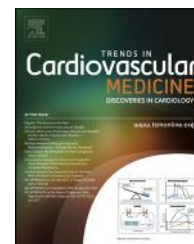


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Amiodarone and dronedarone: An update

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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.

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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].

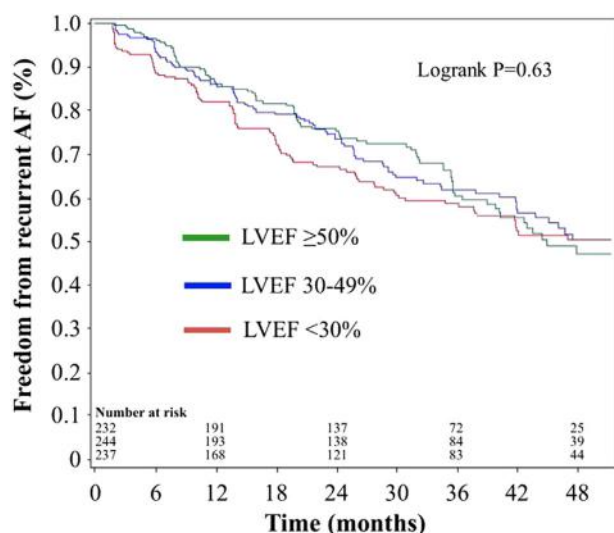


Fig. 1 – Freedom from recurrent AF according to left ventricular function in 713 patients. Pooled analysis of the AFFIRM and the AF-CHF trials. From reference [8].

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 known 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.

In warfarin-treated patients on amiodarone, the mean TTR was only 50% compared to 58% ($p < 0.001$) in subjects not on the antiarrhythmic drug. Similar findings were reported from the pivotal apixaban trial (ARISTOTLE) [14] and from the edoxaban study (ENGAGE AF TIMI 48) [15]. In terms of efficacy in prevention of ischemic events and in terms of safety, all direct oral anticoagulants were at least non-inferior if not superior to warfarin. This was also observed with dabigatran [16]. In clinical practice, therefore, amiodarone can be safely co-prescribed with all of the new direct oral anticoagulants.

Practical considerations in the use of amiodarone

Amiodarone continues to represent the most commonly prescribed antiarrhythmic drug in AF. Whereas it can be safely administered even in patients with advanced structural heart disease and heart failure, its extracardiac side effect profile requires meticulous patient surveillance. The treating clinician needs to consider these toxic effects carefully in every patient. A comprehensive review and clinical guide on the appropriate use of amiodarone have recently been published [7].

Antiarrhythmic drug efficacy of dronedarone in AF

Dronedarone, a non-iodinated benzofuran derivative related to amiodarone, has been approved by regulators in various jurisdictions for the use in non-permanent AF. Like amiodarone, dronedarone is a multichannel blocking drug that has been demonstrated in 2 placebo-controlled randomized trials to be more effective than placebo in maintaining normal sinus rhythm and in controlling the ventricular rate during AF recurrences, but with a comparable side effect profile to placebo [17]. Both trials analyzed together revealed an AF recurrence rate at 12 months of 64.1% in the dronedarone compared to 75.2% in the placebo group (HR = 0.75, 95% CI: 0.65–0.87, $p < 0.001$).

The antiarrhythmic effects of dronedarone have been directly compared to those of amiodarone in a randomized double-blind study comprising 504 patients with persistent AF [18]. The primary endpoint of this study was a composite of recurrent AF or premature study drug discontinuation. This endpoint was observed in 75.1% of patients assigned to receive dronedarone and in 58.8% in those on amiodarone ($p < 0.0001$). Of note, this difference was mainly driven by a significantly higher incidence of recurrent AF in the dronedarone compared to the amiodarone group (63.5% versus 42.0%) after a median treatment duration of 7 months. There were fewer extracardiac side effects in subjects receiving dronedarone than in the amiodarone group.

