NEW TRENDS AND PROGRESS IN ARRHYTHMIAS, ELECTROPHYSIOLOGY, AND CARDIAC RHYTHM MANAGEMENT DEVICES

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At the recent annual congress of the European Society of Cardiology in Paris, a number of important topics related to arrhythmias, electrophysiology, and cardiac rhythm management devices were presented. This article attempts to give a brief overview of the main issues, judged in terms of clinical relevance, scientific perspectives, and technological innovation. Undoubtedly, the announcement of guidelines for the management of patients with supraventricular tachycardia (SVT) was of great importance for clinical practice in the field of arrhythmias.

The following are some of the most intriguing topics from the conference, grouped into three different categories.

2019 ESC GUIDELINES FOR THE MANAGEMENT OF PATIENTS WITH SUPRAVENTRICULAR TACHYCARDIA

This year, for the first time since 2003, the European Society of Cardiology revealed new guidelines for the management of SVT. It is evident that, in the 16 years since the previous guidelines, both arrhythmologists in general and electrophysiologists in particular have become fully aware of the effectiveness of using invasive techniques, such as ablation for the treatment of this type of arrhythmia. Based on existing developments, the new guidelines, following evidence-based medicine, algorithmically indicate the priorities and preferred methodologies for the use of antiarrhythmic drugs and ablation techniques for the treatment of symptomatic patients. It is also of interest to see that the new guidelines have imported the recommendations for pregnant women with a history of SVT.

The main content of the new guidelines could be summarized as follows:

- Vagal maneuvers and adenosine are the treatments of choice for the acute therapy of SVT, which may also provide important diagnostic information.
- In all reentrant arrhythmias and most focal arrhythmias, catheter ablation

should be offered as an initial choice to patients, once the potential risks and benefits have been explained in detail.

- Patients with macro reentrant tachycardias following atrial surgery should be referred to specialized centers for ablation.
- Atrioventricular nodal reentry tachycardia, typical or atypical, can now be ablated with almost no risk of atrioventricular block.
- If a patient undergoes assessment with an electrophysiology study and is found to have an accessory pathway with high-risk characteristics, catheter ablation should be performed.
- Do not use sotalol in patients with SVT.
- Do not use amiodarone in preexcited atrial fibrillation.
- Verapamil is not recommended in wide QRS-complex tachycardia of unknown etiology.
- Consider using ivabradine, when indicated, together with a β-blocker for inappropriate sinus tachycardia.
- Verapamil, diltiazem, and β-blockers remain options for the chronic management of atrioventricular nodal reentry tachycardia, but have been downgraded from class I to class IIa.
- Do not use flecainide or propafenone in patients with left bundle branch block or ischemic or structural heart disease.
- If possible, avoid all antiarrhythmic drugs during the first trimester of pregnancy. If β-blockers are necessary, use only β1-selective agents (but not atenolol). Flecainide or propafenone should be considered for the prevention of SVT in patients with Wolff–Parkinson–White syndrome and without ischemic or structural heart disease (class IIa).
- Amiodarone and digoxin have been dropped as the treatment of choice for the acute management of narrow-complex tachycardia.
- Consider tachycardiomyopathy in patients with reduced left ventricular function and SVT.
- Ablation is the treatment of choice for tachycardiomyopathy due to SVT.
- Atrioventricular nodal ablation with subsequent biventricular or His-bundle pacing (“ablate and pace”) should be considered if the SVT cannot be ablated.

We can see that, based on the previous key messages described in a recent paper,[1] a clear and up-to-date policy has been devised to address the common problem of SVTs, which are known to frequently affect children, adolescents, and/or young adults.

CLINICAL TRIALS AND REGISTRIES

Long-term outcomes of the DAPA trial

DAPA (Defibrillator After Primary Angioplasty) was a prospective, randomized, multicenter controlled study designed to evaluate the survival benefit of early prophylactic use of implantable cardioverter-defibrillators in high-risk patients with ST-segment myocardial infarction (STEMI) after primary percutaneous coronary intervention. The primary end point of the trial was to estimate the all-cause mortality within 3 years of STEMI treated with primary percutaneous coronary intervention in patients with at least one high-risk factor: (i) left ventricular ejection fraction <30% within 4 days; or (ii) thrombolysis in myocardial infarction flow <3 after primary percutaneous coronary intervention.

The trial enrolled 266 patients. During a median follow-up period of 9 years, 24.4% of the patients in the implantable cardioverter-defibrillator group died vs 35.6% in the control group (P=0.02). Sudden cardiac death was numerically lower in the implantable cardioverter-defibrillator group (3.1% vs 5.9%; P=0.521). This mortality difference has been mainly attributed to cardiac deaths, which were significantly higher in the medical group (18.5%) than in the implantable cardioverter-defibrillator group (11.5%). Another interesting finding of the study was that, after 18 months, half of the patients in both groups demonstrated improvement in their left ventricular ejection fraction. The benefit of implantable cardioverter-defibrillators was still preserved vs the group on medical therapy.

