Scientific letters

Concomitant Rivaroxaban and Dronedarone Administration in Patients With Nonvalvular Atrial Fibrillation

Administración simultánea de rivaroxabán y dronedarona en pacientes con fibrilación auricular no valvular

To the Editor,

Direct oral anticoagulants have a wide therapeutic window, a predictable anticoagulant effect, and low risk of drug-drug interactions. They are at least as effective as warfarin for stroke prevention in patients with nonvalvular atrial fibrillation (NVAF) but have a better safety profile, particularly with regard to the risk of intracranial hemorrhage.[1]

Dronedarone is an antiarrhythmic agent currently indicated for the maintenance of sinus rhythm after successful cardioversion in clinically stable adults with paroxysmal or persistent AF.[2] Remarkably, dronedarone significantly reduces the risk of AF recurrence and the incidence of hospitalization due to cardiovascular events or death in patients with paroxysmal or persistent AF.[3,4] However, concomitant treatment with dabigatran and dronedarone is contraindicated, since the area under the curve of dabigatran increases by more than 100% with the addition of dronedarone. However, data on the safety of the coadministration of rivaroxaban with dronedarone is lacking and, for this reason, there is no specific recommendation on this issue in the current EHRA Practical Guide on the use of direct oral anticoagulants in NVAF. In fact, in the EHRA guideline, concomitant rivaroxaban and dronedarone use is marked as a "yellow" interaction, with the recommendation to maintain the original dose, unless 2 or more concomitant 'yellow' interactions are present.[5] The aim of this study was to determine whether there are significant clinical consequences of combining rivaroxaban with dronedarone in NVAF patients.

Twenty-three patients with paroxysmal AF (age 60.9 ± 9.1 years) treated with both drugs concomitantly were included in the study (Table). None of the patients had significant structural heart disease except for 1 with mild left ventricular dysfunction without heart failure. About three quarters of the patients were treated with rivaroxaban 20 mg once daily and all were treated with dronedarone 400 mg twice daily except for 1 treated with dronedarone 200 twice daily due to bradycardia. Most patients had previously taken other antiarrhythmic agents and switched to dronedarone due to AF recurrence or drug intolerance. A total of 30% of patients switched from vitamin K antagonists to rivaroxaban due to lack of adequate international normalized ratio (INR) control or patient preference and 22% switched from dabigatran to rivaroxaban, when dronedarone was initiated. One patient (4.3%) required dronedarone withdrawal due to drug intolerance. At follow-up (9.1 ± 6.7 months), one quarter of the patients had AF recurrence, and there were no thromboembolic or major bleeding events.

Dronedarone is a moderate CYP 3A4 inhibitor, a mild CYP 2D6 inhibitor, and a potent P-gp inhibitor. Rivaroxaban is metabolized via CYP3A4, and is a substrate for the P-gp. Therefore, a potential pharmacodynamic interaction could be expected when both drugs are taken concomitantly.[6] However, data on the safety of this combination is currently lacking. To our knowledge, this is the first study of the consequences of combining rivaroxaban with dronedarone.

Table
Baseline Characteristics and Clinical Events in Patients With Nonvalvular Atrial Fibrillation Treated With Rivaroxaban and Dronedarone

Number of patients	23
Age, y	60.9 ± 9.1
Women, %	52.2
Creatinine clearance ≥ 50 mL/min, %	91.3
LVEF > 50%, %	95.7
Paroxysmal atrial fibrillation (%)	100
Paroxysmal atrial flutter (%)	17.4
Management of atrial fibrillation	
Drug dosage	
Rivaroxaban 20 mg once daily, %	73.9
Rivaroxaban 15 mg once daily, %	26.2
Dronedarone 400 mg twice daily, %	95.6
Dronedarone 200 mg twice daily, %	4.4
Time of concomitant treatment with rivaroxaban and dronedarone, mo	*9.1 ± 6.7*
Previous use of vitamin K antagonists, %	30.4
Previous use of dabigatran, %	21.7
Previous use of antiarrhythmic drugs, %)	73.9
Clinical events during concomitant treatment with rivaroxaban and dronedarone	
Atrial fibrillation recurrence, %	26.1
Liver enzyme elevation, %	0
Thromboembolic events, %	0
Major bleeding, %	0

LVEF, left ventricular ejection fraction.

