Management of ventricular and atrial arrhythmias in humans: towards a patient-specific approach

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The strategy of sudden cardiac death prevention by implantable cardioverter defibrillator, in primary prevention, is mainly based on the value of ejection fraction. That means that the approach is not really patient specific. A lot of implanted patients will not receive any shock. The implantation of large categories of patients is interesting on a global therapeutical point of view but, when considering the economical aspects, it would be more useful to have better selection criteria in order to obtain a more patient-specific approach, avoiding implanting patients who will never receive shocks. The parameters commonly used to select patients for implantations have a good negative predictive value but a low positive predictive value. Concerning atrial fibrillation the approach is quite different. Antiarrhythmic drug treatment has shown many limitations. Antiarrhythmic drugs are useful and safe in atrial fibrillation patients only if the contra-indications are strictly respected. The main difficulty concerns patients with both heart failure and atrial fibrillation. The story of Dronedarone development is illustrative of the necessity of a patient-specific approach in the treatment strategy of atrial fibrillation. The ATHENA trial made with Dronedarone showed a benefit in patients with underlying heart disease but no patient with advanced cardiopathy was included in the study. On the contrary, the PALLAS trial has clearly shown that the drug is contra-indicated in patients with any type of heart failure. In atrial fibrillation, a patient-specific approach is mandatory. This review illustrates the dichotomy of the two different approaches.

Introduction

The approaches concerning preventive treatment of ventricular and atrial arrhythmias in humans are quite different. For ventricular life-threatening arrhythmias there is a relative failure of tools used for at-risk patient identification. Most of these tools have a good negative predictive value but a limited positive predictive value. That concerns ventricular premature beats, Lown criteria, occurrence of non-sustained ventricular tachycardias, heart rate variability, turbulence, T-wave alternance or even programmed ventricular stimulation. Indeed, the ejection fraction remains the gold standard.

For atrial fibrillation there is a large continuum from lone atrial fibrillation in young patients (for example ‘Saturday night atrial fibrillation’) to atrial fibrillation plus severe New York Heart Association class IV heart failure in elderly people. That means that in atrial fibrillation there is a need for a patient-specific approach.

Principles of ventricular fibrillation preventive management

The incidence of sudden cardiac death is progressively increasing in different populations going from the total adult population to multi-risk sub-groups, to patients who experienced any previous coronary event, to patients with ejection fraction <35% or patients with heart failure, to survivals of ventricular tachycardia or ventricular fibrillation and finally to high-risk post-myocardial infarction sub-groups, as it has been clearly demonstrated by Myerburg et al.1 On the contrary, the number of total sudden death events in the global population is in the opposite way: very few in high-risk post-myocardial infarction sub-group and a great number in the total adult population.

The approach to preventive treatment of ventricular fibrillation has completely changed after the publication of the MADIT II trial. The authors2 clearly demonstrated that prophylactic implantable cardiac defibrillator therapy in patients with prior myocardial infarction and reduced left ventricular ejection fraction was able to improve survival. A major change in the paradigm has been observed at the time of MADIT II publication.

Nevertheless, it can be observed that in these patients with an implantable cardiac defibrillator, the number of shocks is very small, as we observed in the EVADef cohort.3 In a group of 415 patients implanted for primary prevention only 30 patients received a shock in a 2-year follow-up. The proportion of patients receiving shocks if they were implanted in secondary prevention is a little higher but remains limited: 470/1859. In other words, the approach of ventricular fibrillation treatment...
by implantable cardioverter defibrillator is really not patient specific. A lot of patients are implanted and very few patients receive shocks. That is mainly due to the fact that we are lacking criteria for selecting these patients. All the criteria we know have a good negative predictive value but a very low positive predictive value. The parameter which is considered, to date, as having the best predictive value, is ejection fraction. We can regret that the researches concerning new parameters predicting ventricular arrhythmias are almost completely stopped. The implantation in large categories of patients may be interesting on a therapeutic point of view but when we consider the economic aspects, it would be more interesting to have better selection criteria to avoid implanting patients who will never receive any shock.

