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Atrial fibrillation (AF) is a common arrhythmia. The management of AF is problematic due to the lack of an efficacious and safe pharmaceutical armamentarium. In addition, AF recurrences and complications impose a huge socioeconomic burden on health payers. Most importantly, prevention of the thromboembolic complications of AF is still an unmet need for the majority of patients at risk, taking into consideration the small proportion of patients under appropriate anticoagulation therapy.1-4

In this context, the European Society of Cardiology (ESC) guidelines are of profound importance and their influence extends beyond the geographical limits of our continent. Thus, the recently published 2012 focused update of the ESC Guidelines for the management of AF may have an important influence on our patients, and because of this fact it would be useful to gain further insight into the new recommendations, focusing on those issues that may have the potential to change our clinical practice.5

Why did the ESC feel the need to update the guidelines on AF management that were published only two years ago? In my view it was the right thing to do, for a number of reasons that will be analyzed in the following paragraphs. To summarize the most important of these reasons, we could say that the guidelines needed to be updated mostly because of ROCKET-AF, ARISTOTLE, ASSERT, PALLAS, and MANTRA-PAF. These pivotal clinical trials, which were published after the 2010 ESC guidelines, along with our increasing experience from the wider use of novel oral anticoagulants (NOACs), are largely responsible for the need for the recent update of the ESC guidelines.

Screening for AF

What is the most important innovative recommendation that was included in the recent ESC guidelines for AF? For many cardiologists, including myself, the recommendation (class I, level of evidence B) of opportunistic screening for AF in individuals aged ≥65 years, using pulse-taking followed by an ECG to allow the timely detection of AF, is the most important point of the new guidelines. This recommendation underlines the importance of brief episodes of asymptomatic AF in the pathogenesis of stroke and the need for early diagnosis of AF at the population level.6,7 It is noteworthy that population screening for AF has the potential to
change our practice in a way similar to the way exercise testing influenced the early diagnosis of ischemic heart disease thirty years ago. However, we should take into consideration that this recommendation was based on data derived from the continuous monitoring of cardiac rhythm. Two years ago, we argued in favor of the important role that the monitoring capabilities of cardiac rhythm management devices may have in the diagnosis and management of AF. The ASSERT study did verify the value of the monitoring capabilities of cardiac rhythm management devices, but inappropriate optimism regarding the role of continuous monitoring of cardiac rhythm has been tempered by reality. Devices in their present form cannot and should not be used to facilitate opportunistic screening for AF, and pulse-taking followed by an ECG should not be expected to diagnose the vast majority of patients with brief episodes of asymptomatic AF.

Prevention of stroke

Prevention of stroke is of the utmost importance in the management of AF. The human and socioeconomic costs related to the inappropriate management of cardioembolic risk have been addressed in the 2012 update of the ESC guidelines for the management of AF. This section of the updated guidelines is of particular merit, given that the available data emphasize the underuse of anticoagulation therapy, not only in Greece, but also in most European countries, including countries with advanced care provided through the national health system, such as Denmark and Sweden.

The most important points concerning stroke prevention and bleeding risk management for the clinician are as follows:

