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Amiodarone and dronedarone: An update

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ABSTRACT

This article provides a contemporary review of the current role of amiodarone and dronedarone in patients with atrial fibrillation who need to undergo rhythm control therapy for relief of symptoms. Amiodarone is the most widely prescribed antiarrhythmic drug for this indication. Recent findings show that its use is not associated with increased mortality even in patients with advanced structural heart disease. However, its extracardiac side effect profile may limit its widespread use. Dronedarone appears to be a useful drug in patients with paroxysmal or persistent atrial fibrillation. However, the compound cannot be used in patients with heart failure. In permanent atrial fibrillation, dronedarone is likewise contraindicated based on findings from the PALLAS trial.

Key words: Atrial fibrillation, Antiarrhythmic drugs, Amiodarone, Dronedarone.

Atrial fibrillation (AF) is the most frequently encountered rhythm disorder in clinical practice. AF affects approximately 6 million people in the European Union, an estimated 6 million individuals in China, and more than 2 million patients in the United States. AF is predominant in patients over the age of 60–70 years, and therefore the prevalence of AF is likely to further increase given the global rise in the elderly population [1]. AF is associated with significant morbidity and mortality, mostly as a consequence of stroke and systemic embolism, but also due to heart failure. In many patients, the arrhythmia causes troublesome symptoms with significant decline in the quality of life of afflicted individuals [1].

Despite important advantages of interventional therapy for AF by means of catheter ablation, the majority of patients—the elderly in particular—are still receiving medical therapy by means of rhythm- or rate-control strategies. Antiarrhythmic drug therapy represents a major treatment strategy in patients with atrial fibrillation (AF) in whom maintenance of sinus rhythm—mostly for symptom relief—is desired. This review focuses on the utility of amiodarone, 1 of the oldest antiarrhythmic drugs, and a related drug, dronedarone, for maintaining sinus rhythm in subjects with AF.

Antiarrhythmic drug efficacy of amiodarone in AF

In general, the efficacy of antiarrhythmic drugs is modest, and clinically successful antiarrhythmic drug therapy may rather reduce than eliminate recurrence of AF. A meta-analysis evaluated 44 randomized controlled trials comparing various antiarrhythmic drugs against control [2]. Overall, the likelihood of maintaining sinus rhythm was approximately doubled by the use of antiarrhythmic drugs. In the Lafuente-Lafuente et al. [2] meta-analysis, the number of patients needed to treat for 12 months to avoid an event was 2–9. Most of the included studies enrolled relatively healthy patients, but some drugs such as disopyramide or quinidine were associated with increased mortality. Hence, current guidelines use the underlying pathology as the major determinant of selection of antiarrhythmic drugs to treat AF patients [1,3].

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Of all antiarrhythmic drugs currently used in AF, amiodarone has the greatest potential to maintain sinus rhythm. For instance, in 1 prospective study 65% of patients randomized to amiodarone versus 37% taking sotalol or propafenone remained in sinus rhythm at 1 year [4]. The SAFE-T trial, the only randomized double-blind study of amiodarone, randomized AF patients to either placebo ($n = 137$ patients), sotalol ($n = 261$ patients), or amiodarone ($n = 267$ patients) [5]. The patient's rhythm was regularly checked at follow-up visits and by weekly transtelephonic monitoring. The study showed a median time of 487 days to recurrence of AF in the amiodarone group compared to 74 in the sotalol and 6 days in the placebo group ($p < 0.001$ for both comparisons). In this study, sustained sinus rhythm was associated with improved quality of life and exercise capacity. Surprisingly, the incidence of side effects in SAFE-T was similar in all 3 groups [5]. This seems to be in contrast to other controlled trials and to clinical practice where amiodarone is often associated with extracardiac side effects [6,7].

The question whether amiodarone's impact on cardiovascular outcomes in AF patients is modulated by left ventricular function has been recently evaluated in a pooled analysis of AFFIRM and AF-CHF trials [8]. Survival free from recurrent AF was assessed in 713 patients randomized to rhythm control, in SR at baseline, and receiving amiodarone as the first antiarrhythmic drug. Over an average follow-up of 40 months, recurrence-free survival rates were 84%, 72%, and 45% at 1, 2, and 5 years, respectively [8]. As shown in Fig. 1, no differences in rates of recurrent AF were found according to left ventricular function. Adjusted all-cause and cardiovascular hospitalizations were comparable with amiodarone and rate control overall and in subgroups with or without severe left ventricular dysfunction. This reemphasizes the efficacy and safety of amiodarone—in contrast to many other agents—in patients with advanced structural heart disease and reduced left ventricular function. Of note, however, these lower AF recurrence rates did not necessarily translate in improvements in quality of life and more importantly, in survival for instance in the AF-CHF trial [3].

