Editorial


Nuevas evidencias, nuevas controversias: análisis crítico de la guía de práctica clínica sobre fibrilación auricular 2010 de la Sociedad Europea de Cardiología

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INTRODUCTION

In keeping with the new philosophy on clinical practice guidelines developed by the Executive Committee of the Sociedad Española de Cardiología (SEC), which was explained in a recent document published in the Revista Española de Cardiología (REC),1 this article discusses the most controversial aspects of the guidelines for atrial fibrillation (AF) published by the European Society of Cardiology (ESC) in 2010.2 These guidelines have inspired a great deal of interest due to the large body of scientific evidence regarding AF that has been compiled in recent years, as well as the new recommendations. The objectives of this review are: a) to evaluate the methodology and chronology developed for the analysis of European guidelines on other subjects,1 and b) to analyze the different guidelines and evaluate their most innovative recommendations, which have generated an interesting debate and contrast with recommendations from more recently published international guidelines. Additionally, the time elapsed between this publication and the release of new evidence allows us to make our comments with more perspective.

METHODS

The Clinical Practice Guidelines Committee of the SEC formed a working group of clinical cardiologists, electrophysiologists, and cardiovascular thrombosis experts (cardiologists and hematologists) with the general objective of reviewing the evidence and recommendations put forth by the aforementioned AF guidelines, as well as new studies published since their appearance. The basis for our review was the ESC guidelines for AF, which have been accepted by the SEC and published in the REC.3 Clinical cardiologists were asked for a general evaluation of all novel aspects of the guidelines, whereas electrophysiologists and thrombosis experts were asked for an evaluation of the topics most closely related to their fields. Using these expert comments, we developed a consensus document, which was approved by all members of the working group. This document was sent for review to another group of 18 experts selected by the SEC’s scientific sections of Clinical Cardiology and Electrophysiology/Arrhythmias, and their comments were added to the final document. Each participant was required to provide a declaration of conflicts of interest in relation to this subject, and these are detailed at the end of this article. Although the experts had total liberty to discuss the subjects that they deemed to be of the highest interest, we did provide a basic questionnaire to serve as a reference and to homogenize the information produced.

GENERAL COMMENTS AND ANALYSIS OF THE METHODOLOGY

The time elapsed between the publication of the older version of the guidelines (4 years)4 and the existence of new and numerous data on several different aspects of AF made a new version necessary, as evidenced by the almost simultaneous release of new European, Canadian, and North American publications.5,6 In contrast to the 2006 guidelines, which were a joint production of the ESC, the American Heart Association (AHA), and the American College of Cardiology (ACC), the new guidelines are independent. The primary reason put forth—the different regulatory systems involved (European Medicines agency [EMA], Food and Drug Administration [FDA])—does not appear to be a sufficient reason to abandon efforts to present a joint analysis of existing scientific evidence compiled from European and American experts, as was
done in 2006. The contradictory aspects and different recommendations given by the various guidelines generate confusion and reduce their value.

In terms of categorizing the 212 recommendations, we must point out that only 35 of them (16%) are of level A quality (evidence derived from multiple randomized clinical trials or meta-analyses), 70 are level B (one single randomized clinical trial or several nonrandomized large studies), and 107 (50%) are level C (expert consensus), thereby reducing the overall value of these recommendations. Most recommendations for managing AF in special situations are of level C. This excess of level C indications, which is not exclusive to European guidelines, could possibly be due to an attempt to cover all possible situations, but it might be preferable to avoid publishing such a large number of personal expert opinions and only highlight those that have clearly demonstrated evidence to support them. This would generate “at minimum” guidelines whose recommendations would be indisputable, and therefore stronger. The guidelines should also point out current information gaps and propose well-designed studies to address them.

NEW DEVELOPMENTS

The most important and/or novel aspects of the results identified by the working group are the following:

1. The concept of long-standing persistent AF.
2. The new symptom classification from the European Heart Rhythm Association (EHRA).
3. The new embolic and hemorrhagic risk scales and criteria.
4. The recommendations for anticoagulants and antiplatelets in ischemic patients with AF, above all when stents have been implanted.
5. The indications for rhythm/rate control strategies and less strict rate control.
6. The role of new antiarrhythmic drugs (dronedarone, vernakalant).
7. The indications for ablation.

