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Original Article

Treatment of Postoperative New Onset Atrial Fibrillation with Repolarization Delaying Agents after Heart Surgery

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Purpose: The aim of this study was to evaluate the efficacy of the multichannel-blocker dronedarone for postoperative new onset atrial fibrillation (POAF) as compared to amiodarone.

Methods: Out of 990 patients who underwent cardiothoracic surgery between March 2011 and March 2012, 166 patients who developed POAF and treated with amiodarone or dronedarone were enrolled in this study.

Results: Eighty-nine patients were treated with amiodarone and 77 patients were treated with dronedarone at discharge. Seventy-five percent of patients with dronedarone were treated initially with intravenous amiodarone but quickly converted to oral dronedarone as soon as the mechanical ventilation was weaned off. The rate of conversion in sinus rhythm was not influenced by the resulting amiodarone-to-dronedarone crossover as compared to oral dronedarone only ($p < 0.247$ at the ICU and $p < 0.640$ at the normal care unit). At hospital discharge sinus rhythm was documented in 44% of the amiodarone patients and 99% of the dronedarone patients ($p < 0.001$). The maintenance of sinus rhythm was demonstrated in 82% of the amiodarone patients versus 81% of the dronedarone patients at 6-month follow-up ($p < 0.804$).

Conclusions: Our data demonstrated the higher conversion rate to sinus rhythm in the early phase in the dronedarone group despite a comparable conversion rate in the mid-term phase compared to amiodarone.

Keywords: heart surgery, antiarrhythmic treatment, atrial fibrillation

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Introduction

Atrial fibrillation (AF) is the most common arrhythmia following cardiothoracic surgery. Depending on the employed intervention, the incidence of postoperative new onset AF (POAF) varies between 16% and 63%.[1)] Although POAF is often detected early and is frequently self-limiting and of short duration,[2)] about 20% of the patients do not convert to sinus rhythm within 24 h.[3)] POAF may also affect postoperative prognosis by causing stroke, cardiac failure, hemodynamic instability, and death.[1,4–6)]

Amiodarone is one of the most common and most effective antiarrhythmic drugs. However, it can cause some serious adverse effects.[7,8)]

Dronedarone is a newer class III antiarrhythmic drug which is structurally related to amiodarone. It is a member of myocardial repolarization delaying agents, but it does not harbor the iodine moieties causing thyroid problems. In addition, its methane sulfonyl group decreases lipophilicity, resulting in a shorter half-life and lower tissue accumulation.[9] As a multichannel blocker, dronedarone affects potassium, sodium, and calcium channels and exerts antiadrenergic effects.

The efficacy and feasibility of dronedarone administration in patients with AF are conflicting depending on the patient population. Two randomized, placebo-controlled phase-III studies with more than 1200 patients with POAF demonstrated that dronedarone was able to reduce AF relapse.[10] That agent helped also controlling the ventricular rate during POAF via blocking the atrio-ventricular node.[11] The placebo-controlled and double-blind ATHENA study proved that dronedarone in patients with paroxysmal or persisting AF and with at least one cardiovascular risk factor reduced the combined endpoint of hospitalization (due to cardiovascular events) and death.[12]

On the other hand, one study with patients suffering from severe, symptomatic cardiac insufficiency needed to be terminated ahead of time due to an increased mortality after dronedarone initiation.[13]

In the present study, we hypothesized that dronedarone administration for POAF was not inferior to amiodarone therapy. We compared the efficacy of short- and mid-term conversion of POAF to sinus rhythm after cardiac surgery.