Freemantle et al. published a mixed treatment comparisons of contemporary antiarrhythmic drugs for which they performed a comprehensive meta-analysis of 39 randomized controlled trials examining amiodarone, dronedarone, flecainide, propafenone, sotalol, or placebo for the treatment of AF [19]. Amiodarone had the largest effect in reducing AF recurrences (HR = 0.22, 95% CI: 0.16–0.29); however, it was

also associated with the highest rate of serious adverse events (HR = 2.41, 95% CI: 0.96–6.06).

Effects of dronedarone on mortality in AF patients

The only antiarrhythmic drug trial in AF patients that was specifically designed to evaluate important clinical endpoints such as mortality or hospitalization was the ATHENA trial, comparing dronedarone to placebo [20]. This multinational study recruited 4628 patients with paroxysmal or persistent AF or flutter and followed them for the primary endpoint of cardiovascular hospitalization and death. Over a mean follow-up of 21 ± 5 months, primary outcome events occurred in 734/2301 (31.9%) dronedarone and in 917/2327 placebo patients [hazard ratio (HR) = 0.76, 95% CI: 0.69–0.84; $p < 0.0001$]. There were 116 deaths (5.0%) in the dronedarone and 139 (6.0%) in the placebo group (HR = 0.84; 95% CI: 0.66–1.08; $p = 0.18$). Among the deaths, there were 63 of cardiovascular origin (2.7%) in the dronedarone group and 90 (3.9%) in the placebo group (HR = 0.71; 95% CI: 0.51–0.98; $p = 0.03$), which was largely due to a reduction in arrhythmic death with dronedarone. There was also a significant reduction in cardiovascular hospitalization in the dronedarone group (secondary endpoint; HR = 0.74, 95% CI: 0.67–0.82, $p < 0.001$).

The results of ATHENA were contrasted, however, by findings of the ANDROMEDA study [21]. This trial was not an AF study and investigated the use of dronedarone versus placebo in patients with symptomatic recently decompensated heart failure requiring diuretic treatment, a LVEF < 0.35 , and at least 1 NYHA class III–IV episode in the month prior to randomization. After the inclusion of 627 patients (310 in the dronedarone group and 317 in the placebo group) and median treatment duration of approximately 2 months, the trial was stopped. Overall, 25 patients in the dronedarone (8.0%) and 12 patients in the placebo group (3.8%) had died (hazard ratio = 2.13, 95% CI: 1.07–4.25, $p = 0.027$). The deaths were predominantly due to worsening heart failure, and there was no evidence of proarrhythmia or an increased incidence of sudden death in the dronedarone group.

Dronedarone was also tested in a randomized double-blind placebo-controlled study in patients with permanent AF (PALLAS trial) [22]. The first co-primary outcome was stroke, myocardial infarction, systemic embolism, or cardiovascular death; and the second co-primary outcome was unplanned cardiovascular hospitalization or death. After enrollment of 3236 patients, the study was also stopped for safety after 42 primary outcome events in the dronedarone group and 19 in patients receiving placebo (HR = 2.24, 95% CI: 1.30–3.85; $p = 0.004$). There were 21 cardiovascular deaths on dronedarone and 10 on placebo (HR = 2.11, 95% CI: 1.00–4.49; $p = 0.05$). A likely explanation for the findings in PALLAS is that in permanent AF the benefits of dronedarone in reverting patients back in sinus rhythm plays not role and may be completely offset by negative side effects of the drug. As a result of these 2 negative trials, dronedarone is contraindicated in patients with heart failure and/or permanent AF.

Another factor perhaps contributing to the unexpected results of PALLAS is represented by the drug–drug interaction, which exists for dronedarone and digoxin. Dronedarone

increases digoxin concentration by P-glycoprotein interaction. In a careful post hoc analysis of the PALLAS trial there was a strong effect of concurrent digoxin use on the adverse effect on dronedarone on cardiovascular death [23]. Compared to the placebo group, dronedarone patients have significantly higher digoxin concentrations. In patients on digoxin, there were 11 arrhythmic deaths on dronedarone and none on placebo, a difference which accounted for most of the observed overall mortality difference. Kaplan–Meier mortality curves are shown in Fig. 2 according to the concomitant use of digoxin in patients randomized to dronedarone or placebo. Hence, close monitoring of patients treated with dronedarone and digoxin (including monitoring digoxin plasma levels) is mandatory to avoid such deleterious drug–drug interactions.