CRITICAL REVIEW OF NOVEL ASPECTS

Long-Standing Persistent Atrial Fibrillation

The ESC guidelines recognize that there are a growing number of patients with AF lasting longer than 1 year (which was labelled as “permanent” AF in the guidelines prior to 2006), who are best treated using a rhythm control strategy (usually ablation techniques). The new guidelines propose a new label, long-standing persistent AF, although this does not translate into any change in the previous “permanent” AF recommendations.

European Heart Rhythm Association Symptom-Based Classification

This classification can be useful because it standardizes symptoms, but it is not very concrete, as it tends to occur with functional classification systems. It does not specify which symptoms are to be evaluated (dyspnea, palpitations, etc.) and it might not be as applicable in paroxysmal AF. Additionally, another previous system already exists, the Canadian classification, which has one more functional class, and it is doubtful that the EHRA will replace the system developed by the New York Heart Association (NYHA), which, although used more for heart failure, is similar. It would be most logical to use one single system universally.

Indications for Anticoagulation Therapy in Non-Valvular Atrial Fibrillation

The changes proposed to the indications for anticoagulation are among the most highly controversial aspects of the ESC guidelines for AF.7 These changes focus on the replacement of the CHADS2 score for estimating embolic risk with the CHA2DS2-VASc score, and use of the HAS-BLED score to assess risk of bleeding.2,3

Embolic Risk Scores

The new CHA2DS2-VASc score lends greater importance to the continuum than the CHADS2 and eliminates the arbitrary categorization of “low-moderate-high” risk. For example, a CHADS2 score of 1, with a 2.8% annual risk, is not the same as a CHADS2 score of 2, with a 4% annual risk. The introduction of the new thrombo-embolic risk score involves a different strategy for managing low-risk patients (those with a CHADS2 score between 0 and 1), since it precisely identifies patients with low thromboembolic risk (0.78% annual risk for patients with a score of 0), with the consequence of notably increasing the indications for anticoagulation therapy, since only males younger than 65 years and with no other risk factors would not need anticoagulants (only 8.6% of the patient population).8 Two different fundamental reasons have been put forth to justify the introduction of this new system: a) to incorporate major risk factors that were not included in the CHADS2 (vascular disease, age between 65 and 75 years, and female sex), and b) the approval of new anticoagulants with a better safety profile than warfarin and acenocoumarol. No consensus exists in the medical literature regarding whether the new criteria included, such as female sex and a history of vascular disease limited to angina, are in fact associated with a greater embolic risk in patients with AF.9,10 The guidelines do state that the diagnosis of angina often is not reliable, and that other more objective criteria must be developed in order to establish the presence of coronary vascular disease. The embolic risk of some of the old factors from the CHADS2 score that have been retained in the CHA2DS2-VASc is also unclear, such as in well-controlled arterial hypertension,11 “clinical” heart failure (in the absence of left ventricular systolic dysfunction), and the existence of associated cardiopathies, such as hypertrophic or restrictive cardiomyopathy, as discussed in the 2010 ESC guidelines.4

Although the CHA2DS2-VASc score was developed using the data from one single observational study published in Chest,5 several studies later validated it by comparing it with the CHADS2 score,12,13 North American and Canadian guidelines6,14 reject using the new CHA2DS2-VASc, arguing that its impact on clinical decisions has not been established as superior to that of CHADS2 and that the new score is more complex and difficult to remember. The initial study5 only had one patient out of 7329 with a score of 0, making it difficult to make recommendations. Another limitation is the vague recommendation given for patients with a score of 1 (antiplatelets or anticoagulants, but preferably anticoagulants) or 0 (antiplatelets or no antithrombotic treatment, as preferred).