- The term “valvular AF” is practically restricted to imply that AF is related to rheumatic valvular disease (predominantly mitral stenosis) or prosthetic heart valves.
- Antiplatelet agents in general, and aspirin in particular, have been inappropriately overused for the prevention of stroke in patients with AF. The ESC guidelines emphasize that “the risk of major bleeding or intracranial hemorrhage with aspirin is not significantly different to that of oral anticoagulants, especially in the elderly.” In addition it has been documented that “aspirin–clopidogrel combination therapy has additional efficacy, compared with aspirin monotherapy, but at additional risk for major bleeding. Thus, aspirin monotherapy should be confined to those who refuse any oral anticoagulants and cannot tolerate aspirin–clopidogrel combination therapy due, for example, to excessive bleeding risk.” Clearly, then, antiplatelets should not be considered as part of our armamentarium to prevent stroke in AF patients, with the exception of patients who are unable to receive any oral anticoagulant. This message is clear and in accordance with the available evidence in the literature.
- The advantages of the CHA2DS2-VASc score over the CHADS2 score, especially in identifying “truly low-risk” patients, are now well documented and thus it should be preferred in the evaluation of thromboembolic risk. Similarly, the HAS-BLED bleeding score has been validated in several independent cohorts. A HAS-BLED value ≥3 indicates high bleeding risk.
- Oral anticoagulant therapy should be the therapy of choice for patients with a CHA2DS2-VASc score ≥1, with one important exception: females with gender as the only risk factor (practically all those aged <65 years or with lone AF) should receive no antithrombotic therapy. This is a new recommendation that may solve the clinical problems we often face when treating young women who often suffer from anemia due to menorrhea.
- Regarding oral anticoagulation therapy, the 2012 update of the ESC guidelines for the management of AF summarized recent data from trials, accumulating experience from clinical practice and recommendations from medical associations in a global perspective. The 2012 update committee recommends NOACs “as broadly preferable” to vitamin K active substances (VKAs) in the vast majority of patients with non-valvular AF. Although the guidelines committee suggests that strict adherence to approved indications and careful post-marketing surveillance are strongly recommended, it is obvious that NOACs represent the therapy of choice for the majority of our patients. As a result of this recommendation, accumulating clinical experience (dabigatran has already exceeded 1,000,000 patient/years on treatment), wider availability and lower cost will definitely boost the wider application of oral anticoagulation to the majority of AF patients throughout Europe. It is possible that this is the most important contribution we may expect from NOACs. Based on epidemiological data, we could
claim that the penetration of oral anticoagulation to patients who did not receive VKAs for various reasons may be more important than optimization of anticoagulation in patients already receiving VKAs.

- The guidelines rightfully claim that there are no data available from direct comparisons between dabigatran, rivaroxaban and apixaban, although cost-effectiveness analyses in various settings have been published for dabigatran. Furthermore, no specific, widely available antidote exists for the NOACs.

- The oral anticoagulants of choice in stable patients with ischemic heart disease continue to be VKAs. The main advantage of VKAs is the fact that they can be administered as monotherapy in stable patients with ischemic heart disease and AF, minimizing the bleeding risk. However, the 2012 update of the ESC guidelines suggests that “... after one year, management can be with OAC alone in stable patients, where OAC can be adjusted-dose VKA therapy or probably a NOAC.” Indeed, there is little doubt that NOACs will claim the role of monotherapy in stable coronary heart disease patients, but for the time being there is no evidence to justify such a recommendation. We should be very careful in extrapolating findings from subgroup analyses of the 3 pivotal studies (RELY, ROCKET-AF and ARISTOTLE), aiming to expand the indications of NOACs. The choice of the word “probably” by the authors of the guidelines is indicative of the reservations we should have on this issue. On the other hand, in cases with a high stroke risk in ischemic patients unable to receive VKAs, or patients who have been proved to be labile INR users, NOACs should rightfully be considered as the logical therapeutic choice.

- Invasive management of stroke risk should be considered for only a few patients. In particular, the committee suggests that interventional, percutaneous left atrial appendage closure may be considered in patients with a high stroke risk and contraindications for long term oral anticoagulation (class IIb, level B), while surgical excision of the left atrial appendage may be considered in patients undergoing open heart surgery (class IIb, level C).

Cardioversion of AF

The guidelines committee recommend vernakalant for pharmacological cardioversion in patients with no or moderate structural heart disease. Vernakalant is contraindicated in patients with hypotension <100 mmHg, recent (<30 days) acute coronary syndrome, New York Heart Association (NYHA) class III and IV heart failure, severe aortic stenosis, and QT interval prolongation (uncorrected QT >440 ms). Vernakalant has proved to show satisfactory efficacy and safety. Approximately 50% of patients are cardioverted to sinus rhythm within 90 minutes after the start of treatment. However, the high cost of vernakalant represents the most important factor that limits its wider use.

