which only consider BBs and CAs for long-term heart rate control and restrict the use of digitalis to patients with heart failure.¹³ Digitalis drugs have few negative dromotropic effects in adrenergic states, as usually occur during paroxysmal AF episodes. The data from the FANTASIA registry¹⁴ show that the most widely used drugs for heart rate control in AF patients in Spain are BBs in most patients (60.2%), followed by digoxin (19.5%) and, to a lesser extent, CAs (10.7%). The guidelines recommend the combination of BBs or CAs with digitalis. However, these drug combinations are controversial because the results published on these combinations are discordant.

The guidelines barely consider combined heart rate and rhythm control, despite the possible effects of drug interactions. Combinations of some of these drugs can enhance their negative chronotropic effects. This is the case for the combined use of BBs and the type C antiarrhythmic drugs flecainide and propafenone because both types of drugs profoundly affect sinus node function. They should thus be used with caution in elderly patients or patients with suspected sinus node dysfunction. Recent publications discourage the combination of dronedarone with any agents that depress atrioventricular conduction, such as digoxin, given that the PALLAS trial¹⁵ linked their combined use with increased mortality (relative risk up to 7.3 times higher than digoxin or dronedarone in monotherapy). This combination is even discouraged in the European data sheet for dronedarone and it is striking that it has not been reflected in the new guidelines.

Atrioventricular node ablation and pacemaker implantation is one way to achieve heart rate control after drug therapy failure. However, the guidelines have largely ignored the type of cardiac resynchronization device, whether single-chamber, dual-chamber, or triple-chamber.

RHYTHM CONTROL THERAPY IN ATRIAL FIBRILLATION

The first major comment of the guidelines in this area is that the benefits of rhythm control therapy are limited to symptom improvement. Because there are no data on reduced mortality, there are no guidelines for asymptomatic patients. The publication of new studies such as the CABANA (Ablation Versus Anti-arrhythmic Drug Therapy for Atrial Fibrillation Trial) trial (NCT00911508) are eagerly awaited.

There are no changes in the indication or in the usual cardioversion procedure in patients with new-onset AF. Antiarrhythmic drug selection is based on their safety profile in the different heart diseases.

The guidelines note that the new drugs, such as vernakalant, do not significantly improve efficacy and recommend which agents are suitable for each disease.

An alternative option is ablation, which is awarded a IIa recommendation. This class of recommendation might be a source of controversy due to the considerable number of randomized studies showing that ablation is superior to antiarrhythmics in patients without previous antiarrhythmic therapy. Because most recurrences are observed in the first months after vascular surgery, the guidelines comment that amiodarone reduces recurrence for 4 weeks, but not for longer times. Intermittent amiodarone use after vascular surgery is associated with greater mortality and more hospitalizations vs continuous use. The effectiveness of new drugs such as ranolazine or combinations of antiarrhythmic drugs such as dronedarone and ranolazine is called into question due to recent publications.

The guidelines affirm that ablation is clearly superior to antiarrhythmic drugs when one of these drugs has previously failed. Although studies comparing ablation and antiarrhythmic drugs in untreated patients are mentioned, the findings are not collected in a specific comment.

The guidelines note that, apart from antrum isolation, no technique has been shown to be superior to catheter ablation for either paroxysmal or persistent FA. The usefulness of certain interesting techniques, such as rotor ablation, remains to be shown in clinical trials. However, cryoablation is not inferior to conventional point-to-point ablation. Although experts indicate that cavotricuspid isthmus ablation should be performed in patients with AF and atrial flutter, there are no conclusive data supporting the effectiveness of this approach.

Surprisingly, despite the recent position document of the EHRA with other societies on periprocedural antithrombotic management,¹⁶ this article has not been cited. Due to recent evidence, the guidelines state that patients treated with VKAs should maintain this treatment during the procedure. However, the guidelines fail to note whether the benefit observed in patients with AF is long-lasting. Thus, there are doubts about the general suitability of anticoagulant maintenance, whether VKAs or NOACs, during ablation procedures (IIb).

Because AF and ventricular dysfunction frequently coexist and worsen each other's symptoms, it is important to define the value of ablation in these patients. The guidelines fail to cite any study showing that ablation boosts ventricular function recovery in patients with either adequate or inadequate ventricular heart rate control¹⁷ and that the main determinant of ventricular function recovery failure is the presence of myocardial infarction. No convincing evidence is put forward showing that ablation is superior to strict control of ventricular heart rate with node ablation and subsequent resynchronization device implantation. However, the guidelines do state that ablation is superior to amiodarone in patients with ventricular dysfunction and an implantable device.

