Safety, Side Effects and Relative Efficacy of Medications for Rhythm Control of Atrial Fibrillation in Hypertrophic Cardiomyopathy

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In patients with hypertrophic cardiomyopathy (HC), atrial fibrillation (AF) is common, often poorly tolerated and difficult to treat. Limited data exists regarding safety or efficacy of drug therapy for AF rhythm control in HC patients. We performed a retrospective analysis of patients with HC followed >6 months, treated with amiodarone, sotalol, dofetilide, or disopyramide for rhythm control of non-postoperative AF. The duration followed on each medication, reasons for discontinuing, and incidences of adverse events were recorded. Confounding factors including maximum ventricular septal thickness, age, left ventricular ejection fraction, and gender were assessed. Ninety-eight patients had 130 drug treatments (defined as a continuous time on 1 drug); 23 patients were treated with >1 medication. The probability of remaining on a single antiarrhythmic drug at 1 year was 62% and at 3 was 42%. Maximum ventricular septal thickness (hazard ratio 1.05, p = 0.03) and presence of resting outflow gradient (hazard ratio 2.50, p = 0.002) were associated with discontinuation of therapy. Patients treated with amiodarone or sotalol had no serious safety events suggesting that these medications may be reasonably safe. Amiodarone was least likely to be discontinued for inefficacy (8.5%), but likely to be discontinued for side effects (19%). The probability of remaining on sotalol was 74% at 1 year and 50.0% at 3 and it was only discontinued for side effects in 2%. A small number of patients were treated with disopyramide and dofetilide. In conclusion, our data suggest that amiodarone and sotalol are likely safe, and that sotalol may be particularly attractive given its low rate of side effects and low rate of discontinuation. **© 2019 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2019;123:1859−1862)**

Hypertrophic cardiomyopathy (HC) is the most common genetic heart disease and atrial fibrillation (AF) occurs in almost one-quarter of HC patients with an incidence of 2% per year.[1] Although the risk of heart failure and stroke for HC patients with AF may be lower with modern treatments than previously believed,[2] these patients are frequently symptomatic and thus a rhythm control strategy is often pursued.

Limited data exist on treatment of AF in HC and thus an optimal strategy has not been defined. Data exists for use of amiodarone,[3] however potential toxicity constrains its use, particularly in younger individuals. There is extremely limited data on sotalol[4] and there are concerns about its safety. Disopyramide was shown to be safe treating heart failure symptoms in HC patients,[5] however its efficacy for rhythm control in AF remains unknown. Limited data exists for Dofetilide.[6] Other antiarrhythmic drugs (AADs) have not been significantly studied for AF in HC.

Methods

In this single center retrospective analysis, the experience with AADs for rhythm control of symptomatic AF in HC is described. Patients were included if treated for rhythm control for symptoms of AF with one or more of amiodarone, sotalol, dofetilide, or disopyramide for at least a 6-month period between 2004 and 2016. Patients with only postoperative or asymptomatic AF were excluded. Patients were monitored clinically (including renal function and QTc) at regular intervals as deemed appropriate by their treating physician. The duration of therapy, reasons for discontinuing each medication, and serious safety events (sustained ventricular tachycardia [VT], ventricular fibrillation, QTc prolongation, syncope, death, stroke, and bradyarrhythmias) were assessed from chart review. Patient factors, including age, left ventricular ejection fraction (LVEF), maximum left ventricular wall thickness, gender, history of nonsustained VT or sustained VT, and presence of a resting left ventricular outflow tract gradient ≥30 mm Hg were examined for their association with efficacy and safety.

Kaplan-Meier analysis was used to estimate efficacy. A multivariable Cox proportional hazards regression model was utilized to identify factors associated with efficacy. We defined efficacy as the time until drug was discontinued.

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Table 1
Patients' characteristics, total patients = 98, total AAD treatments = 130