In conclusion, the new CHA2DS2-VASc contributes several advantages over the previous version, especially by providing a better assessment of embolic risk in patients with a score <2 on the CHADS2, but the optimal treatment strategy in these low-risk patients continues to be unclear, as well as the importance of the isolated presence of peripheral vascular disease, well-controlled hypertension, heart failure with no systolic dysfunction, and female sex. However, some recent studies have found a higher incidence of embolism in patients with peripheral artery disease or myocardial infarctions15 and in women.16
Risk of Bleeding Score

The European guidelines propose the use of the HAS-BLED score for risk of major bleeding (hypertension, kidney or liver failure, history of stroke or bleeding, unstable international normalized ratio [INR] values, age $\geq$65 years, use of drugs that could interfere with homeostasis, and alcohol) based on one single study, the European AF registry, although the score was validated in later reports. Although the risk of bleeding is relevant, several hemorrhagic risk factors from this score are also applicable for embolism, which may result in similar procedural recommendations for both conditions. We must also point out that the guidelines do not establish a contraindication for anticoagulants with a HAS-BLED score of 3 or higher, but rather recommend a close follow-up protocol with these patients, whether they take anticoagulants or antiplatelets. The risk of bleeding should be evaluated in all of these patients, and not just in those taking oral anticoagulants, since the use of acetylsalicylic acid (ASA) is also associated with a risk of bleeding, sometimes higher than that of anticoagulants.

Recommendations for Anticoagulant Therapies

This section generated the greatest conflict between the recommendations set forth by the European and North American societies. In fact, the new American guidelines in this category are no different from those published jointly by both groups in 2006. According to the European guidelines, for patients with only one risk factor (65–74 years, heart failure/left ventricular dysfunction, hypertension, diabetes mellitus, vascular disease, or female sex), anticoagulants are recommended over antiplatelets. This is the most notable difference between the two versions of the European guidelines (from 2006 and 2010) or between the new version and the American guidelines, since this affects a significant number of patients (those considered to be at low or moderate risk). The new recommendation has been supported by a Danish study but refuted by a Spanish one. In the latter study, involving a general population with AF, the embolic risk was very low and was similar with or without anticoagulation therapy in patients with a CHA2DS2-VASc score between 0 and 1. Some discord can also be observed with generally established concepts. Specifically, ASA is recommended over anticoagulants in female patients younger than 65 years and without other risk factors (class IIb recommendation, level C). Another clearly different recommendation is the preference to withhold antithrombotic treatment in low-risk patients (CHA2DS2-VASc of 0; class Ila recommendation, level B). Lastly, the recommendations for anticoagulants used in cardiovascular are all supported only by level B or C evidence. Although the quality of anticoagulation is not discussed in the recommendations, it is interesting to read the points that the ESC guidelines make on this subject. They affirm that if the time within the therapeutic range is less than 60, the benefit of anticoagulants as opposed to antiplatelets can be completely lost. This is a critical aspect of anticoagulation therapy in AF patients currently receiving treatment in Spain, as in other countries. Logically, this is only applicable to current antivitamin K anticoagulants, and such issues would not pose a problem with the new anticoagulants available.

Antithrombotic Drugs

In patients with contraindications for antivitamin K therapy due to incapacity to achieve high quality anticoagulation, as well as for patients that simply reject it, the new ESC guidelines recommend using ASA (75-100 mg/day) along with clopidogrel (75 mg/day). This is a class Ila recommendation, level B, and is also incorporated into the updated American guidelines, although as a class IIIb. The RE-LY study had already been published, but the ESC guidelines did not incorporate the use of dabigatran into its recommendations, since it still did not have EMA approval at the time of publication. The guidelines do mention that dabigatran at 150 mg every 12 h can be considered as an alternative to antivitamin K in patients with a HAS-BLED score $<$2 and a CHA2DS2-VASc score $>$1, and that 110 mg of dabigatran every 12 h can be an alternative in patients with a HAS-BLED score $>$3, or in patients with a CHA2DS2-VASc score of 1. After the FDA approved the use of dabigatran, the updated ACCF/AHA/HRS guidelines included a recommendation to use it as an alternative to antivitamin K drugs, with a B level of evidence. This recommendation completely avoids showing any preference, does not mention risk-specific doses, and limits its discussion to the contraindications listed on the drug's technical data sheet. Canadian guidelines recommend the use of dabigatran over antivitamin K in patients with a CHADS2 score of 1 or greater in the majority of patients. New drugs, such as apixaban (AVERROES study, apixaban vs ASA; ARISTOTLE study, apixaban vs warfarin) and rivaroxaban (ROCKET-AF study, apixaban vs warfarin) have proven more effective and safer than traditional anticoagulants, but the official guidelines still do not recommend their use. These drugs quite possibly might replace traditional oral anticoagulants in the near future, and will deserve a special update when enough time and a broader perspective have been devoted to the analysis and comparison of these drugs.