Methods

Study design and patient selection

This cohort study included consecutive 166 patients who developed POAF during or after cardiac surgery and treated with amiodarone or dronedarone between March 2011 and March 2012. The index surgical interventions were: on- or off-pump coronary artery bypass grafting (CABG), cardiac valve replacement, or surgery in case of aortic dissection. To include only patients with preoperative sinus rhythm, the patients with pre-existing AF in the preoperative electrocardiogram (ECG) were excluded (n = 218). Patients who died within 8 days postoperatively (n = 6) or converted spontaneously to sinus rhythm, i.e. without any antiarrhythmic drug (n = 37), were also excluded. In case that the patient died later than 8 days after surgery, the last available ECG was analyzed. After occurrence of intra- or postoperative new-onset AF immediate treatment was started with correction of electrolytes and volume. If these procedures did not terminate POAF, an electric cardioversion or other antiarrhythmic drugs were considered depending on the hemodynamic situation. The acute therapy with amiodarone for treatment of postoperative AF was performed as previously recommended.[14,15] Briefly, 150 mg of amiodarone was infused in 30 min. Immediately after 1 mg/kg was administered intravenously for 6 h followed by 0.5 mg/kg for 18 h, amiodarone was oralized. This particular treatment standard was implemented at our institution because of its advantages regarding hospital stay reduction and prevention of side effects.[14,15] Data of 14 patients needed to be excluded as they were treated neither with amiodarone nor with dronedarone. **Figure 1** summarizes the patient selection criteria. The study protocol was approved by the institutional review board and complies with the principles outlined in the declaration of Helsinki.

Demographic and clinical data

Demographic (age, gender, weight, and height) and clinical data (cardiovascular risk factors, left ventricular pump function, and rhythm-related medication) were collated as well as data on the surgical procedures (**Table 1**). Rhythm-relevant medications (i.e. beta-blockers, calcium-antagonists, etc.) were recorded up to 6 months postoperatively.

Electrocardiograms

Multiple ECGs were analyzed for AF at five time points: pre-, intra-, early postoperatively on the ICU, 8 days after surgery (at discharge), and 6 months after surgery (at follow-up). Medico software, version 25 (Cerner Health Services, Inc., Malvern, PA, USA) was used for the ECG analysis.

Study endpoints

Primary endpoint was the rate of patients in sinus rhythm at hospital discharge, and secondary endpoints were the number of patients who maintained sinus rhythm at 6 months of follow-up. Main side effects of amiodarone including but not limited to bradycardia, atrio-ventricular block, ventricular arrhythmia, interstitial pneumonia, and liver poisoning were not observed.

Statistics

After data collection was completed, the individual data sets were anonymized, before statistical analysis