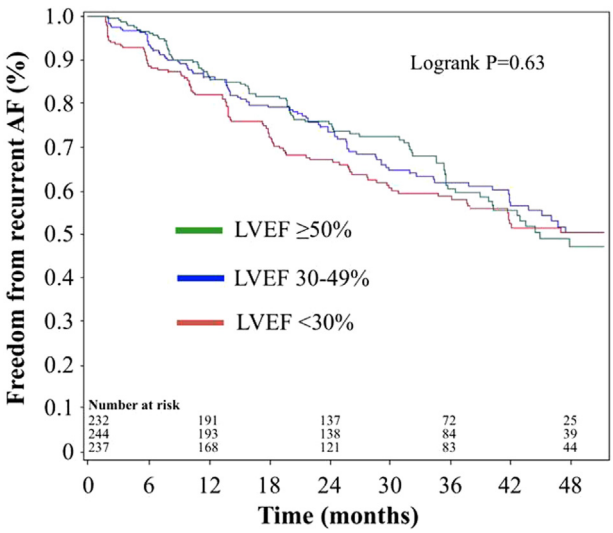

Fig. 1 – Freedom from recurrent AF according to left ventricular function in 713 patients. Pooled analysis of the AFFIRM and the AF-CHF trials. From reference [8].

Effects of amiodarone on mortality in AF patients

Amiodarone is the most commonly used antiarrhythmic drug to treat supraventricular and ventricular arrhythmias [7]. Given the side effect profile of the drug with many extracardiac harmful effects, the effects of amiodarone on mortality remain controversial. Evidence to answer this question is now available from several meta-analyses [9,10] and from large registry studies [11].

Piccini et al. [9] performed a meta-analysis of studies using amiodarone for primary prophylaxis of sudden cardiac death. Compared to placebo/control, there was a 29% and a 18% reduction in sudden death and cardiovascular mortality, respectively, in high-risk patients treated with amiodarone. More relevant to the topic of this review is a meta-analysis presented by Doyle and Ho [10]. The analyzed 12 randomized controlled trials including 5060 patients with persistent AF. Amiodarone was more effective than a placebo or rate control drug in achieving sinus rhythm. Of note, the use of amiodarone as part of a strategy to achieve sinus rhythm was not associated with an increase in all-cause mortality compared to control (4.7 versus 3.9 per 100 patient-years; relative risk = 0.95, 95% CI: 0.81–1.11). When the analysis was restricted to AF patients with severe heart failure ($n = 1587$), amiodarone was again not associated with elevated mortality compared to placebo or rate control drug [10].

Findings from a recent very large registry study using data from the Department of Veterans affairs national health system are in accordance with these data [11]. A total of 122,465 patients with newly diagnosed AF were studied of whom 11,655 (9.5%) received amiodarone; follow-up comprised 353,168 patient-years. Amiodarone was prescribed as an initial therapy in higher risk patients compared to individuals not receiving the drug. In unadjusted analysis, amiodarone recipients had a slightly higher mortality compared to non-recipients (87 versus 73 deaths per 1000 person-years, $p < 0.001$). After multivariate adjustment or applying propensity-matched analysis, there was no significant difference in mortality (multivariate hazard ratio = 1.01, 95% CI: 0.97–1.05, $p = 0.51$ and propensity-matched hazard ratio = 1.02, 95% CI: 0.97–1.07, $p = 0.45$). Consistent results were observed in patients with chronic renal disease, coronary disease, or heart failure.

In contrast, however, NYHA class II or III heart failure patients receiving amiodarone for prevention of sudden death, the drug had no favorable effect on survival [12].

Amiodarone and anticoagulation in AF

Amiodarone is a moderate inhibitor of both, P-glycoprotein and cytochrome P450 3A4 (CYP3A4) hence, it is well know that anticoagulation by means of warfarin in amiodarone-treated subjects yields lower time in therapeutic range (TTR) and potentially more complications when compared to warfarin use in patients not on this antiarrhythmic compound. This has been recently reemphasized in a subgroup analysis of the ROCKET-AF trial [13]; in this trial, 8% of patients were receiving amiodarone and either warfarin or rivaroxaban.