

Review

Prospects for Combination Antiarrhythmic Drug Therapy in Cardiology: Is It Time for a Polypill?

Anatoly O. Rubanenko¹, Andrey A. Garanin¹, Anton R. Kiselev²

¹ Samara State Medical University, Samara, Russia

² National Medical Research Center for Therapy and Preventive Medicine, Moscow, Russia

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Abstract: In this article, we discuss the feasibility of combination antiarrhythmic drug therapy in the form of a polypill. In our opinion, this type of treatment is currently limited by various factors discussed in this article. Large-sample studies are needed to evaluate the efficacy and safety of different antiarrhythmic drug combinations in patients with atrial fibrillation, as well as supraventricular and ventricular arrhythmias.

Keywords: antiarrhythmic drug therapy, combination therapy, arrhythmia, polypill.

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Correspondence to Anatoly O. Rubanenko. Address: Samara State Medical University, 89 Chapaevskaya St., Samara 443099, Russia. Phone: +79272010944. E-mail: a.o.rubanenko@samsmu.ru.

Introduction

The feasibility to combine multiple drugs in a single pill or capsule (known as a polypill) is a highly relevant issue in the treatment of cardiovascular diseases, especially given the frequent prescription of multiple medications to patients. For example, a patient with symptomatic chronic heart failure with reduced left ventricular (LV) ejection fraction currently must take at least four drugs [1]. The use of a polypill leads to a simplification of the patient's treatment regimen, a reduced incidence of adverse drug interactions, a more pronounced synergistic effect, and cost benefits [2]. In addition, the use of a polypill improves treatment adherence, as shown by data from the FOCUS (Fixed-Dose Combination Drug for Secondary Cardiovascular Prevention) and IMPACT (IMProving Adherence using Combination Therapy) studies [3, 4]. At the same time, the polypill may also have some limitations in its use, such as insufficient personalization of treatment, difficulties in assessing the cause of side effects, and the need for additional clinical studies to confirm efficacy and safety [2].

Currently, the polypill is used primarily for the treatment of hypertension and the management of cardiovascular risk factors. The use of the polypill in patients with coronary artery disease (including acute coronary syndrome and myocardial infarction), as well as diabetes mellitus, with or without concomitant hypertension, appears relevant [2].

Treating various arrhythmias is a complex issue, as these patients often require multiple medications, and in some cases, combination antiarrhythmic therapy. It is worth noting that, despite its relevance, this topic is rarely discussed in modern publications.

The goal of this review is to discuss the feasibility of combination antiarrhythmic therapy in the form of a polypill.

Material and Methods

A literature search was conducted in the PubMed database using the following keywords: 'antiarrhythmic drugs', 'combination', and 'arrhythmia'. We analyzed a total of 883 literature sources published during the last decade. Scientific articles published in English between 2015 and 2025 in the clinical trials publication format met inclusion criteria for the study, while incomplete baseline data, studies that did not evaluate combinations of antiarrhythmic drugs, publication language other than English, unavailable full-text information from published sources, reviews, systematic reviews, and meta-analyses formed exclusion criteria.

Two authors independently identified relevant sources. Disagreements between authors were resolved by consensus. Following the screening protocol, we ruled out 380 records. In the final stage of analysis, 498 full-text articles were excluded. Therefore, after screening process, five published sources were selected for this review.

Results

Atrial fibrillation

Two main approaches to treating patients with atrial fibrillation (AF) are rhythm control and heart rate (HR) control. Both approaches have their advantages and disadvantages for different categories of patients, but the rhythm control strategy involves the active use of antiarrhythmic drugs such as amiodarone, sotalol, propafenone, flecainide, and others.

Rhythm control in atrial fibrillation

When choosing a rhythm control strategy in patients with AF, it is recommended to use a single antiarrhythmic drug. If it is ineffective, another antiarrhythmic drug, preferably from a different class, should be prescribed [5]. It is necessary to take into account relatively high risk of developing various side effects of antiarrhythmic drugs, such as a proarrhythmic effect, conduction disorders, decreased myocardial contractility, hypotension, damage to internal organs, etc. In some cases, when combining different antiarrhythmic drugs, the risk of side effects may increase, especially in the presence of impaired heart structure and function [5]. In addition, a long-term therapy with antiarrhythmic drugs most often does not have a beneficial effect on mortality and other cardiovascular events, and amiodarone therapy is even associated with increased mortality, which was confirmed by some studies [6, 7]. Thus, long-term combination therapy with Class I and Class III antiarrhythmic drugs in patients with AF is currently discouraged because of proarrhythmic and other side effects. At the same time, Class IC antiarrhythmic drugs (e.g., propafenone) are recommended for combination therapy with Class II beta-blockers (BB) or Class IV non-dihydropyridine calcium channel blockers (CCB) to prevent possible transformation of AF to atrial flutter with high conduction speed to the ventricles [5]. A combination of amiodarone and BB is also possible for long-term rhythm control in patients with AF. A combination of propafenone and BB can be used to prevent AF in pregnant women if BB-only therapy is ineffective. Thus, the addition of BB or, less commonly, CCB to Class IC and III antiarrhythmic drugs is a possible combination in patients with AF to implement a rhythm control strategy.