SURGERY AND ATRIAL FIBRILLATION

The most notable contribution in this area concerns ablation that is not combined with another type of surgery. The development of videothoracoscopy and bipolar radiofrequency ablation with cryotherapy has simplified the procedure and has reduced complications to such an extent that it can be considered another surgical option for the treatment of AF. Effectiveness rates ranging between 70% and 90% justify its use in patients who have undergone failed percutaneous procedures.

HYBRID THERAPY

The guidelines discuss 2 aspects of hybrid rhythm control therapy involving antiarrhythmic drugs: their combined use with either

catheter ablation or pacemakers. Regarding the first approach, although the guidelines establish that it appears to be common knowledge to use antiarrhythmic drugs in patients with AF recurrence after an ablation procedure, no guidelines or strength of recommendation are established for its use, despite various studies showing a lower incidence of AF and fewer hospitalizations after ablation.¹⁸ The guidelines mention the possible use of cavotricuspid isthmus ablation and continued antiarrhythmic drug therapy—mainly with type IC antiarrhythmic drugs—in patients with AF and organized atrial flutter, but no strength of recommendation is provided. In the European and North American guidelines for supraventricular tachycardia treatment, a strong recommendation (I and IIa) is awarded to this approach.

The guidelines also mention combination hybrid therapy involving a pacemaker and antiarrhythmic drugs, largely due to the negative chronotropic effects of these drugs. Pacemakers permit the use of higher doses of these drugs. However, catheter ablation can sometimes obviate the need for antiarrhythmic drugs and pacemakers. Some of these patients have reverse remodeling of the sinus node, which can return after AF termination with ablation.¹⁹ However, early sinus node dysfunction can be unmasked by the antiarrhythmic drugs and would require monitoring.

SPECIFIC SITUATIONS

This section has been reorganized to remove the brief comments of previous guidelines on hyperthyroidism and pulmonary disease.

The guidelines stress the need to use medical records and other tests to evaluate the presence of channelopathies and other cardiomyopathies in young patients without apparent structural heart disease but with AF; systematic genetic studies are not considered necessary. The section on sport and AF is well supported, although it might be imprecise, even confusing, regarding the effects of detraining.

Another development is that the pertinent information on AF (and other atrial arrhythmias) in adult patients with congenital heart disease is organized in a separate section. However, the recommendations are level C only, except for those referring to atrial flutter.

AREAS WITH GAPS IN EVIDENCE

The guidelines highlight 9 specific situations requiring appropriately powered randomized trials to robustly establish an adequate recommendation level. Some of these are especially relevant, such as anticoagulation in patients with AF and severe chronic kidney disease, anticoagulation after a bleeding or stroke event, the optimal timing of cardioversion for new-onset AF without anticoagulation, and atrial appendage occlusion for stroke prevention.

There is a lack of scientific evidence in diverse areas of knowledge supporting some of the recommendations or preventing their implementation. Examples include AHREs, the role of anticoagulation in biological prostheses and rheumatic mitral valve disease, and the role of ablation in persistent AF. Questions remain regarding atrial appendage closure/occlusion, because the indications included in the clinical guidelines are different from those evaluated in the main clinical studies, and the need to maintain anticoagulation after device implantation.

CONCLUSIONS

Although the guidelines have a strong clinical focus and have incorporated the relevant available evidence, it is patently clear that many of the situations considered require greater scientific support.

A notable inclusion is the integrated management of AF because this approach recognizes the epidemiological importance of the disease, its relationship with other risk factors, the need for early detection, its multidisciplinary treatment, and the role played by the patient.

The largest section deals with anticoagulant therapy and considers various related factors such as the correct indication, bleeding risk, and its combination with antiplatelet agents or atrial appendage exclusion. All of these factors interact and have distinct effects due to differences in clinical situations.

The guidelines consider heart rate and rhythm control therapies, with few changes, and lack definitions in specific situations, such as certain hybrid therapies or the role of ablation. However, the surgical setting is considered.

Special situations are defined, and areas lacking clarity are recognized.

There are some important changes concerning the classifications of paroxysmal and persistent AF, the role of female sex as an embolic risk factor, and the abandonment of the HAS-BLED stratification scale of bleeding risk, among others, which could lead to some confusion upon their incorporation into clinical practice.