Although this trial offers great insight into the potential benefit of early use of implantable cardioverter-defibrillators in high-risk patients after a myocardial infarction, it cannot be considered conclusive because of its premature termination and the results need to be confirmed by larger randomized trials.[2]

Association between implantable cardioverter-defibrillator use for primary prevention and mortality

This study was based on the Swedish Heart Failure Registry (SWEDE-HF), involving patients who fulfilled the European Society of Cardiology criteria for primary prevention implantable cardioverter-defibrillator use. It is worth mentioning that the calculation of propensity scores was based on 31 clinically relevant variables. The aim of this trial was to evaluate the association between primary prevention implantable cardioverter-defibrillators and all-cause mortality in a large, contemporary cohort of patients with heart failure with reduced ejection fraction (HFREF)

with a focus on prespecified subgroups (eg, ischemic heart disease, age, time of enrollment, and sex).

Of 16702 eligible patients in SwedeHF, 1599 (9.6%) had an implantable cardioverter-defibrillator. The unusually low number of implantable cardioverter defibrillator implantations in Sweden was cause for comment. The study population consisted of 1305 patients who were treated with an implantable cardioverter-defibrillator compared with 1305 patients who were not. The researchers found that implantable cardioverter-defibrillator use was associated with a 4.2% absolute reduction in the risk of all-cause mortality at 1 year (HR, 0.73; 95% CI, 0.60-0.90) and a 2.1% absolute reduction in the risk of all-cause mortality at 5 years (HR, 0.88; 95% CI, 0.78-0.99). It is important to mention that the reduction in both short- and long-term mortality associated with primary prevention implantable cardioverter-defibrillators was consistent in all subgroups evaluated.

This study supports the current guideline recommendations for use of implantable cardioverter-defibrillators in primary prevention in patients with HFREF and is a reminder of the need to expand the use of implantable cardioverter-defibrillators in clinical practice.[3]

AFIRE study

The AFIRE study (Atrial Fibrillation and Ischemic events with Rivaroxaban in patients with stable coronary artery diseasE) is a multicenter, prospective, randomized, open-label, parallel-group study conducted in patients aged ≥20 years with nonvalvular atrial fibrillation and coronary artery disease. At this point, it is worth mentioning that it is common practice to use anticoagulants in combination with antiplatelet agents in patients with atrial fibrillation and coronary artery disease. The current guidelines support monotherapy with oral anticoagulants after 12 months of combination therapy. However, this approach had not been supported by evidence from randomized controlled trials. The AFIRE study aimed to investigate whether rivaroxaban monotherapy is noninferior to combination therapy (rivaroxaban plus an antiplatelet agent) in patients with atrial fibrillation and stable coronary artery disease more than 1 year after revascularization or in those with angiographically confirmed coronary artery disease not requiring revascularization.

Two primary end points were set. The primary efficacy end point was stroke, systemic embolism, myocardial infarction, unstable angina requiring revascularization, or death from any cause. As the primary safety end point, the investigators intended to assess the major bleeding events, as defined according to the criteria of the International Society on Thrombosis and Haemostasis. A total of 2236 patients from 294 centers in Japan were randomly assigned to two groups. The incident rate of the primary efficacy end point was of 4.14% per year for patients

in the monotherapy group and 5.75% per year for the patients in the combination therapy group (*P*<0.001 for noninferiority). The incident rate of the primary safety end point was significantly lower for monotherapy compared with combination therapy (1.62% vs 2.76% per year; HR, 0.59; 95% CI, 0.39-0.89; *P*=0.0115). In addition, both all-cause mortality (1.85% vs 3.37%; HR, 0.55; 95% CI; 0.38-0.81) and the rate of adverse clinical events (3.90% vs 6.28% per year) were significantly lower for patients on rivaroxaban monotherapy than for those on combination therapy. The results confirm the noninferiority of the oral anticoagulation monotherapy with rivaroxaban over the combination therapy of an anticoagulant plus a P2Y12 inhibitor, as regards both efficacy and safety. The above data could support a review of the current guideline recommendation for antithrombotic treatment of patients with atrial fibrillation and coronary artery disease.[4]

ENTRUST-AF PCI trial

The current guidelines for patients with atrial fibrillation undergoing percutaneous coronary intervention with stent placement recommend the use of oral anticoagulation with a vitamin K antagonist combined with dual antiplatelet therapy with acetylsalicylic acid (aspirin) and P2Y12 inhibitors (triple therapy).