Jin S. et al. (2024) studied 45 patients and discovered that the combination of digoxin with amiodarone/propafenone and a BB could effectively improve short-term arrhythmia recurrence rates in patients after ablation of persistent AF [8]. Alternatively, the combination of amiodarone and digoxin, despite its effectiveness, may be associated with increased patient mortality, as demonstrated in the 2020 study by Chang JY et al. [9]. In their study, the combination of amiodarone and digoxin in patients with AF increased overall mortality vs. digoxin monotherapy: odds ratio (OR) 1.6, 95% confidence interval (CI) 1.47-1.83, $p < 0.001$. Moreover, the median follow-up period of patients was 1.482 days in digoxin monotherapy vs. 1.317 days in combination therapy [9]. It should be noted that digoxin in AF is used primarily in HR control strategy [5].

Heart rate control in atrial fibrillation

Currently, BB, CCB, digoxin, and amiodarone are recommended for HR control in patients with AF. However, amiodarone is used in these patients for long-term treatment only if HR control cannot be achieved with some of the other aforementioned drugs or with pacemaker ablation/implantation for the reasons mentioned above [5]. It is also recommended to initiate therapy in these patients with a single drug, while combination therapy with HR-lowering drugs (such as BB and verapamil/diltiazem) should be used with extreme caution if a specific HR target is required. In such situations, HR should be carefully monitored using regular 24-hour ECG monitoring [5]. Medications such as amiodarone and sotalol, despite their HR-lowering effect, are not recommended for HR control strategy in

patients with AF [5]. The use of a combination of BB and digoxin in patients with AF may be associated with increased mortality vs. BB monotherapy, as demonstrated in the GLORIA-AF registry [10].

Therefore, in patients with AF, the use of combination antiarrhythmic therapy with Class I and III drugs is significantly limited due to the relatively high likelihood of increased side effects, mortality, and the lack of large-sample studies in this field. At the same time, in certain clinical situations, a combination of Class IC and Class III drugs with BB or, less commonly, with CCB may be considered. In any case, the vast majority of patients with AF are prescribed antiarrhythmic drugs as monotherapy, which substantially limits the potential use of these drugs in a polypill. It is also important to remember that the choice of antiarrhythmic drugs in patients with structural heart disease/LV dysfunction is also significantly limited [5].

Ventricular arrhythmias

The use of combinations of antiarrhythmic drugs in treatment of patients with ventricular arrhythmias is also somewhat limited. When prescribing antiarrhythmic therapy to patients with various ventricular arrhythmias, it is necessary to take into account that the vast majority of these drugs cause prolongation of the QT interval and, therefore, can provoke the development of torsades de pointes ventricular tachycardia, have an unfavorable chronotropic effect, can aggravate the course of chronic heart failure, etc. [11]. These effects can often occur when prescribing combination antiarrhythmic therapy. However, the use of more modern antiarrhythmic drugs in combination can be accompanied by a decrease in the incidence of ventricular tachycardia. A clinical case report describes the effective use of a combination of dronedarone (Class III), mexiletine (Class IB), and bisoprolol (Class II) to reduce ventricular tachycardia burden in a patient with an implantable cardioverter defibrillator [12]. Furthermore, this combination of antiarrhythmic drugs, administered for 11 months, did not have any side effects [12].

At the same time, combinations of Class IC/Class III drugs and BB appear feasible with careful monitoring. BB, sotalol, amiodarone, or a combination of BB and amiodarone are recommended for antiarrhythmic treatment of ventricular extrasystoles in patients with structural heart disease/LV dysfunction.

Amiodarone or a combination of amiodarone and a BB are recommended for paroxysms of ventricular tachycardia/ventricular fibrillation in patients with structural heart disease or LV dysfunction who refuse or are unable to undergo implantable cardioverter-defibrillator (ICD) placement.

Also, in some clinical situations (e.g., catecholaminergic polymorphic ventricular tachycardia), a combination of flecainide and a BB may be appropriate [11]. There are published reports of the beneficial effect of a combination of flecainide and sotalol/metoprolol in patients with arrhythmogenic right ventricular cardiomyopathy undergoing ICD placement and catheter ablation [13]. However, that study included patients who had failed both antiarrhythmic drug monotherapy and catheter ablation [13].

In general, patients with ventricular arrhythmias, as well as those with AF, are most often treated with antiarrhythmic drug monotherapy, with limited options for combination therapy.