These guidelines are welcome for persuasively arguing for a need for systematic care in patients with AF.

CONFLICTS OF INTERESTS

However, the following authors declare financial relationships with entities that may have interests in certain aspects of the article: F. Arribas: consulting (Boehringer-Ingelheim, Daiichi Sankyo, Lina Nova), presentations (Boston Scientific, Bayer), educational presentations (Medtronic, Boston Scientific, Biosense), attendance at meetings (Medtronic, Lisa Nova, Boston Scientific). I. Roldán: presentations (AstraZeneca). J. L. Merino: board member (Daiichi Sankyo, Biosense, Sanofi), consulting (Biotronik, Cardiome, Daiichi Sankyo, Medtronic, Sanofi, Sorin), presentations (Biotronik, Boston Scientific, Medtronic, St. Jude, Sanofi), educational presentations (St. Jude), attendance at meetings (Biotronik, Boston Scientific, Medtronic, St. Jude, Sanofi), symposium sponsorship (Bayer, Boehringer-Ingelheim, Pfizer, Cardiome, Boston, Equipamiento Scientific, Medtronic, St. Jude, Sorin, Microport). R. Ruiz: consulting (Medtronic, Boston Scientific), presentations (Medtronic, Boston Scientific, St. Jude). L. Mont: consulting (St. Jude Medical, Boston Scientific, Johnson & Johnson, Medtronic, Boehringer), expert testimony (St. Jude, Boston Scientific, Johnson & Johnson, Medtronic, Boehringer-Ingelheim), presentations (St. Jude, Boston Scientific, Johnson & Johnson, Medtronic, Boehringer), educational presentations (Johnson & Johnson). F. Marín: consulting (Daiichi Sankyo, Bayer), attendance at meetings (Daiichi Sankyo, Bayer), presentations (AstraZeneca), research project (Pfizer/BMS, Boehringer-Ingelheim). V. Barrios: member of the board of directors (Bayer, Boehringer-Ingelheim and Daiichi Sankyo), consulting (Bayer, Boehringer Ingelheim, Daiichi Sankyo), presentations (Bayer, Boehringer-Ingelheim, Daiichi Sankyo, Pfizer). G. Barón: consulting (Bayer, Boehringer-Ingelheim, Daiichi Sankyo, Pfizer), expert testimony (Bayer, Boehringer-Ingelheim, Daiichi Sankyo, Pfizer), presentations, manuscript preparation (Bayer), attendance at meetings (Bayer, Pfizer). E. Díaz: consulting (Medtronic, Boston Scientific), presentations (Medtronic, Boston Scientific, St. Jude Medical, Biotronik), educational presentations (Medtronic, Boston Scientific, St. Jude, Biotronik), attendance at meetings (Medtronic, St. Jude). J. L. Ferreira: presentations (Daiichi Sankyo, Pfizer). N. Pérez-Castellano: consulting (Medtronic, Boston Scientific, St. Jude Medical, Livanova), presentations (Medtronic, Boston Scientific, St. Jude Medical, Livanova), manuscript preparation (Boston Scientific), attendance at meetings (Boston Scientific). A. Tello: grants (Astra Zeneca), presentations (Amgen, Astra Zeneca, Merk, Biosensors), attendance at meetings (Daiichi Sankyo). F.

Alfonso: attendance at meetings. I. Ferreira-González: presentations (Bayer, Pfizer, Boehringer-Ingelheim), educational presentations (Bayer, Pfizer, Boehringer, Abbott), consulting (Bayer). L. Rodríguez-Padial: presentations (MSD, Pfizer, Rovi, Daiichi Sankyo, Amgen, Sanofi), attendance at meetings (Menarini, Servier, Sanofi).

APPENDIX. AUTHORS

SEC Working Group for the 2016 ESC Guidelines for the Management of Atrial Fibrillation: Fernando Arribas, Inmaculada Roldán, José Luis Merino, Vanessa Roldán, Ángel Arenal, Juan Tamargo, Ricardo Ruiz-Granell, Lluís Mont, Manuel Anguita and Francisco Marín.

Reviewers for the 2016 ESC Guidelines for the Management of Atrial Fibrillation: Vivencio Barrios Alonso, Gonzalo Barón y Esquivias, Juan Cosín Sales, Ernesto Díaz Infante, Carlos Escobar Cervantes, José Luis Ferreira Gutiérrez, José M. Guerra Ramos, Francisco Javier Jiménez Candil, Nicasio Pérez Castellano, Antonia Sambola Ayala, and Antonio Tello Montoliu.