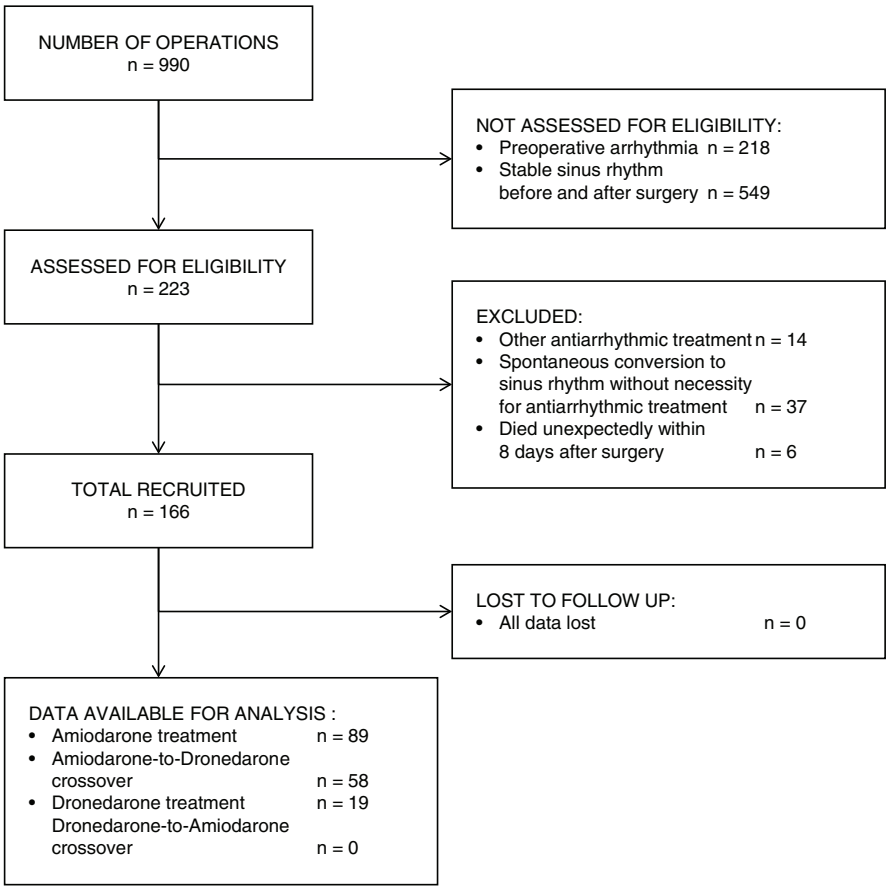

Fig. 1 Selection of the study population.

was started. The statistical analysis was performed using IBM SPSS Statistics, version 24 (Armonk, NY, USA). The study relevant variables were summarized for all study participants and according to the amiodarone or the dronedarone treatment. Unless otherwise indicated continuous variables are presented as mean ± SD or median (25th to 75th percentile) according to the normality of their distribution and compared using either Student's *t*-test or Mann–Whitney test. Categorical variables are reported as percentages and tested by Pearson's chi-square test or, when validity conditions were not satisfied, by Fisher's exact test.

Results

Clinical characteristics and antiarrhythmic treatment considerations

The average age of the study population was 69 ± 11 years. Male gender prevailed (69% males versus 31% females), although there was no statistical difference with regard to the gender between amiodarone and dronedarone treatment groups ($p < 0.143$). The patients were treated either with amiodarone (n = 89) or dronedarone (n = 77). In the amiodarone group POAF developed either intraoperatively or on the ICU and was treated in both cases with intravenous amiodarone. After discharge from the ICU the intravenous administration was converted to oral administration of amiodarone and it was continued orally onwards. In the dronedarone group POAF developed predominantly on the ICU. In 58 out of the 77 patients (75%) intravenous amiodarone was initiated, but quickly converted to oral dronedarone after weaning from the mechanical ventilation and successful oral alimentation to prevent potential relapse in AF during the further postoperative course. Out of these 77 patients, 39 patients experienced conversion in sinus rhythm under acute amiodarone therapy, and oral dronedarone therapy was continued to maintain sinus rhythm. The remaining 19 patients (25%), who experienced conversion in sinus rhythm without intravenous amiodarone during the ICU stay, were adjusted primarily to oral dronedarone to further maintain sinus rhythm and to prevent potential relapse in POAF, respectively. However, the inherently resulting amiodarone-to-dronedarone crossover did not have any

Table 1 Baseline characteristics and outcomes of the study population

	All patients (n = 166)	Amiodarone (n = 89)	Dronedarone (n = 77)	p-value
Sex (%)				
Male	69	74	64	0.143
Female	31	26	36	
Age at surgery (years)	69 ± 11	69 ± 11	70 ± 10	0.391
Body mass index (kg/qm)	28 ± 5	28 ± 4	28 ± 5	0.939
Preoperative symptoms and comorbidities				
LV ejection fraction, normal (%)	52	51	53	0.730
LV ejection fraction, subnormal (%)	48	49	47	
LV ejection fraction, highly reduced (%)	0	0	0	
NYHA I (%)	32	27	38	0.140
NYHA II (%)	32	27	38	0.140
NYHA III (%)	33	38	27	0.136
NYHA IV (%)	33	38	26	0.094
Hypertension (%)	82	85	78	0.212
Hyperlipidemia (%)	20	17	23	0.294
Diabetes mellitus (%)	25	17	34	**0.012**
Insulin (%)	11	15	8	0,169
Smoking (%)	20	26	13	**0.038**
CAD-1 (%)	8	10	5	0.240
CAD-2 (%)	10	6	16	**0.035**
CAD-3 (%)	49	49	48	0.859
Left main disease (%)	20	18	23	0.390
Mitral valve insufficiency ≥II Grade (%)	7	8	6	0.734
COPD (%)	12	13	10	0.541
Medical therapy				
ACE inhibitor (%)	41	44	38	0.421
Beta blocker (%)	49	47	52	0.541
Calcium antagonists (%)	10	8	12	0.405
Surgical details and outcomes				
Coronary artery bypass grafting (%)	32	27	38	0.140
Biological aortic valve replacement (%)	23	25	22	0.689
Mechanical aortic valve replacement (%)	3	3	3	0.771
Biological mitral valve replacement (%)	3	2	4	0.535
Mechanical mitral valve replacement (%)	1	1	0	0.351
Mitral valve repair (%)	2	2	3	0.883
Tricuspid valve repair (%)	1	1	0	0.351
Aortic replacement (%)	10	8	12	0.405
Death (%)				
Survivor	95	92	97	0.135
Non-survivor	5	8	3	