Table 1. Studies on combination antiarrhythmic drug therapy used in this review

Authors	Sample size	Drug combination	Results
Jin S., et al. [8]	n=45	digoxin + amiodarone/ propafenone + β -blocker	Improved short-term recurrent rates in patients after ablation of persistent AF at 3 weeks (34.48% vs. 0%, $p < 0.01$) and 1 month (44.84% vs. 6.25%, $p = 0.02$) vs. the control group
Chiang J.Y., et al. [9]	n=5.040	amiodarone + digoxin (n=1.473)	Increased all-cause mortality in patients with AF (HR 1.6; 95% CI: 1.470-1.829)
Lam S.H.M., et al. [10]	n=14.201	β -blocker + digoxin	Increased risk of major cardiovascular events (HR 1.35; 95% CI 1.09-1.68) and overall mortality (HR 1.28; 95% CI 1.04-1.57) in patients with AF vs. BB monotherapy
Ermakov S., et al. [14]	n=8	flecainide + sotalol/ metoprolol	In six of eight patients with ARVC, ventricular arrhythmia control was achieved, on average, for 35.5 months
Ciriello G.D., et al. [17]	n=14	flecainide + propranolol + amiodarone	Effective third-line combination therapy for suppressing atrioventricular reentrant tachycardia

BB, beta-blockers; AF, atrial fibrillation; OR, odds ratio; CI, confidence interval; HR, hazard ratio; ARVC, arrhythmogenic right ventricular cardiomyopathy.

Supraventricular arrhythmias (except atrial fibrillation)

Patients with these arrhythmias also have limited options for combination antiarrhythmic drug therapy for the reasons outlined above. However, ivabradine in combination with a BB can be used in these patients (for instance, for sinus tachycardia) [14]. Various combinations of antiarrhythmic drugs can be used to treat patients with atrial flutter (e.g., a combination of a BB/CCB and digoxin when choosing a HR control strategy). However, when treating patients, it is important to remember that Class IA and Class IC antiarrhythmic drugs have little or no effect on atrial flutter and should not be used without a BB due to the risk of atrial rate deceleration and the possibility of 1:1 conduction to the ventricles [14]. Thus, among antiarrhythmic drugs for the elimination of atrial flutter, Class III drugs (dofetilide, ibutilide, amiodarone) are mainly used, while a combination with Class I drugs in this case seems inappropriate. In addition, before deciding on long-term therapy, patients with atrial flutter should first undergo catheter ablation; if the latter is not possible, then BB/CCB therapy should be employed; and only if the previous methods are ineffective, amiodarone treatment can be prescribed [14]. In pregnant women with supraventricular extrasystole, a combination of digoxin with a BB or CCB can be used [15], albeit treatment should be initiated in most cases with monotherapy. A small study conducted by Ciriello GD et al. (2023) was dedicated to the effectiveness of triple antiarrhythmic therapy in newborns with refractory atrioventricular reentrant tachycardia [16]. The authors demonstrated that the combination of flecainide with propranolol and amiodarone was effective in patients who were refractory to one or two antiarrhythmic drugs in suppressing atrioventricular recurrent tachycardia without significant side effects [16]. It is worth noting that triple combinations of antiarrhythmic drugs in this study were considered only as a third-line strategy; consequently, their use in real-world clinical practice will be limited.

Therefore, the antiarrhythmic drug combinations for the treatment of supraventricular arrhythmias and other rhythm disorders presented in this article have limited application.

A summary of the studies cited in this article is presented in [Table 1](#). In general, combinations of Class I and Class III antiarrhythmic drugs can be used only in a limited number of patients with strict indications and careful monitoring. Combinations of Class I and Class III antiarrhythmic drugs with BB or, less commonly, CCB are used in clinical practice for broader indications. However, it should be remembered that in the vast majority of cases, patients with various rhythm disorders receive monotherapy with antiarrhythmic drugs. In clinical practice, it is often necessary to titrate the dose of antiarrhythmic drugs, as well as reduce their dose in the case of side effects. Antiarrhythmic

drugs have numerous side effects; hence, drug combinations can exacerbate them. Furthermore, data on the efficacy and safety of combination therapy with antiarrhythmic drugs is insufficient, and most of such studies were based on small sample sizes. Furthermore, currently, polypill primarily includes drugs proven effective in the management of cardiovascular risk factors and the improvement of patient prognosis. In most cases, antiarrhythmic drugs (e.g., amiodarone) either do not affect patient mortality or may even increase it. In our opinion, all the considerations discussed in this article limit the possibility of including various combinations of antiarrhythmic drugs in a polypill.

Conclusion

We believe that the feasibility of using combination antiarrhythmic drug therapy in a polypill is currently limited in clinical practice for a number of reasons, including limited indications for its use, the need for dose titration, frequent side effects, lack of favourable effect on mortality or even an increased risk of mortality and the insufficient number of studies examining all of these aspects. Future studies on large samples examining various combinations of antiarrhythmic drugs will likely clarify the feasibility of including them in a polypill.

Conflict of interest

The authors declare no conflicts of interest.

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Authors:

Anatoly O. Rubanenko – MD, PhD, Associate Professor, Department of Propaedeutic Therapy with a Course in Cardiology, Samara State Medical University, Samara, Russia. <https://orcid.org/0000-0002-3996-4689>.

Andrey A. Garanin – MD, PhD, Associate Professor, Director of the Scientific and Practical Center for Remote Medicine, Samara State Medical University, Samara, Russia. <https://orcid.org/0000-0001-6665-1533>.

Anton R. Kiselev – MD, DSc, Professor, Head of Coordinating Center for Fundamental Research, National Medical Research Center for Therapy and Preventive Medicine, Moscow, Russia. <http://orcid.org/0000-0003-3967-3950>.