Our study has some limitations. First, a limited number of patients were included. Second, although most patients had normal renal function, one quarter were taking rivaroxaban 15 mg one daily. This could have counterbalanced the effect of the increase in the area under the curve of rivaroxaban. Finally, the follow-up was insufficiently long to establish the efficacy and safety of the combination in the long-term.

In conclusion, our work is the first study that provides evidence that the concomitant administration of both drugs is safe and is not associated with significant adverse events. However, these results need to be validated by further studies.

CONFLICTS OF INTEREST

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Selection of the Best of 2016 in Clinical Cardiology: Continuum of Care; Relationship Between Cardiology and Primary Care

Selección de lo mejor del año 2016 en cardiología clínica: continuidad asistencial; relación entre cardiología y atención primaria

To the Editor,

Efforts to reduce cardiovascular morbidity and mortality and improve quality of life among chronic heart disease patients require appropriate coordination between cardiology and primary care services. For example, ensuring suitable continuity between these services has been shown to reduce hospitalization in chronic heart failure patients by allowing optimization of medical treatment and early identification of decompensations.[1]

Patients with ischemic heart disease are at high risk of new ischemic events. Cardiac rehabilitation units provide exemplary care to patients recovering from an acute event; however, the very nature of primary care make it the optimal setting for further improvement in long-term secondary prevention, through the promotion of life style changes and measures to ensure that patients adhere to treatment during follow-up.

A recent study conservatively estimated the global direct health-care cost of physical inactivity in 2013 at $54 billion, with $31 billion of this total paid by the public sector; moreover, evaluation of indirect costs indicated that deaths related to physical inactivity cost an estimated $14 billion in lost productivity, with physical inactivity causing 13 million disability-adjusted life-years.[2] Most costs were incurred in high-income countries (81% of health-care costs and 60% of indirect costs). Physical inactivity is thus linked not only to high cardiovascular morbidity and mortality, but also to a substantial economic burden.[2] It is therefore incumbent on cardiology and primary care services to coordinate efforts to encourage patients to adopt appropriate life style changes.

Poor treatment adherence is a major barrier to secondary prevention in ischemic heart disease patients. The many causes of treatment nonadherence include the chronic nature of the disease, the high frequency of asymptomatic or weakly symptomatic disease, medication copayments, and lack of awareness among physicians and patients; however, the most important cause is without doubt treatment complexity. Poor treatment adherence increases cardiovascular morbidity and mortality and health care costs. For some patients, the use of a polypill is a valid approach to tackling this problem. This approach can be advantageous for patients with a history or high risk of treatment nonadherence, those who are poorly controlled with equipotent doses and have adherence problems, those who are well controlled with the individual polypill components, and those with a high medication burden to treat comorbidities. In contrast, polypill medication is contraindicated in patients predicted not to achieve or at least come close to achieving the therapeutic goals recommended in clinical practice guidelines, as well as in those with intolerance or allergy to one of the polypill components. In Spain, a polypill is currently available composed of aspirin (100 mg), atorvastatin (20 mg), and ramipril (2.5-10 mg).[3]

Prevention of thromboembolic complications is essential in patients with atrial fibrillation. The risk is effectively reduced with vitamin K antagonists, and recent research shows that the risk of complications is low in patients with a well-controlled INR.[4] However, in Spain and other European countries, anticoagulation is inadequate in approximately 40% of nonvalvular atrial fibrillation patients managed with vitamin K antagonists through their primary care center.[5] In patients with nonvalvular atrial fibrillation, direct-acting oral anticoagulants are at least as effective as warfarin in preventing stroke and systemic embolism but have a better safety profile, especially regarding the risk of intracranial hemorrhage. These drugs, moreover, provide stable and predictable anticoagulation, rendering periodic anticoagulation tests unnecessary. Unfortunately, the use of these drugs in Spain is heavily restricted, both in primary care and in cardiology services; moreover, these restrictions differ between the various Spanish autonomous communities and impede appropriate access to these