impact on the clinical course of POAF as compared to dronedarone only (p <0.247 for conversion to sinus rhythm at discharge and p <0.640 for conversion to sinus rhythm at 6 months follow-up), for which reason both dronedarone subgroups, with and without crossover, were merged and analyzed together (**Table 1**).

Amiodarone versus dronedarone for treatment of POAF

The conversion of POAF to sinus rhythm was dependent on the antiarrhythmic drug and occurred with different dynamics. At postoperative day 8 (i.e. at discharge), ECG analysis showed sinus rhythm in 44% of the amiodarone patients and in 99% of the dronedarone patients (p <0.001). Six months later, sinus rhythm was demonstrated in 82% of the amiodarone patients and 81% of the dronedarone patients (p <0.804, **Fig. 2**). Thus the observed differences in the conversion rates at discharge were attenuated at 6 months follow-up. This was attributed to the antiarrhythmic regimen, which was changed by the cardiologist after hospital discharge. Both drugs, amiodarone and dronedarone, were

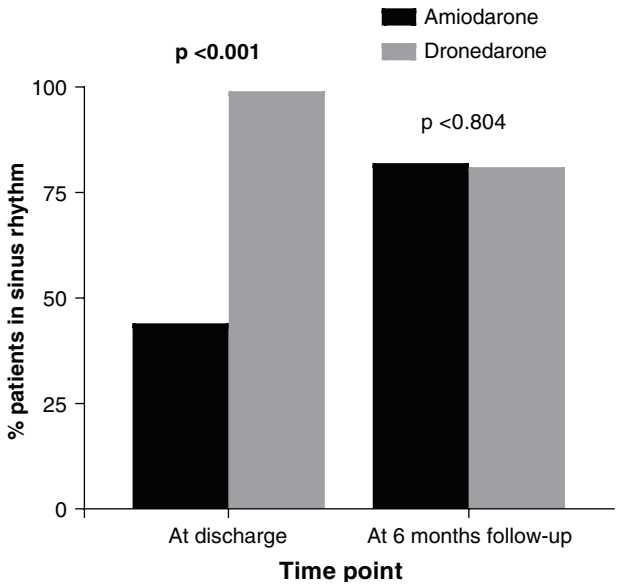

Fig. 2 Probabilities for conversion to sinus rhythm at discharge and at 6 months follow-up according to amiodarone or dronedarone treatment.