Dronedarone and anticoagulation in AF

There appears to be less of an interaction between warfarin and dronedarone than that observed for amiodarone, although this has not been studied in depth. Regarding the use of new oral anticoagulants in patients receiving dronedarone, not much evidence is available. In fact, only few patients were enrolled in the pivotal trials on direct oral anticoagulants that were treated with dronedarone. Hence, a firm conclusion appears impossible, but caution should be exercised, since dronedarone—like amiodarone—is a potent

inhibitor of the P-glycoprotein transport system. Of note, dronedarone co-medication is not allowed in subjects anticoagulated with dabigatran.

Post marketing data on dronedarone use in AF

Several analyses using administrative datasets concerning the use of dronedarone in AF have been published. Perhaps the most comprehensive one stems from the Swedish Patient Register comprising 174,995 subjects with AF during 2010 and 2012 [24]. Of these, 4856 received dronedarone according to the Swedish Drug Register; 170,139 patients served as controls. Patients prescribed dronedarone were younger and healthier than controls. The annual mortality rate was 1.3% in those who received dronedarone, and 14% in the control population. Of note, no sudden deaths or deaths due to liver failure were reported among dronedarone users. Following propensity score matching and adjustment for possible confounders, dronedarone patients had a lower mortality than controls (HR = 0.41, 95% CI: 0.33–0.51). The conclusion of this study was, therefore, that dronedarone, as prescribed in clinical practice in Sweden, did not expose patients to increased risk of death.

Similar data stemming from US claims databases have confirmed this experience. Wu et al. [25] reported data on more than 38,000 AF patients who received more than 1 dronedarone prescription. During long-term follow-up