**Principles of atrial fibrillation management**

It has been clearly established that the number of adults with atrial fibrillation will quickly grow in the next decades in all developed and emerging countries. In 2050, this number can be estimated to around 5 million people in the USA. The economic burden of this quick increase may be major. In the COCAF study, 5 to around 5 million people in the USA. The economic burden of this important contribution has led to the development of the ablation procedures for the treatment of atrial fibrillation. It has been relatively easy to demonstrate that ablation is more effective that antiarrhythmic drug treatment for the maintenance of sinus rhythm. Nevertheless, it is important to emphasize that all these trials have been made in patients for whom a previous antiarrhythmic drug treatment had failed. Furthermore, the endpoints of these trials were in most of the cases sinus rhythm maintenance and not mortality as it has been made in the trials comparing strategies like AFFIRM. It will be very important, in the future, to analyse the data of large trials like CABANA, which is randomizing ablation vs. antiarrhythmic drug treatment as a first choice. Nevertheless, the interpretation of the results will probably be difficult.

**Limits of atrial fibrillation antiarrhythmic treatments**

A lot of drugs, in the past, have been proposed to treat atrial fibrillation. In the 1980s, many class I antiarrhythmic drugs were in development. All these developments have been stopped after the results of the CAST trial known in 1989.6 These data were not concerning the atrial level but the same conclusion has been drawn for atrial arrhythmias, mainly after the publications of Coplen et al.7 and Flaker et al.8 It was clear at that time that class I antiarrhythmic drugs had to be avoided in patients with heart failure and/or coronary artery disease. So, the next drugs that have been developed were not class I antiarrhythmic drugs and the interest has moved to class III. The limits of class III have been demonstrated, mainly to be due to the risk of torsades de pointes induction. Furthermore, data coming from the trials comparing rhythm and rate control strategies have also contributed to the scepticism of the prescribers.9 The most important of these trials was the AFFIRM study showing no difference between rhythm and rate control strategies. Nevertheless, it has also been demonstrated that sinus rhythm maintenance was a factor of good prognosis.10 The problem is that it is necessary, when maintaining sinus rhythm, to avoid drugs which could be deleterious or procedures which could be harmful. Finally, the consensus was that rhythm control could be the better choice for younger patients, highly symptomatic patients, or patients with few risk factors of relapse. On the contrary, rate control could be the better choice for older patients, asymptomatic patients, or patients with few symptoms and patients with advanced underlying heart disease.

The group of Haïssaguerre et al.11 demonstrated in 1998 that pulmonary vein foci were playing a major role in the genesis of atrial fibrillation. This important contribution has led to the development of the ablation procedures for the treatment of atrial fibrillation. It has been relatively easy to demonstrate that ablation is more effective that antiarrhythmic drug treatment for the maintenance of sinus rhythm. Nevertheless, it is important to emphasize that all these trials have been made in patients for whom a previous antiarrhythmic drug treatment had failed. Furthermore, the endpoints of these trials were in most of the cases sinus rhythm maintenance and not mortality as it has been made in the trials comparing strategies like AFFIRM. It will be very important, in the future, to analyse the data of large trials like CABANA, which is randomizing ablation vs. antiarrhythmic drug treatment as a first choice. Nevertheless, the interpretation of the results will probably be difficult.
Dronedarone development in the treatment of atrial fibrillation

For many years, all the scientists have conducted researches to try to obtain an antiarrhythmic drug which could be as effective as Amiodarone but without its side effects, mainly extracardiac side effects of which thyroid dysfunction is the most frequent. That is the story of Dronedarone development. Dronedarone is a benzofuran derivative without iodine substituent. In this development the first step was to demonstrate that the drug was able to maintain sinus rhythm as compared with placebo. It has been done in ADONIS and EURIDIS trials.13 To be sure that the drug could be prescribed in patients with heart failure, a specific trial has been conducted, the ANDROMEDA study, but unfortunately this trial has been stopped because of overmortality in patients treated by Dronedarone. When the trial has been stopped, the number of death was 12 in the placebo group and 25 in the Dronedarone group.14 The patients included in ANDROMEDA had severe heart failure (class IV).