ENTRUST-AF-PCI (Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen following successful coronary stenting in atrial fibrillation patients) was a randomized, open-label, phase 3b trial whose primary objective was to assess the incidence of major or clinically relevant nonmajor bleeding (ISTH) over a 12-month period in patients with atrial fibrillation undergoing percutaneous coronary intervention with stent placement, who were receiving treatment with edoxaban in combination with a P2Y12 inhibitor vs the triple therapy currently recommended by the guidelines. A total population of 1506 patients from 18 different countries participated in this trial. Patients were randomly assigned either to edoxaban (60 mg once daily) plus a P2Y12 inhibitor for 12 months or to a vitamin K antagonist in combination with a P2Y12 inhibitor and aspirin (100 mg once daily for 1 to 12 months).

The trial showed that the antithrombotic regimen with a full dose (60 mg once daily) of edoxaban in combination with a P2Y12 inhibitor was noninferior to triple therapy with a vitamin K antagonist as regards the risk of major or clinically relevant nonmajor bleeding events over 12 months. In addition, the two different regimens demonstrated similar rates with respect to the main efficacy outcome-a composite of death from cardiovascular causes, stroke or systemic embolic events, myocardial infarction, or definite stent thrombosis.[5]

NEW RESEARCH STUDIES AND SUBANALYSES OF KNOWN TRIALS

AliveCor ECG recording and a deep learning model to predict atrial fibrillation

The AliveCor product KardiaMobile represents an FDA-cleared, smartphone-enabled device with a capability for single-lead ECG recording. Researchers used a deep learning model where the objective was to predict atrial fibrillation from normal sinus rhythm ambulatory ECG data. They trained a deep convolutional neural network on 1 984 581 normal ECGs from 19 267 patients with (i) only normal ECG recordings or (ii) at least 30% of the ECGs with atrial fibrillation. Using an operating point with equal sensitivity and specificity, the model's sensitivity and specificity was 73.1%. Using an operating point with high specificity (90.0%), the model's sensitivity was 48.0%. Although these are early findings that still need validation, they suggest that artificial intelligence might be a potential new tool for the early diagnosis and appropriate treatment of atrial fibrillation.[6,7]

Sudden cardiac death in endurance racing

The main objective of this study was to investigate preventable factors for sudden cardiac death in endurance races. The study included 1 073 722 runners who participated in 46 long-distance Parisian races during 2006 and 2016. Researchers collected all incidents of sudden cardiac death that occurred over the 10-year period and attempted to correlate them with race characteristics, such as temperature and air pollution, as well as the age and sex of the participants. The results showed that 36 sudden cardiac deaths occurred during this time, with 7 of them being related to high temperature (heat stroke) and 25 due to myocardial ischemia. Researchers found that, of the 25 patients who died of myocardial ischemia, one-third of them demonstrated symptoms during the race that did not prevent them from continuing. Another very interesting finding is a correlation between the air pollution index and the occurrence of events. Elevated levels of microparticles and sulfur derivatives were present in the majority of the events. It is obvious that sudden cardiac death in long-distance endurance races could be, to some extent, preventable. For this to happen, it is necessary for participants to be adequately educated; organizing committees also need to be more concerned and strict about the external factors that prevail during the different races.[8]

Arrhythmia services in 22 African countries

Morbidity and mortality due to arrhythmias in African countries are still a distressing topic, as high rates persist. It was this fact that motivated the Pan-African Society of Cardiology to address the matter by conducting this study. The investigators collected data from 22 countries in the period between 2011 and 2018 regarding the availability of human resources (pacemaker operators, electro-

physiologists), use of drugs, cardiac implantable electronic devices, ablation techniques, and the availability of facilities to perform these invasive procedures.

The results showed a direct correlation between the cost of cardiac implantable electronic devices compared with the GDP per capita and the device implantation rate, highlighting the need to reduce the cost of these procedures. Another interesting finding is the availability of antiarrhythmic and antithrombotic drugs, with some countries completely lacking this possibility (Tunisia: non–vitamin K-dependent oral anticoagulants) and most of the drugs being unequally available over the African market, with only 17% of the countries using all of the non–vitamin K-dependent oral anticoagulants. It is of course worth mentioning that 20% of the countries did not implant pacemakers, while none of the sub–Saharan countries, apart from South Africa, was able to perform complex ablation with 3D mapping. The survey confirms all previous reports about the inadequate confrontation of arrhythmias in most African countries, especially in the sub–Saharan area, and calls for immediate restructuring of the public health policies.[9]