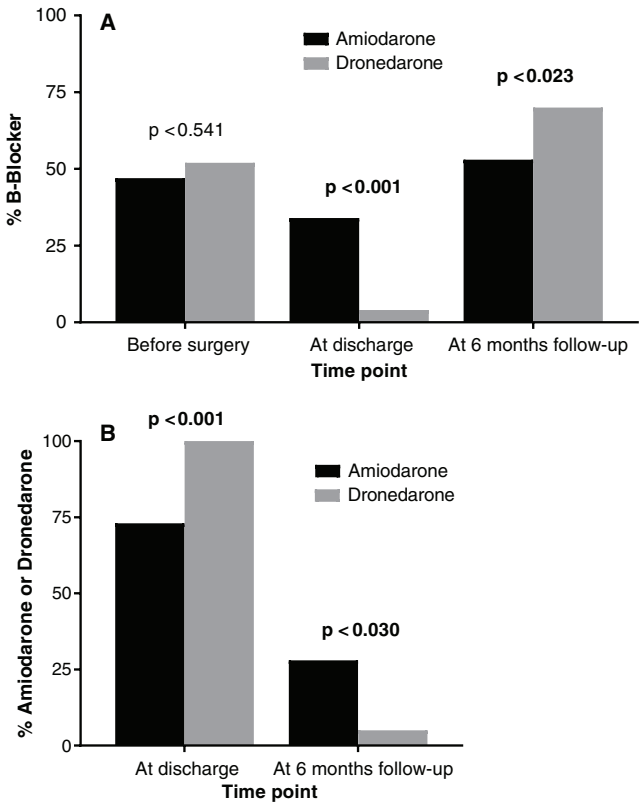

Fig. 3 Antiarrhythmic management at discharge and at 6 months follow-up.

discontinued and replaced by beta-blockers at 6 months follow-up, but the dronedarone group was more severely impacted as compared to the amiodarone group. Beta-blockers were administered in the amiodarone group in 34% of the cases at discharge and in 53% at 6 months follow-up. In contrast, in the dronedarone group beta-blockers were administered in 4% of the cases at discharge and in 70% at 6 months follow-up (**Fig. 3A**). Accordingly, the amiodaron administration decreased from 73% at discharge to 28% at 6 months follow-up in the amiodarone group as compared to the dronedarone group, where the dronedarone administration decreased from 100% at discharge to 5% at 6 months follow-up (**Fig. 3B**).

Surgical interventions, AF, and the probability for postoperative conversion to sinus rhythm according to antiarrhythmic treatment

The most common surgical intervention was CABG (n = 53 patients) followed by surgical aortic valve replacements (SAVR, n = 44 patients). Short- and mid-term results of amiodarone and dronedarone concerning the conversion to sinus rhythm and its maintenance are shown in **Table 2**. There were significant differences in the short-term, drug-dependent results. In the amiodarone group, 46% of the CABG and 48% of the SAVR patients, who suffered from POAF, were converted to sinus rhythm at discharge, while in the dronedarone group conversion rate was 100% for both types of surgery ($p < 0.001$ for CABG and $p < 0.001$ for SAVR). However, these early postoperative significant differences were attenuated at later follow-up. Six months after surgery, 79% of the patients with CABG and 88% of the patients with SAVR, who underwent amiodarone treatment, remained in sinus rhythm. In contrast the proportion of patients, who were treated with dronedarone and remained in sinus rhythm at 6 months follow-up, was lower: 69% for CABG and 84% for SAVR, without statistical significance ($p < 0.402$ for CABG and $p < 0.717$ for SAVR) (**Table 2**).

Discussion

The main findings of this study were (1) the incidence of conversion to sinus rhythm in the early phase of medical therapy after cardiac surgery was significantly higher under dronedarone as compared to amiodarone, and (2) the maintenance rate of sinus rhythm at 6 months of follow-up was similar for both therapies.

POAF worsens the prognosis of these patients by significantly increasing the risk of severe complications

Table 2 Probability for postoperative conversion to sinus rhythm according to surgical interventions and antiarrhythmic therapy

	All patients	Amiodarone	Dronedarone	p-value
Coronary artery bypass grafting (n = 53)				
Sinus rhythm at discharge (%)	75	46	100	**<0.001**
Sinus rhythm at 6 months follow-up (%)	74	79	69	0.402
Aortic valve replacement (n = 44)				
Sinus rhythm at discharge (%)	70	48	100	**<0.001**
Sinus rhythm at 6 months follow-up (%)	86	88	84	0.717

such as stroke, heart failure, prolonged hospitalization, or even death.[16–21] Therefore an early intervention is necessary. Like amiodarone antiarrhythmic drugs often present undesirable side effects, which in some cases are severe. Hence, pharmacological therapy is often limited.[22] Indications for performing electrical cardioversion in patients with post-CABG AF are hemodynamic instability, myocardial ischemia, acute pump failure, and elective restoration of normal sinus rhythm after a failed pharmacological attempt. Cardioversion can be associated with thromboembolism if POAF is present for more than 48 h; therefore, the focus of treatment with electrical cardioversion has to remain on serious hemodynamic instability.[22]

