Benefit-Risk Assessment of Current Antiarrhythmic Drug Therapy of Atrial Fibrillation

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ABSTRACT

Over the last decade, several rhythm-versus rate-control trials in patients with atrial fibrillation (AF) have failed to demonstrate benefit of the rhythm control strategy with respect to mortality and morbidity. This had led to the guideline recommendation that antiarrhythmic drug therapy should be considered predominantly for symptomatic improvement of patients. Recent trials and meta-analyses have demonstrated that amiodarone is the most antiarrhythmic drug currently available. However, its use has been associated with many adverse effects. Currently, dronedarone is the only available antiarrhythmic drug which has shown a reduction in cardiovascular hospitalizations in medium-risk AF patients. However, the drug was associated with increased mortality in patients with recently decompensated heart failure. Hence, antiarrhythmic drug therapy has to be evaluated in patients with AF on an individual patients basis.

Introduction

Atrial fibrillation (AF) is the most frequently encountered rhythm disorder in clinical practice. It affects approximately 6 million people in the European Union, an estimated 6 million individuals in China, and >2 million patients in the United States.

Atrial fibrillation is predominant in patients age >60–70 years, and therefore the prevalence of AF is likely to further increase given the global rise in the elderly population.¹ Atrial fibrillation 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 affected individuals.¹

Despite significant 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. This brief review focuses on risk and potential benefits of antiarrhythmic drug therapy in AF.

Rate vs Rhythm Control in Atrial Fibrillation

Approximately a decade ago, several randomized controlled clinical trials were conducted to address questions about optimal management strategy for AF, the so-called rate-vs-rhythm-control trials.^{2–7} Total or cardiovascular mortality was the primary endpoint in 2 of these trials.^{3,7} Both trials convincingly demonstrated a lack of survival advantages in patients in whom sinus rhythm was restored by means of cardioversion and maintained with antiarrhythmic drugs. The remaining 4 studies were not powered for mortality endpoints, but they failed to show any significant differences in the utilized surrogate endpoints, such as symptomatic improvement (2) or composites of various kinds^{4–6} (Table).

As a consequence of these trials failing to demonstrate benefit of the rhythm-control strategy, many physicians abandoned efforts to restore and maintain sinus rhythm in their patients. Accordingly, hospital admissions for AF as a principal diagnosis declined by about 2% per year from 2002 to 2004, as recently reported.⁸ This was paralleled by a marked decline in prescription of antiarrhythmic drugs, most evident for class IA agents.⁸ The trend of reduced admission for AF was reversed between 2004 and 2006, mainly as a result of increasing use of catheter ablation attempting to cure AF, which increased by about 30% per year in the United States. Although catheter ablation has the potential to alleviate symptoms of AF, there is still no trial showing a survival benefit following this procedure. Of note, over the last 2 years several groups have reported long-term outcomes after AF ablation with respect to recurrence rates of the arrhythmia. Rates of AF-free

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Table 1. Rhythm- and Rate-Control Trials

Trial (Year)	No. of Patients	Primary Outcome Measure	Primary Results
PIAF (2000)	252	Symptomatic improvement (palpitations, dyspnea, dizziness)	76 patients in rate control, 70 patients in rhythm control; $P = 0.317$
AFFIRM (2002)	4060	All-cause mortality	25.9% in rate control, 26.7% in rhythm control; $P = 0.08$
RACE (2002)	522	Composite endpoint (CV death, CHF hospitalization, thromboembolic complications, severe hemorrhage, pacemaker implantation, SAE)	17.2% in rate control, 22.6% in rhythm control; $P = 0.11$
STAF (2003)	200	Composite endpoint (stroke/TIA, systemic embolism, CPR)	10 events in rate control, 9 events in rhythm control; $P = 0.99$
HOT CAFÉ (2004)	205	Composite endpoint (death, thromboembolic complications, intracranial or other major bleeding)	OR: 1.98 (95% CI: 0.28–22.3); $P = 0.71$
AF CHF (2008)	1376	Cardiovascular death	25% in rate control, 27% in rhythm control; $P = 0.59$

Abbreviations: AF CHF, Atrial Fibrillation and Congestive Heart Failure; AFFIRM, Atrial Fibrillation Follow-Up Investigation of Rhythm Management; CHF, congestive heart failure; CI, confidence interval; CPR, cardiopulmonary resuscitation; CV, cardiovascular; HOT CAFÉ, How to Treat Chronic Atrial Fibrillation; OR, odds ratio; PIAF, Pharmacological Intervention in Atrial Fibrillation; RACE, Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation Study; SAE, serious adverse event; STAF, Strategies of Treatment of Atrial Fibrillation; TIA, transient ischemic attack.

survival varied between 47%⁹ and 78%¹⁰ over a mean follow-up period of 4–5 years. Success rates of course depend on patient populations, operator experience, and—perhaps most notably—on methods used to search for recurrent arrhythmias. Thus, even with the use of ablation techniques, there is no evidence for survival benefit of the rhythm-control strategy as yet.

