

# Clinical implications from the European Heart Rhythm Association consensus document on antiarrhythmic drug therapy

Emin Evren Özcan, Bülent Görenek<sup>1</sup>

Department of Cardiology, Faculty of Medicine, Dokuz Eylül University; İzmir-Turkey

<sup>1</sup>Department of Cardiology, Faculty of Medicine, Eskişehir Osmangazi University; Eskişehir-Turkey

## ABSTRACT

The recently published consensus document by the European Heart Rhythm Association presents a patient-tailored pharmacological antiarrhythmic treatment approach targeting the arrhythmia mechanism. This document comprehensively reviews the indications, side effects, and contraindications of antiarrhythmic drugs. In this paper, we reviewed novel treatment concepts offered by the consensus document.

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## Introduction

Despite revolutionary developments concerning catheter ablation therapies and device technologies, little has changed in pharmacological antiarrhythmic therapy over the last decades. Currently, antiarrhythmic drugs (AADs) are far away to cure arrhythmias, but they are an important treatment option for suppressing them, and they are widely used. Although many guidelines have been published to determine AAD indications, pharmacological treatment strategies are highly variable in clinical practice, and evidence-based medicine is less applied compared with other treatment modalities.

For this purpose, the European Heart Rhythm Association (EHRA) and the European Society of Cardiology Working Group on Cardiovascular Pharmacology convened a Task Force, with representation from the Heart Rhythm Society and Asia Pacific Heart Rhythm Society, published a practical document classifying antiarrhythmic treatment options and summarizing the indications and side effects (1). This consensus document offers valuable recommendations in detail. Here, we will focus on novel concepts in pharmacological antiarrhythmic therapy and less known but important recommendations, not covering all details.

## Paradigm shift in treatment strategy and drug development

Initially, the authors classified AADs and reviewed the recent developments in clinical pharmacology. The widely used tradi-

tional Singh–Vaughan Williams classification based on the effects of AADs on cardiac ion channels is explained in detail (2). Next, limitations of this empirical approach are compressively discussed, and a new pathophysiological approach is offered. The traditional approach is based on the AAD properties with the final aim of altering the excitability, conduction, or automaticity, irrespective of the specific mechanism of arrhythmia; however, the modern AAD therapy is based on discovering the critical components of arrhythmia and identifying the vulnerable parameters. For example, the mechanism of an atrioventricular (AV) nodal re-entrant tachycardia is a re-entry in the AV node, and because it generates L-type calcium channel-dependent action potentials, the arrhythmia can be targeted by calcium channel blockers, adenosine, or beta-blockers. Unfortunately, in many patients, the underlying mechanisms of arrhythmias are not clear; thus, the authors agree the need of an empiric AAD therapy based on the diagnosis.

This novel approach requires a better understanding of the action potential rather than the empirical antiarrhythmic therapy. Understanding the details of membrane action potential is crucial for both effective treatment and less side effects. The authors summarize the paradigm shift in AAD development and provide some examples of novel drugs

Vernekalan blocks INa channels at faster rates and at more positive action potential. The atrial membrane potential is more

**Address for correspondence:** Dr. Bülent Görenek, Eskişehir Osmangazi Üniversitesi, Tıp Fakültesi, Kardiyoloji Anabilim Dalı, Meşelik Kampüsü, Eskişehir-Türkiye  
Phone: +90 222 229 22 66 E-mail: bulent@gorenek.com

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positive than the ventricular membrane potential, and this difference increases during tachycardia. Therefore, it is called an atrial-specific drug. These properties of vernekalant imply a lower risk of ventricular proarrhythmia, particularly when the heart rate slows in heart failure patients.

Ranolazine, a drug with antianginal properties, has a high affinity for late component of the sodium current ( $I_{NaL}$ ). The Ranolazine Implantable Cardioverter-Defibrillator study demonstrated a significant reduction in ventricular tachycardia with ranolazine (3).

Other potential future AADs that will target different parameters such as excitability and effective refractory period (IKur and TASK channels), re-entry and refractoriness ( $I_{SK}$ ), and atrial remodeling through  $Ca^{2+}$  signaling molecules (calpains, calcineurin) are also reviewed (4).

### **New concept: The patient, the arrhythmia, and the drug**

Patient-tailored drug selection is a novel concept offered by the consensus document. Authors underline the difference between treating the disease and treating the arrhythmia. They remind the The Cardiac Arrhythmia Suppression Trial (CAST) study as an example, how effective antiarrhythmic therapy can be potentially dangerous, particularly in the presence of structural heart disease (5). The decision to start therapy should balance the efficacy and safety.

### **The patient**

The consensus document individualizes the recommendations for pharmacological therapy based on patient's characteristics. The presence of an arrhythmia in a patient with structural heart disease is not an unusual condition. Unfortunately, these patients have higher risks of proarrhythmia with AADs. The authors state valuable recommendations related with four different clinical entities:

- Class IA, IC, and III membrane-active AADs other than amiodarone or sotalol, are not recommended in patients with significant structural heart disease, such as cardiomyopathy, left ventricular dysfunction, myocardial infarction, and myocardial ischemia. The authors emphasize that sotalol is associated with increased mortality due to proarrhythmia and can be used in patients with coronary artery disease preferably with an implantable cardioverter-defibrillator (ICD) (6).
  - It is advised to avoid the use of Class IA, IC, and III AADs in patients with substantial LVH ( $\geq 1.4$  cm) other than amiodarone, dronedarone, or sotalol and disopyramide.
  - Disopyramide is recommended in patients with obstructive hypertrophic cardiomyopathy for symptom improvement. In patients with atrial fibrillation, it can increase the ventricular rate and should be used with beta-blockers.
  - In the presence of congenital heart disease, AADs should be reserved to selected cases because they are frequently poorly tolerated due to negative inotropic effects.
- Patients with tachyarrhythmia and pre-existent bradycardia

or conduction disturbances present another challenging scenario. All AADs may induce bradycardia or may cause AV conduction block. Caution is warranted in all patients with a history of syncope, sinus bradycardia, or AV conduction disturbances including PR prolongation.