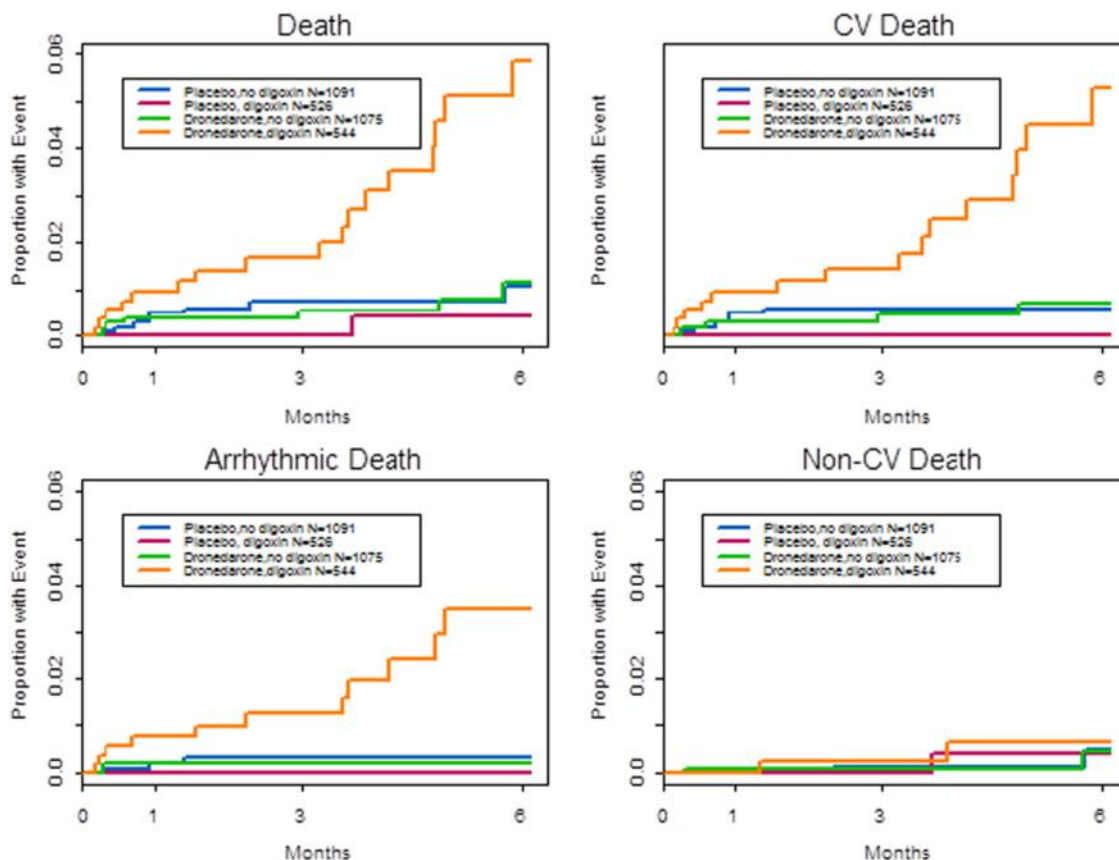


Fig. 2 – Kaplan–Meier survival plots for 4 mortality outcomes in patients on dronedarone or placebo with or without concomitant digoxin therapy. Findings from the PALLAS trial in patients with permanent AF. From reference [23].

(nearly 3 years), data indicated that dronedarone has mostly been used appropriately in compliance with US prescribing in the target populations.

A third study also using US insurance claims database examined 10,455 adult AF patients with a new treatment of dronedarone, amiodarone, sotalol, flecainide, or propafenone between 2009 and 2010 [26]. No significant differences were observed in the risk for outcome events between all antiarrhythmic drugs. The only exception was a higher risk for cardiovascular events observed in patients on amiodarone who were free of a history of heart failure. The authors concluded that dronedarone could be an alternative to amiodarone for these patients, which reflects current prescribing recommendations.

Therapeutic considerations

Antiarrhythmic drug therapy continues to be a major treatment principle in patients with AF in whom rhythm control is warranted. Dronedarone can be safely used for this purpose if patients are carefully selected, as proposed in contemporary treatment guidelines. In subjects with little or no structural heart disease, dronedarone is about as effective as class I drugs. The compound should not be prescribed in patients with permanent AF or in those with significant structural heart disease. Because of its well-known extracardiac toxicity, amiodarone is almost never the antiarrhythmic drug of first choice. There is increasingly a choice between catheter ablation of AF and administration of amiodarone, which needs individual treatment decisions. Amiodarone represents the antiarrhythmic drug of choice, however, when patients with reduced left ventricular function need rhythm control medication.

Future developments

Amiodarone remains the most widely used antiarrhythmic drug in AF. The side effect profile of this compound, however, requires drug discontinuation in a substantial proportion of patients [7]. Dronedarone can be used safely in patients with paroxysmal or persistent AF with the contraindications of concomitant heart failure or presence of permanent AF. These shortcomings emphasize the need to develop effective, but safer antiarrhythmic drugs in the future. A currently explored avenue is represented by the fixed combination of low-dose dronedarone with low-dose ranolazine. This combination has been demonstrated in preclinical models to exert antiarrhythmic efficacy that is superior to that of each compound alone [27]. The potent synergistic effects resulted in atrial-selective depression of Na⁺-channel-dependent parameters and effective suppression of AF. A proof-of-concept study in 134 patients with implanted pacemakers has confirmed such synergistic effects in the clinical setting [28]. Ranolazine (750 mg BID) combined with dronedarone (225 mg BID) over 12 weeks reduced AF burden by 59% compared to placebo ($p = 0.008$) while ranolazine (750 mg BID)/dronedarone (150 mg BID) yielded a 43% AF reduction ($p = 0.072$). Both combinations were well tolerated. This fixed drug combination deserves further evaluation in larger outcome trials.

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