Antiarrhythmic Drug Efficacy in Atrial Fibrillation

As discussed in detail in the recent European Guidelines for the management of AF, antiarrhythmic drug therapy to maintain sinus rhythm is relief of AF-related symptoms.¹ This implies that patients who become asymptomatic after sufficient rate control should not generally receive antiarrhythmic drugs.

In general, the efficacy of antiarrhythmic drugs is modest, and clinically successful antiarrhythmic drug therapy may rather reduce than eliminate recurrence of AF. A recent meta-analysis evaluated 44 randomized controlled trials comparing various antiarrhythmic drugs against control.¹¹ Overall, the likelihood of maintaining sinus rhythm was approximately doubled by the use of antiarrhythmic drugs. Of all antiarrhythmics examined, amiodarone was the most effective one. In the Lafuente-Lafuente et al meta-analysis, the number of patients needed to treat for 12 months was 2–9.¹¹ Most of the included studies enrolled relatively healthy patients, but some drugs such as disopyramide or quinidine were associated with increased mortality. Figure 1 shows choice of antiarrhythmic drugs recommended in the new guidelines. Of note, the underlying pathology is the

Figure 1. Choice of antiarrhythmic drug therapy according to underlying pathology. Unstable = cardiac decompensation within the prior 4 weeks. Antiarrhythmic agents are listed in alphabetical order within each treatment box. ? = evidence for “upstream” therapy for prevention of atrial remodeling still remains controversial. Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CAD, coronary artery disease; CHF, congestive heart failure; HT, hypertension; LVH, left ventricular hypertrophy; NYHA, New York Heart Association. Reproduced with permission.¹

major determinant of selection of antiarrhythmic drugs to treat AF patients.

Of all antiarrhythmic drugs currently approved for use in AF, amiodarone has the greatest potential to maintain sinus rhythm. In contrast to many other agents, amiodarone can be safely administered in patients with structural heart disease. The Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T), for instance, randomized AF patients in a double-blind manner to either placebo ($n = 137$), sotalol ($n = 261$), or amiodarone ($n = 267$).¹² Each 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 with 74 days in the sotalol group 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, except for minor bleeding.¹² This seems to be in contrast to other controlled trials and to clinical practice, where amiodarone is often associated with extracardiac side effects.¹³

Antiarrhythmic Efficacy of Dronedaron

Recently, a new antiarrhythmic drug, dronedarone, has been approved by regulators in North America, Europe, and other jurisdictions for the use in nonpermanent AF. Dronedaron is a new multichannel blocking drug which has been demonstrated in the European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedaron for the Maintenance of Sinus Rhythm (EURIDIS) and the American-Australian-African Trial with Dronedaron in Atrial Fibrillation or Flutter Patients for the Maintenance of Sinus Rhythm (ADONIS) 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.¹⁴ Both trials analyzed together revealed an AF recurrence rate at 12 months of 64.1% in the dronedaron group compared with 75.2% in the placebo group (hazard ratio [HR]: 0.75, 95% confidence interval [CI]: 0.65–0.87, $P < 0.001$).

In the A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedaron 400 mg bid for the Prevention of Cardiovascular Hospitalization or Death from Any Cause in Patients with Atrial Fibrillation/Atrial Flutter (ATHENA) trial, dronedaron has been shown to reduce important clinical endpoints such as cardiovascular hospitalizations or death¹⁵ in medium risk patients with AF. In a post-hoc analysis of the ATHENA trial, Page et al evaluated the rhythm- and rate-controlling effects of dronedaron.¹⁶ The median time to first AF recurrence in the study was 498 days in the placebo group and 737 days in the dronedaron group ($P < 0.001$). There were fewer cardioversions and less development of permanent AF in patients receiving active treatment. Therefore, these findings are consistent with those observed in the 2 pivotal efficacy trials of dronedaron.¹⁴

The antiarrhythmic effects of dronedaron have been directly compared with those of amiodarone in a randomized double-blind study comprising 504 patients with

persistent AF.¹⁷ The primary composite 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 dronedaron 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 dronedaron group compared with the amiodarone group (63.5% vs 42.0%) after median treatment duration of 7 months. There were fewer extracardiac side effects in subjects receiving dronedaron than in the amiodarone group.

Freemantle et al recently published their mixed treatment comparisons of contemporary antiarrhythmic drugs, for which they performed a comprehensive meta-analysis of 39 randomized controlled trials examining amiodarone, dronedaron, flecainide, propafenone, sotalol, or placebo for the treatment of AF.¹⁸ 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) (Figure 2A and 2B).

Thus, available evidence from randomized controlled trials and from comprehensive meta-analyses demonstrates that the antiarrhythmic efficacy of dronedaron in maintaining sinus rhythm is inferior to that of its mother compound, amiodarone. The latter is currently the most efficacious antiarrhythmic compound for the treatment of AF.