Although the consensus report recommends implantation of a pacemaker before the initiation of AAD in patients with symptomatic bradyarrhythmias, it is reasonable to offer ablation as an alternative to pacemaker implantation. We believe that many tachyarrhythmias can be cured with ablation and that the need for pacemaker implantation can be canceled or at least postponed. It should be kept in mind that sodium channel blockers (Class IA and IC) may increase the pacing threshold, but this is rarely clinically relevant.

Although the efficacy of AAD therapy appears to be similar in men and women, the risk of proarrhythmias appears to be greater in women than in men (7). Physiological changes in older age significantly affect the pharmacokinetics of AADs and increase the risk of proarrhythmia (8). Similarly, reduction in renal function may have important implications for antiarrhythmic therapy. Procainamide and sotalol should be avoided in patients treated with hemodialysis. The dose of flecainide should be at least half of the usual recommended dose. Conversely, dialysis has little impact on amiodarone clearance, and no dosage adjustment is necessary (9).

### **The arrhythmia**

The management of arrhythmias and therapies related with them are comprehensively discussed in the document. Each type of arrhythmia individually reviewed, drugs of choice, their recommended doses, contraindications, and precautions are listed in the related tables. Flow charts prepared for specific clinical conditions facilitate to remember the management of different scenarios.

### **The drug**

It should be kept in mind that most of AADs have a narrow therapeutic window and that almost all AADs may produce proarrhythmic effects. Unfortunately, both underlying diseases and comorbidities are dynamic. Therefore, not only a careful pre-administration assessment but also a follow-up for proarrhythmic effects is indicated (10). Appropriate laboratory and diagnostic tests should be part of the follow-up protocol; these tests should include ECG and other tests according to the patient's profile and AAD characteristics.

The pharmacokinetics and pharmacodynamics of AADs are discussed in detail. The absorption, distribution, biotransformation, and elimination of drugs are summarized with particular examples. For example, propafenone increases the plasma levels of digoxin, metoprolol, propranolol, and warfarin. Dose adjustment recommendations are included for commonly used drug combinations in daily practice. For example, non-antivitamin K oral anticoagulant dose reduction should be considered when

amiodarone is a concomitant medication. Dabigatran and edoxaban dose reduction is also recommended when taken simultaneously with verapamil. All AADs have interactions, and drug interactions are described on two pages. The authors recommend evaluating the possible interactions of any antiarrhythmic drug with any concomitant therapy using web-based tools (e.g., [www.drugs.com](http://www.drugs.com), [www.crediblemeds.org](http://www.crediblemeds.org)). The importance of monitoring AADs and indications for pharmacokinetic monitoring is also listed.

### Is it safe to initiate AAD out of the hospital?

Initiation of any AAD implies some risk of adverse event, including proarrhythmic effects. For this reason, when the risk of proarrhythmia is high, in-hospital drug initiation is recommended (11). However, for financial and practical reasons, this approach is limited to selected patients at high risk.

The high-risk criteria for Class IC AADs are bundle branch block or a wide QRS duration (>120 ms), structural heart disease, left ventricular dysfunction (<0.40), tachyarrhythmia with a rapid ventricular response, history of ventricular tachyarrhythmias, or concurrent treatment with drugs having a negative inotropic effect.

The high-risk criteria for Class IA and class III AADs are a long-QT interval (QTc >460 ms), female sex, bradycardia or long-RR intervals, excessive QT/QTc lengthening during treatment (>550 ms or >25% over baseline), structural heart disease, left ventricular hypertrophy, heart failure, hypokalemia or hypomagnesemia, or reduced renal function. In-hospital drug initiation is rarely indicated for amiodarone because of its slow onset action and long half-life.

Previous in-hospital testing with intravenous flecainide or propafenone did not predict the safety of the "pill-in-the-pocket" approach and is not recommended by the document (12).

### Safety issues for patients treated with antiarrhythmic drugs

Initially, mechanisms promoting proarrhythmia are reviewed. Drug-substrate and drug-drug interactions associated with proarrhythmia are listed. The authors not only discuss the factors facilitating proarrhythmia but also offer life-saving treatment options. For example, they offer three key actions for drug-induced torsade de pointes (TdP):

- Intravenous administration of magnesium sulfate, irrespective of serum magnesium levels (i.e., 2 g bolus followed by another 2 g bolus and by continuous infusion in case of arrhythmia persistence).
- Increasing heart rate (to reverse bradycardia and to prevent pauses that may prolong repolarization and promote TdP) by means of isoproterenol or overdrive pacing at rates >70 beats per minute.
- Correction of hypokalemia, replenishing serum potassium to the high-normal range (i.e., 4.5-5.0 mEq/L).

As we discussed above, AADs cannot cure but suppress arrhythmias. That means long term, sometimes life-long treatment.

Therefore, extracardiac toxicities are not rare. Drug-specific side effects are listed in a table. Particularly, the toxicity of amiodarone is comprehensively reviewed. The importance of follow-up and patient education is emphasized.

## Conclusion

The consensus document presents a patient-tailored antiarrhythmic treatment approach that targets the arrhythmia mechanism. It provides a perspective on future drugs and summarizes the indications of currently available drugs, along with their side effects and contraindications. This document is so intense that it would not be an exaggeration to call this document as a summary of the previous EHRA guidelines.

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