CABANA: atrial fibrillation type substudy

A subanalysis of the CABANA trial (Catheter ABlation vs ANti-arrhythmic drug therapy for Atrial fibrillation) found that radiofrequency catheter ablation was not superior to antiarrhythmic therapy in terms of efficacy and safety over a 5-year period in patients with new-onset or untreated atrial fibrillation, although it could provide better quality of life. In this study, researchers investigated the impact of atrial fibrillation type on the outcome of ablative or drug therapy. Researchers discovered a gap in the data concerning patients with persistent and long-standing persistent atrial fibrillation, as most previous trials had demonstrated the effectiveness of catheter ablation only in patients with paroxysmal atrial fibrillation. Another main objective of the trial was to assess the correlation between atrial fibrillation type and the progression or regression of the arrhythmia over time. Of the 2204 subjects who participated in the CABANA trial, 42% had paroxysmal atrial fibrillation, 48% persistent atrial fibrillation, and 10% long-standing persistent atrial fibrillation.

The results of this subanalysis showed that the primary composite end point of death, disabling stroke, severe bleeding, and cardiac arrest was similar for the different categories of atrial fibrillation patients. Interestingly, however, results related to all-cause mortality or cardiovascular hospitalization showed that patients with paroxysmal and persistent atrial fibrillation had a better outcome when treated with catheter ablation, while patients with long-standing persistent atrial fibrillation had a higher event rate when treated with catheter ablation compared with drug therapy. It is important to mention that ablation demonstrated

superiority over drug therapy in decreasing atrial fibrillation recurrence, regardless of the atrial fibrillation type. Furthermore, it was more effective in decreasing the rates of all three types of atrial fibrillation and increasing the proportion of patients in normal sinus rhythm.[10,11]

Real-life scenarios for catheter ablation in patients with heart failure and atrial fibrillation

The recent CASTLE-AF trial (Catheter Ablation vS convenTionaL thErapy for patients with Atrial Fibrillation and left ventricular dysfunction) indicated the superiority of catheter ablation over drug therapy for atrial fibrillation patients with heart failure in terms of all-cause mortality and hospitalization for worsening atrial fibrillation. Researchers looked into the French Nationwide Heart Failure database and investigated how the CASTLE-AF trial reflected real-life scenarios. They identified 252 395 atrial fibrillation patients with heart failure, of whom almost 99.5% were treated with conservative therapy, while the remaining 0.5% underwent catheter ablation, mostly in less experienced centers. French investigators carried out 1:1 propensity score matching, which confirmed the CASTLE-AF findings of lower all-cause mortality and heart failure–related hospitalization in unselected atrial fibrillation patients undergoing catheter ablation.[12,13]

ATTEST trial

The ATTEST trial (Atrial Fibrillation Progression Trial) was a controlled, randomized trial whose main object was to investigate how radiofrequency catheter ablation compares with antiarrhythmic therapy in relation to the progression of paroxysmal atrial fibrillation to persistent atrial fibrillation or atrial tachycardia. The results demonstrated the superiority of catheter ablation over antiarrhythmic therapy, with 17.5% of patients treated with antiarrhythmic drugs over a 3-year period developing persistent atrial fibrillation, in contrast to patients undergoing radiofrequency catheter ablation, of whom only 2.4% saw their disease progress. The authors suggested that paroxysmal atrial fibrillation ablation could be up to 10 times more effective than conservative therapy in preventing the progression of the disease. This trial reinforces recent findings suggesting that early radiofrequency ablation in patients with paroxysmal atrial fibrillation could prevent the progression of the disease, drastically increasing the patients' quality of life.[14]

Stereotactic body radiotherapy for resistant ventricular tachycardia

Researchers from the Czech Republic proposed an upgrade to stereotactic body radiotherapy, a new technique in the field of electrophysiology for the treatment of resistant ventricular tachycardia. The authors of the trial integrated electroanatomical voltage mapping with cardiac CT, enabling the precise stereotactic body radiotherapy of the substrate to be identified in the electrophysiology study.

This is an innovative method for treating patients who have undergone unsuccessful catheter ventricular tachycardia ablation (≥2), both endo- and epicardial. Researchers merged CARTO-derived 3D models with CT-derived 3D models and proceeded to the noninvasive, gamma-knife–driven ablation of the ventricular tachycardia. Undoubtedly, this advancement in treating ventricular tachycardia resistant to catheter ablation could be of great importance in the future in the field of electrophysiology.[15,16]

CONCLUSIONS

Summarizing the evaluation of the issues presented at the annual European Society of Cardiology congress in Paris this year, we could argue that, in the field of arrhythmias and electrophysiology, there is very limited development in pharmacology and antiarrhythmics for the management of arrhythmias, whereas, in contrast, therapeutic techniques related to biotechnology applications are gaining ground. ■

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