Antiarrhythmic Drug Efficacy and Benefit on Clinical Outcomes

Besides causing symptoms, AF is associated with increased mortality and morbidity. Moreover, the arrhythmia is a leading cause of hospitalization for cardiovascular reasons.¹⁹ Hence, the question arises whether attempts to maintain sinus rhythm by means of antiarrhythmic drugs are associated with beneficial effects on hard clinical outcomes such as mortality or hospitalization. The AFFIRM trial demonstrated a trend toward increased mortality in patients who were assigned to rhythm control therapy.³ In the Atrial Fibrillation and Congestive Heart Failure (AF-CHF) study, there was no significant difference in the primary endpoint of cardiovascular mortality between the rhythm- and the rate-control treatment arm.⁷ In this trial, 82% of patients assigned to rhythm control received therapy with amiodarone.

For the endpoint of hospitalization, Wyse et al showed for patients in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) study a significant increase in the need for cardiovascular hospitalization in the rhythm-control arm (46% vs 36%, $P < 0.001$).²⁰ This was also confirmed in the AF-CHF study.⁷ In this study, heart failure patients with concomitant AF derived no benefit from rhythm control (predominantly with amiodarone) in terms of hospital admissions. Specifically, the proportion of patients who required hospitalization was higher in the rhythm-control group than in the rate-control group (64% vs 59%, $P = 0.06$), particularly during the first year (46% vs 39%, $P = 0.001$).

A post-hoc analysis of the AFFIRM data demonstrated that cardiovascular hospitalization was highly predictive of subsequent death ($P < 0.001$).²⁰ An important conclusion

Figure 2. (A) Effects of antiarrhythmic drugs on recurrence of atrial fibrillation. Hazard ratios along with 95% confidence intervals are shown. (B) Effects of antiarrhythmic drugs on withdrawal due to adverse events. Hazard ratios along with 95% confidence intervals are shown. Reproduced with permission.¹⁸

from this analysis was that cardiovascular hospitalization turned out to represent the only reliable surrogate endpoint for mortality. A very recent report from the Stockholm Cohort Study on Atrial Fibrillation (SCAF) confirmed this association between cardiovascular hospitalizations and subsequent death.²¹

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.¹⁵ This multinational study recruited 4628 patients with paroxysmal or persistent AF or flutter and randomized them to treatment with dronedarone 400 mg twice daily or placebo. The primary endpoint was a composite of cardiovascular hospitalisation and death. Among 2301 patients randomized to dronedarone, primary outcome events occurred over mean follow-up was 21 ± 5 months in 734 (31.9%). Among 2327 patients randomized to placebo, primary outcome events occurred in 917 (39.4%; HR: 0.76, 95% CI: 0.69–0.84, $P < 0.0001$). There were 116 deaths (5.0%) in the dronedarone group 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 Antiarrhythmic Trial with Dronedaron in Moderate to Severe CHF Evaluating Morbidity Decrease (ANDROMEDA) trial.²² This trial investigated the use of dronedarone in patients with symptomatic recently decompensated heart failure requiring diuretic treatment, a left

ventricular ejection fraction <0.35 , and ≥ 1 New York Heart Association class III–IV episode in the month prior to randomization. Patients were assigned to dronedarone 400 mg twice daily or placebo. The primary efficacy evaluation was the incidence of all-cause mortality and hospitalization. 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. Twenty-five patients in the dronedarone group (8.0%) and 12 patients in the placebo group (3.8%) had died (HR: 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. At present, there is no valid explanation for these strikingly different findings of the 2 studies. However, results of ANDROMEDA helped to define contraindications for the use of dronedarone.

In the aforementioned mixed treatment comparison of antiarrhythmic drugs in AF patients by Freemantle and coworkers, all randomized controlled studies with 5 antiarrhythmic drugs were evaluated with respect to mortality.²¹ As shown in Figure 3, none of the 3 drugs dronedarone, amiodaron, or sotalol had a beneficial effect. In contrast, dronedarone was the only agent that apparently was not associated with an increase in mortality. Therefore, despite the superior efficacy of amiodaron in terms of prevention of recurrent AF, no survival benefit emerged for this compound.

Conclusion

The current evidence base on antiarrhythmic drug treatment in AF indicates that amiodaron is the most effective compound in terms of prevention of AF recurrences.

Figure 3. Effects of antiarrhythmic drugs on all-cause mortality in studies involving >100 patients in either treatment arm. Hazard ratios along with 95% confidence intervals are shown. Reproduced with permission.¹⁸

However, this appears not to translate in a survival benefit or a reduced rate of cardiovascular hospitalizations. On the other hand, dronedarone is the only drug for which 1 trial has demonstrated a reduction in cardiovascular hospitalization and all-cause mortality in patients with paroxysmal or persistent AF. However, these positive results are somewhat contrasted by the negative findings of a heart failure trial. More evidence is therefore needed to establish a positive benefit-risk ratio of antiarrhythmic drug therapy in patients with AF.

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