Perioperative Management of Oral Anticoagulants

Another important topic is the perioperative management of these drugs. The guidelines give a class Ila level C recommendation that treatment after surgery must be resumed on the same night of the procedure or the following morning with normal maintenance doses, as long as the patient is hemostatically stable. The supporting text only gives information on warfarin and phenprocoumon, two oral anticoagulants with an extremely long half-life, and does not make any reference to acenocoumarol, which is the drug most commonly used in Spain. Whereas a patient that starts warfarin treatment at normal doses may not reach an INR $>$2 for 7 to 10 days, effective values can be reached with acenocoumarol within 3 to 5 days. In the postoperative period following surgical procedures with a high risk of bleeding (placement of a pacemaker, transurethral resection of the prostate, etc.), it may be advisable to delay treatment with acenocoumarol 24 h to 48 h or more, keeping in mind the embolic risk as well. With regard to the new anticoagulation drugs, this is one aspect about which we have very little information, requiring further study (when to suspend/resume treatment, monitoring activity, reversion of their effects in the case of emergency surgery, etc.).

Indications for Antithrombotic Treatment in Patients With Ischemic Heart Disease and Atrial Fibrillation

This is a completely new section in the ESC guidelines, and is based on consensus (level C evidence) and class Ila or IIb recommendations, and thus should be approached with caution. Additionally, there are some discrepancies between the written recommendations and the explanatory support table (Table 11 in the guidelines). The text gives the class Ila recommendation with level C evidence of the need for triple therapy (ASA at 75–100 mg/day + clopidogrel at 75 mg/day + oral anticoagulants) during 1 month in the case of metallic stents, and 3 to 6 months in the case of drug-eluting stents or following an acute coronary syndrome with or without a coronary surgical intervention, with closely controlled INR between 2 and 2.5 (class IIb, level C). Following this
triple therapy, the guidelines recommend switching to oral anticoagulants + clopidogrel at 75 mg/day (or ASA + antiacids), without specifying whether to maintain this double treatment beyond 1 year postimplantation of the stent (class IIa, level C). In contrast, the explanatory table (Table 11, which does not have categorized recommendations) states that this double treatment is recommended only for the first year and that oral anticoagulants suffice thereafter, suspending clopidogrel/ASA, both in metallic and drug-eluting stents. In patients with HAS-BLED scores >3 and elective metallic stents, the guideline recommends suspending the triple therapy after 1 month and continuing with only oral anticoagulants. The authors maintain that the coronary disease can be considered stable 1 year after the stent has been placed, and in this context, oral anticoagulants suffice. However, studies have shown that delayed and incomplete endothelialization, which can cause late thrombosis, can be detected even 4 years after the implantation of a drug-eluting stent, although there is no conclusive evidence from randomized studies indicating whether after that point anticoagulants and antiplatelets work better than anticoagulants alone. It appears that more data is needed in order to establish more concrete recommendations in this area. As long as this information gap exists, these recommendations must be taken with caution.

Controlling Rhythm or Rate?

The text of the new guidelines clearly supports that controlling the rhythm is not better that controlling the rate, at least in the initial treatment of AF. There is no clear advantage to either methodologic in terms of mortality and stroke (AFFIRM,26 cardiovascular death in patients with heart failure (RACE),27 cardiovascular death in patients with an ejection fraction <35% (AF-CHF),28 or quality of life (AFFIRM, RACE, PIAF,29 and STAF30). Based on this evidence, the text states that “the deleterious effects of antiarrhythmic drugs may have offset the benefits of sinus rhythm,” and that “the underlying heart disease impacts prognosis more than AF itself.”