The ATHENA trial15 has demonstrated that the drug was able to decrease morbi-mortality in patients with atrial fibrillation. ATHENA included patients with coronary artery diseases but few patients with heart failure (around 12% of patients had a left ventricular ejection fraction <45%). The ATHENA trial showed a decrease in the primary endpoint which was cardiovascular hospitalizations and deaths.15 Nevertheless, it has been observed that Dronedarone, in this trial, was not decreasing all-cause mortality, but only cardiovascular mortality. Finally in the DIONYSOS trial16 we have compared Dronedarone with Amiodarone on a primary endpoint, which was mixing both sinus rhythm maintenance and lack of drug discontinuation. Even with this combined endpoint, Amiodarone obtained better results than Dronedarone.

The good results of the ATHENA trial allowed obtaining the registration of the drug by the regulatory agencies. After that it has been decided to conduct the PALLAS trial. The PALLAS study was concerning patients with permanent atrial fibrillation. It is important to know that according to the inclusion criteria, it was possible to enrol patients with symptomatic heart failure, defined as hospitalization for heart failure between one month and up to 1 year prior to randomization and currently stable class II or III symptoms, and patients with left ventricular fraction <40%. In other words, these patients were more severe than those included in ATHENA. The results of PALLAS17 were really catastrophic. Looking at the baseline characteristics it was clear that an important proportion of patients had a history of heart failure (around 70%). The results showed an increase in the number of deaths (25 vs. 30 in the placebo group), cardiovascular deaths (21 vs. 10), arrhythmic deaths (13 vs. 4), strokes (23 vs. 10), unplanned cardiovascular hospitalizations (113 vs. 59), and heart failure hospitalizations (43 vs. 24).

It is possible to consider that atrial fibrillation, in fact, emerges along the cardiovascular continuum and is a contributing factor in many cardiovascular conditions (Figure 2). There is a red line when considering the treatment of these patients. Drugs like Dronedarone may be very useful in patients with minor underlying heart disease but it is becoming dangerous to prescribe such a drug in patients with more severe heart diseases.

‘Tailor-made’ choice of antiarrhythmic drugs

Antiarrhythmic drugs remain safe if they are correctly prescribed and if the contra-indications are carefully respected.18 For rhythm control, if there is no or minimal heart disease, it is possible to use Dronederone, Flecaïnide, Propafenone, or Sotalol. If there is hypertension with left ventricular hypertrophy Dronedarone may be indicated. In patients with coronary artery disease the only possibilities to use are Dronedarone and Sotalol. In patients with heart failure it is now obvious that Dronedarone has to be completely avoided. The European guidelines will be modified on this point. For rate control it is necessary to analyse the type of lifestyle. If the patient has an inactive lifestyle digitalis is proposed. If the lifestyle is active it is necessary to look at associated diseases. If there is no associated disease or only a hypertension it is possible to use beta-blockers, Diltiazem, Verapamil, or digitals. In the case of heart failure, beta-blockers (Carvedilol, Bisoprolol, Metoprolol, Nebivolol) or digitals may be used. If there is a chronic obstructive pulmonary disease Diltiazem, Verapamil, and digitals can be used and for beta-blocking it is necessary to prescribe only beta 1 selective blockers. The recommendations show that a patient-specific approach is necessary in the choice of the treatment for atrial fibrillation patients. After 20 years of controversies concerning the risk of mortality induced by antiarrhythmic drugs19 it is well established that, if antiarrhythmic drugs are carefully prescribed in the strict respect of contra-indications, this risk remains very low, as demonstrated by the nationwide survey made in Denmark.20

In conclusion, the treatment of ventricular fibrillation by the implantable cardioverter defibrillator is not a ‘patient-specific’ therapy and only ejection fraction remains the really discriminant. Nevertheless, a more ‘patient-specific’ approach could have a major interest in terms of cost of care, avoiding implantation of patients who will never receive shocks. On the contrary, in atrial fibrillation, there are many different situations from lone atrial fibrillation to severe heart failure and a ‘patient-specific’ approach is mandatory. The opposite results of ATHENA and PALLAS are illustrative of the necessity of this approach.
Conflict of interest: Conferences / Grants / Boards : Sanofi – Aventis, Meda.

References