Short-term results of dronedarone exhibited in our study advantages over amiodarone as the conversion rate to sinus rhythm was markedly higher. These remarkable short-term results could be attributed to its modified chemical structure and variable pharmacokinetics and -dynamics. As compared to amiodarone, dronedarone has a quicker onset of action which presents an impressive advantage.[9] In fact, peak plasma concentrations are reached within 3–6 h. Thus, POAF can be treated earlier and help avoiding the development of atrial remodeling that might induce POAF in the mid- and probably in the long-term.

The improved action of dronedarone is likely due to its modified chemical structure. The addition of a methyl sulfonyl group and the lack of the iodine moieties are not only responsible for the shorter plasma half-life resulting in a reduction of accumulative effects and organ toxicity, but they also reduce side effects on the thyroid gland.[9] The ATHENA study, the largest clinical study to date with an antiarrhythmic drug for AF, showed that dronedarone significantly reduced the risk of cardiovascular-related hospital admissions and death by 24% in patients with paroxysmal or persistent AF.[12] The cardiovascular death rate was reduced by 29%. Because of the rate-regulating, antihypertensive, and anti-adrenergic properties of dronedarone, it has been speculated that this antiarrhythmic could also be of clinical use in permanent AF. This hypothesis should be tested in the follow-up study PALLAS (permanent AF outcome study using dronedarone on top of standard therapy) trial.[23] The hope was to be able to demonstrate a substantial reduction in cardiovascular events with dronedarone in a planned study group of almost 11,000 patients with permanent AF and additional risk factors. This hope was disappointed: about a year after its start, and PALLAS was stopped prematurely in July 2011 due to an observed unfavorable development in the dronedarone arm. A total of 38 deaths were recorded during the follow-up period, of which 13 occurred in the placebo arm and 25 in the dronedarone arm. Based on these results, the outpatient prescription of dronedarone was significantly reduced by the general practitioners.

However, in this study, we observed the higher conversion rate to sinus rhythm in the early phase in the dronedarone group despite a comparable conversion rate in the mid-term phase compared to amiodarone. This result may indicate the new insight into the management of POAF in the early phase, especially for patients with poor cardiac functions on whom sustained POAF may worsen the patient's condition severely. Dronedarone, with its rapid onset of effect, its fewer adverse effects, and its overall remarkable short-, mid-, and long-term results, is a drug that presents several advantageous features for this very particular population.

Spontaneous conversion to sinus rhythm occurs in almost 70% of patients with AF of less than 72 h duration,[9] and a clinical duration of AF of less than 24 h at presentation is the best predictor of spontaneous conversion. The high rate of spontaneous conversion highlights the importance of having a control group when assessing the efficacy of active pharmacological cardioversion strategies. In our study cohort, patients who did not have spontaneous conversion to sinus rhythm in a timely manner received active therapies to restore

sinus rhythm. In our study the patients are nonspontaneous converted and therefore active conversion pharmacological strategies were performed. Due to the current publications it is possible that some of our study patients, in both groups, would have had spontaneous conversion if they had not received these active therapies.

Study limitations

The current study is a retrospective analysis with prespecified hypothesis. Of course, there are methodological limitations that are inherent in retrospective design. Another limitation is that the decision on the particular treatment with amiodarone or dronedarone was taken nonrandomly by the respective cardiac surgeon.

Conclusions

This study on 166 patients who underwent cardiac surgery describes the efficient treatment of POAF in patients who received dronedarone. Despite observed unfavorable outcomes by PALLAS trial, our result may indicate the new insight into the management of POAF in the early phase, especially for patients with poor cardiac functions on whom sustained POAF may worsen the patient's condition severely. The results of our retrospective study must however first be confirmed in a prospective manner on a large group of patients. Because of the retrospective nature of our analysis, we could not adjust for this confounder.

Disclosure Statement

None.

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