This strong supporting evidence in the text contrasts with the table of recommendations, in which the rate control alone has a Ia indication in elderly patients with minor symptoms (EHRA I), and rhythm control is recommended in all other circumstances, based on dubious contrasting evidence (IB, IIaB, or IIaC). A recent article31 published after the ESC guidelines publication, with 5171 “real life” patients confirmed the results from previous trials, demonstrating that the incidence of cardiovascular events does not depend on the strategy of controlling rhythm or rate, although the progression of permanent AF was slower in patients with controlled rhythm. It appears, then, that the recommendations table from the ESC guidelines puts more emphasis on the control of rhythm than is observable in the evidence provided and in the text of the document, which may generate a greater rate of prescribing antiarrhythmic drugs and more indications for ablation in persistent or permanent AF. This fact is reinforced by the large section of the document dedicated to this topic, both in the amount of text and in the number of tables and figures. It is true that these data may not be generally applicable to young patients, who are not included in the aforementioned studies, and that the results from the ATHENA study appear to confirm the advantages of controlling sinus rhythm, although this was not a primary objective of the study.

With regard to optimal rate in permanent or persistent AF, the European guidelines recommend a value <110 bpm, based on the results from the RACE II study,32 which demonstrated that results were similar with different levels of rate control (<110 bpm vs <80 bpm), and this is the same recommendation made by the North American guidelines.33 The Canadian guidelines recommend reaching <100 bpm, since only 22% of the patients assigned to the less strict control group had a rate >100-110 bpm.33,34 Rate control must be in accordance with the symptoms and functional limitations caused by tachyarrhythmia, including the risk of developing tachycardiomyopathy or decompensation in chronic heart failure.

New Antiarrhythmic Drugs

The ESC guidelines introduce broad recommendations regarding a new antiarrhythmic drug, dronedarone. The recommendations made on this drug are based on nonpermanent AF studies, such as the ATHENA,32 the DIONYSOS,35 and the study by Singh et al.36 A previous study involving patients with severe heart failure (ANDROMEDA)37 had to be suspended early due to increased patient mortality, leading to a contraindication for this medication in these patients. Table 1 summarizes the information regarding dronedarone available at the time the guidelines were published. Despite the lack of trials in permanent AF patients (except for some small studies), the European guidelines consider its use “reasonable” in this context, with a IIaB indication in the absence of heart failure. Ten months after these recommendations were made, we observed the premature interruption of the PALLAS study,38 which had the goal of examining 10 800 patients with permanent AF and some type of cardiovascular risk factor (among them ventricular dysfunction), in order to evaluate morbidity and mortality risks with this drug as compared to a placebo. The protocol excluded patients with a NYHA functional class IV or unstable III. The study was halted when 1349 patients were included, due to an excess of cardiovascular events in the group receiving dronedarone.

Until the results from the PALLAS study have been scrutinized in detail, dronedarone can be indicated in patients with temporary AF and structural heart disease without severe heart failure (class IV, with recent episodes of decompensation), in contrast to other antiarrhythmics. However, the contrasting recommendations for this situation (IA in the European guidelines2 or IIaB in the American guidelines6)7 raise questions. Additionally, this is always mentioned as the first option of antiarrhythmics in figures (the most important visual message), over flecainide, propafenone, and sotalol, even in patients with no or minimal structural damage. The figure captions indicate that the medicines follow in alphabetical order, which has raised suspicions as it gives the impression of favoring the most recent drug commercialized, with no evidence that this is superior to the previously available types in terms of preventing recurrence. Moreover, the concept of structural cardiopathy is not uniform in the various guidelines. Whereas the European guidelines include patients with ventricular hypertrophy secondary to hypertension in this group, Canadian guidelines include any antiarrhythmia when hypertrophy is present, in the absence of other heart diseases and significant repolarization anomalies in the electrocardiogram (which could be a marker for proarrrhythmia).35 The European guidelines discuss this in the text, but the figures only recommend dronedarone or amiodarone.

As evidenced in Table 1, the studies that favor the use of dronedarone were carried out in transient AF and were compared with a placebo. In the only comparative study involving another drug,35 the efficacy of dronedarone was significantly lower in avoiding AF recurrence as opposed to amiodarone (63.5% vs 42%), with only a slight and insignificant trend towards a lower rate of suspended treatment due to adverse effects (10.4% vs 13.3%). The guidelines are clear that the most effective and safest drug for patients that need to maintain sinus rhythm (due to severe structural cardiopathy and/or advanced or unstable heart failure)
is amiodarone. Some recent articles39,40 based on daily experience have concluded that although the extra-cardiac side effects of amiodarone are more severe than those of other antiarrhythmics, in the doses used for AF and with a strict follow-up protocol, these complications can be minimized by simply suspending treatment in the majority of patients.