SEC Guidelines Committee: Alberto San Román, Fernando Alfonso, Fernando Arribas, Arturo Evangelista, Ignacio Ferreira, Manuel Jiménez, Francisco Marín, Leopoldo Pérez de Isla, Luis Rodríguez Padial, Pedro L. Sánchez, Alessandro Sionis, and Rafael Vázquez.

REFERENCES

- Anguita M, Fernández-Ortiz A, Worner F, et al. La Sociedad Española de Cardiología y las guías de práctica clínica de la SEC: hacia una nueva orientación. *Rev Esp Cardiol.* 2011; 64:795-796.
- Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS: The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC, endorsed by the European Stroke Organisation (ESO). *Eur Heart J.* 2016. Available at: <https://doi.org/10.1093/eurheartj/ehw210>
- Gómez-Doblas JJ, Muñoz J, Alonso Martín JJ, et al. Prevalence of atrial fibrillation in Spain. OFRECE study results. *Rev Esp Cardiol.* 2014;67:259-269.
- Joundi RA, Cipriano LE, Sposato LA, et al., on behalf of the Stroke Outcomes Research Working Group. Ischemic stroke risk in patients with atrial fibrillation and CHA2DS2-VASc score of 1. Systematic review and meta-analysis. *Stroke.* 2016;47:1364-1367.
- Abumuaileq RR, Abu-Assi E, Raposeiras-Roubin S, et al. Comparison between 3 bleeding scoring systems in nonvalvular atrial fibrillation patients. What can the new ORBIT score provide? *Rev Esp Cardiol.* 2016;69:1112-1114.
- Esteve-Pastor MA, García-Fernández A, Macías M, et al. Is the ORBIT bleeding risk score superior to HAS-BLED score in anticoagulated atrial fibrillation patients? *Circ J.* 2016;80:2102-2108.
- Apostolakis S, Sullivan RM, Olshansky B, et al. Factors affecting quality of anticoagulation control among patients with atrial fibrillation on warfarin: the SAME-TT₂R₂ score. *Chest.* 2013;144:1555-1563.
- Roldán V, Cancio S, Gálvez J, et al. The SAME-TT₂R₂ score predicts poor anticoagulation control in af patients: a prospective 'real-world' inception cohort study. *Am J Med.* 2015;128:1237-1243.
- Roldán I, Marín F. On the way to a better use of anticoagulants in nonvalvular atrial fibrillation. Proposed amendment to the therapeutic positioning report UT/V4/23122013. *Rev Esp Cardiol.* 2016;69:551-553.
- Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. *N Engl J Med.* 2011;364:806-817.
- Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet.* 2014;383:955-962.
- Makris M, Van Veen JJ, Tait CR, et al. Guideline on the management of bleeding in patients on antithrombotic agents. *Br J Haematol.* 2013;160:35-46.
- January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation.* 2014;130:2071-2104.
- Roldán-Rabadán I, Anguita-Sánchez M, Marín F, et al. Current antiarrhythmic therapy for nonvalvular atrial fibrillation in Spain. Data from the FANTASIA registry. *Rev Esp Cardiol.* 2016;69:54-60.
- Hohnloser SH, Halperin JL, Camm AJ, et al. Interaction between digoxin and dronedarone in the PALLAS trial. *Circ Arrhythm Electrophysiol.* 2014;7:1019-1025.
- Sticherling C, Marín F, Birnie D, et al. Antithrombotic management in patients undergoing electrophysiological procedures: a European Heart Rhythm Association (EHRA) position document endorsed by the ESC Working Group

- Thrombosis, Heart Rhythm Society (HRS), and Asian Pacific Heart Rhythm Society (APHRS). *Europace*. 2015;17:1197-1214.
17. Hsu LF, Jaïs P, Sanders P, et al. Catheter ablation for atrial fibrillation in congestive heart failure. *N Engl J Med*. 2004;351:2373-2383.
 18. Roux JF, Zado E, Callans DJ, et al. Antiarrhythmics After Ablation of Atrial Fibrillation (5A Study). *Circulation*. 2009;120:1036-1040.
 19. Hocini M, Sanders P, Deisenhofer I, et al. Reverse remodeling of sinus node function after catheter ablation of atrial fibrillation in patients with prolonged sinus pauses. *Circulation*. 2003;108:1172-1175.
 20. Holmes DR, Reddy VY, Turi ZG, et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet*. 2009;374:534-542.