Antiarrhythmic drug therapy

Antiarrhythmic therapy for the prevention of AF has not progressed in the way other areas have during the last decade. It is now clear that use of antiarrhythmics may increase morbidity and/or mortality in a variety of clinical situations.14

- The case of dronedarone is illustrative. The authors of the 2010 ESC guidelines for AF, encouraged by the impressive results of the ATHENA trial, suggested dronedarone as the first antiarrhythmic option for the majority of patients with paroxysmal AF. In the recent 2012 update dronedarone is still the first option for the majority of patients. However, sotalol (followed by dronedarone) is recommended as the drug of choice for patients with coronary heart disease, and amiodarone is recommended as the only choice for patients with heart failure. Dronedarone, which regrettably is not available in Greece, was proved to be the only antiarrhythmic drug so far to improve cardiovascular prognosis in the ATHENA15 study, but showed disappointing results, worsening the prognosis of patients with heart failure, in the ANDROMEDA16 and the PALLAS17 trials. Notably, PALLAS enrolled patients with permanent AF and was prematurely stopped having enrolled 3236 patients out of a planned 10,800.

- Out of respect for the basic principles of evidence-based medicine we should evaluate data from the 3 pivotal studies of dronedarone (ATHENA, ANDROMEDA and PALLAS) in a balanced way. There is no doubt that dronedarone should not be administered to patients with heart failure or to patients with permanent AF, but at the same time we should respect the fact that the results of dronedarone in patients with
no or minimal heart disease are unique in the area of antiarrhythmic therapy in general. In this context the recommendations of the 2012 guidelines are evidence-based and well balanced.

• Clinicians should be aware of the side effects of antiarrhythmic therapy and should protect their patients from exposure to multiple proarrhythmic factors (e.g. concomitant use of other proarrhythmic agents) in combination with antiarrhythmic drugs. Always keep in mind that, with the exception of the GESICA trial, which enrolled 516 patients mostly with non-ischemic cardiomyopathy due to Lyme disease, no trial has shown that antiarrhythmic therapy may improve the prognosis of our patients in a variety of clinical settings.\textsuperscript{18}

**Catheter ablation of AF**

Catheter ablation of AF has been upgraded in the 2012 update of the ESC guidelines for AF. The reason for that is the accumulating experience from the wider application of the methods in Europe and the results from the MANTRA-PAF and the RAAFT II trials.\textsuperscript{19,20}

• Catheter ablation for AF should be performed in well organized centers by experienced operators. The guidelines underline the results of the pilot survey of AF ablation within the EURObservational Research Programme, which reported the outcome of more than 1000 ablation procedures carried out in high-volume centers throughout Europe. In this report, acute severe complication rates were 0.6% for stroke, 1.3% for tamponade, 1.3% for peripheral vascular complications, and around 2% for pericarditis.\textsuperscript{21} However, it is clearly evident that catheter ablation improves quality of life, reduces hospitalization and is definitely more effective than any drug therapy available.

• For the first time, the ESC guidelines (following the paradigm of the Heart Rhythm Society in the USA) recommend catheter ablation of AF as first-line therapy. The 2012 update recommends catheter ablation for AF in selected patients with symptomatic paroxysmal AF as an alternative to antiarrhythmic drug therapy, considering patient choice, benefit, and risk. (class IIa, level B).

• The recommendation for patients under antiarrhythmic therapy is as follows: “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 center (class I, level A). The key words for the caring clinician are *symptomatic paroxysmal AF and experienced center.*

**Concluding remarks**

The writer of this commentary on the 2012 update of the ESC guidelines for the management of AF is convinced that these guidelines are more important than they seem. The most important innovations are the recommendations for opportunistic screening over the age of 65 years, the role of NOACs as broadly preferred over VKAs for the prevention of stroke, and the acceptance of catheter ablation of AF as first line therapy.

Although new and recently updated, the ESC guidelines on AF are expected to be updated again soon. The reason for this is the rapidly evolving field of drug therapy for stroke prevention and the expected strides in the field of antiarrhythmic therapy. In addition, more randomized trials investigating the long-term efficacy of catheter ablation are expected within the next 2 years (e.g. the CABANA trial). Meanwhile, we should try to improve the care we offer to patients suffering from this arrhythmia, in line with the ESC guidelines. However, we should always keep in mind that guidelines are a mixture of science and diplomacy, and do not take into account the unique characteristics and needs of all our patients. An individualized approach to some patients is not only allowed in specific cases, but is often considered imperative.

**References**


13. Rash A, Downes T, Portner R, Yeo WW, Morgan N, Chan