In addition to the premature interruption of the PALLAS study,38 in the months following the publication of these guidelines several isolated cases of severe acute liver failure that may be related to the use of dronedarone have been reported, prompting the recommendation of strict controls for liver function before starting treatment, after 1 week, and every subsequent month for the first 6 months of treatment. However, these effects are also described in other available drugs, specifically amiodarone, as can be observed in the technical data sheet for this drug.

In conclusion, very serious reflection on the role of dronedarone seems necessary. In fact, very recently the EMA and the Agencia Española de Medicamentos y Productos Sanitarios (Spanish Agency for Medicines and Health Products) released a new report41 concluding that dronedarone continues to have a favorable cost-benefit ratio in a small subgroup of patients, but that its use should be limited to that population alone (paroxysmal or persistent AF following effective cardioversion), and only after exploring other therapeutic alternatives. It is contraindicated in cases of hemodynamic instability, heart failure, and left ventricular systolic dysfunction, or history of any of these conditions, permanent AF, and renal or pulmonary toxicity related to the previous use of amiodarone. Additionally, its use involves stricter control at follow-up appointments, including cardiovascular, liver, kidney, and pulmonary function. We must also add that the cost of dronedarone in Spain is higher than that of other antiarrhythmics (18 times more expensive than amiodarone), although well-designed cost-benefit studies are needed that take into account other costs as well as the drugs purchased (hospitalizations, ablation, etc.) in order to establish the real cost differences between different medications. Table 2 shows the current cost of treatment with the different available antiarrhythmics.

After these guidelines were published, results from the AVRO study were released on the use of vernakalant, a new drug that is very effective and has a faster rate of action than those previously available for reversion to sinus rhythm in AF.42 Vernakalant was more effective and just as safe as amiodarone in this study.

### Indications for Ablation

We commend the caution shown by the European guidelines in recognizing that the potential benefits of ablation in individual patients “must be sufficient potential benefit to justify a complex ablation procedure associated with possibly severe complications.” In these cases, the guidelines recommend taking into account several factors such as the phase of the disease, the size of the left atrium, the presence and severity of the underlying disease, the possible therapeutic alternatives, and the preference of the patient. We also support the emphasis placed by these guidelines on the need for experienced professionals and healthcare centers to carry out these procedures (>50 cases/year according to the American guideline). Under these conditions, all guidelines concur that ablation is recommended in patients with symptomatic paroxysmal AF in which at least one antiarrhythmic drug has failed. The North American guidelines established a IA indication, based on the high level of evidence, whereas the European and Canadian guidelines assign this a level of IIa. For ablation in persistent AF, all 3 guidelines give a IIa recommendation, with level B evidence. More studies are needed to obtain further information in this field, such as which is the best technique to use. For example, following the publication of the guidelines, a study that registered the rate of silent strokes following the procedure showed that these values varied widely depending on the technique used, and could reach 7% of cases53 although the repercussions of these lesions are yet to be known.

### CONCLUSIONS AND SUMMARY

The avalanche of new evidence regarding several aspects of the management of AF in recent years, along with important and relevant implications for clinical practice, necessitated the release of new guidelines regarding this pathology. In contrast with previous publications, which were joint efforts between the ESC and North American cardiology societies, three different guidelines have been released within a short period of time, which we feel generates more confusion than benefit. The guidelines include an
excess of recommendations based on level C evidence (ie, only from consensus or expert opinions, without the support of incontrovertible evidence), and too few with level A evidence. Guidelines should focus on explicitly established results, avoid an excess of expert opinions, and establish which are the topics that still involve large information gaps in order to stimulate studies that resolve existing doubts and produce clear evidence.

Although the recommendations from the guidelines regarding novel topics are generally prudent, there are inconsistencies in several aspects, some of which are related to articles published in the months following the release of the guidelines. In contrast, other recommendations have received even more support from the appearance of new evidence. This makes us reflect on the need for rapid updates to these guidelines when new evidence arises with special clinical relevance (for example, the favorable results from new oral anticoagulants and from vernakulant, and the negative results from the PALLAS study regarding dronedarone), without waiting several years until an entire new guideline is produced.

CONFLICTS OF INTEREST


REFERENCES