Epidemiologic characteristics	Sotalol (n = 45)	Amiodarone (n = 47)	Disopyramide (n = 18)	Dofetilide (n = 20)	
Male	31(69%)	27 (58%)	12 (67%)	14 (70%)	p=0.61
Average age (years)	55.2 ±12.2	55.4 ± 14.6	55.5 ± 11.4	58.0 ± 11.5	p=0.87
Average body mass index (kg/m^2)	29.7 ± 6.1	30.3 ± 7.4	28.9 ± 6.2	28.4 ± 5.1	p=0.56
Family history of HC	19 (42%)	20 (43%)	9 (50%)	6 (30%)	p=0.36
Family history of SCD	8 (18%)	7 (15%)	3 (17%)	3 (15%)	p=0.98
History of NSVT prior to AAD	16 (36%)	10 (21%)	4 (22%)	3 (15%)	p=0.18
History of sustained VT prior to AAD	5 (11%)	5 (11%)	1 (6%)	2 (10%)	p=0.69
History of syncope prior to AAD	8 (18%)	6 (13%)	1 (6%)	2 (10%)	p=0.46
Echocardiographic characteristics					
Left ventricular ejection fraction	57.7 ± 13.5	58.4 ± 13.7	61.4 ± 8.9	56.5 ±14.2	p=0.44
LVOT obstruction at rest ≥30 mm Hg	13 (29%)	19 (40%)	5 (28%)	1 (5%)	p=0.005
Intracavitary gradient present	2 (4%)	2 (4%)	2 (11%)	1 (5%)	
LVOT obstruction valsalva ≥30 mm Hg	16 (36%)	20 (43%)	8 (44%)	2 (44%)	p=0.02
LA size (mm)	45.3 ± 5.6	47.4 ±7.2	43.3 ± 5.4	44.3 ± 11.2	p=0.21
Maximum LV septal thickness	18.8 ± 6.4	18.4 ±4.5	18.0 ±4.8	16.9 ± 5.3	p=0.64
Prior AF procedures					
Surgical MAZE procedure	3 (7%)	4 (9%)	1 (6%)	3 (15%)	
Catheter radiofrequency ablation	6 (13%)	10 (%)	2 (11%)	4 (20%)	
Catheter cryo ablation	1 (2%)	0	0	0	

Longer times on the drug indicated higher efficacy. People still on the drug at the end of the study were censored. Medications were prescribed for control of clinical symptoms, thus the duration of treatment with a given drug was assessed as a proxy for efficacy. Although only 25% of patients were treated with more than one medication, we accounted for correlation within patients using the robust sandwich estimator for the cox regression, and mixed models and generalized estimating equations for the analyses in Table 1.

Results

Ninety-eight patients had 130 AAD treatments; 23 patients were treated with more than 1 medication (Table 1). Mean ages at start of treatment were 55.4 ± 14.6 years for amiodarone (n = 47), 55.2 ± 12.2 for sotalol (n = 45), 55.5 ± 11.4 for disopyramide (n = 18), and 58 ± 11.5 for dofetilide (n = 20). The mean duration of treatment on AAD was 3.1 ± 1.9 years for amiodarone, 2.3 ± 2.3 for sotalol, 1.7 ± 2.8 for disopyramide, and 2.2 ± 1.7 for dofetilide. The mean LVEF was 58.2 ± 13.1%; 21 (16%) had LVEF less than 50%. The average maximum LV wall thickness was 18.2 ± 5.4 mm. Twenty-one (16%) had a family history of HC, 22 (17%) had previous myectomy, 8 (6%) had previous alcohol septal ablation, 11 (8.5%) had previous MAZE, and 22 (22.4%) had previous AF ablation. Sixty-one (47%) had a primary prevention implanted cardiac defibrillator (ICD) placed for one or more risk factors and 9 (7%) had a secondary prevention ICD. Patients' previous procedures for AF rhythm management are detailed in Table 1. Patients in this cohort were rarely treated with catheter ablation after starting AAD therapy: 2 amiodarone, 2 dofetilide, and 1 sotalol.

No instances of sudden cardiac death were observed and no serious side effects were seen in patients on amiodarone or sotalol. There were 3 safety events during follow-up for disopyramide (anaphylaxis n = 1, sustained VT n = 1 and QTc prolongation on routine electrocardiogram [EKG] monitoring n = 1) and 3 for dofetilide (symptomatic bradycardia n = 1, syncope n = 2). Only 1 sustained ventricular arrhythmia was observed in a 50-year-old disopyramide-treated patient with HCM with obstruction and a family history of sudden cardiac death and a secondary prevention ICD for previous VT. While on treatment with disopyramide 200 mg twice daily he relieved 3 shocks for polymorphic VT. Documented inefficacy caused cessation for 4 (8.5%) patients on amiodarone, 12 (8.7%) on sotalol, 5 (22.2%) on disopyramide and 6 (15.8%) on dofetilide (Table 2). At 1 year the probability of remaining on a single AAD was 62% and 42% at 3 years. Maximum septal thickness (hazard ratio [HR] = 1.05, p = 0.03) and presence of a resting outflow gradient ≥30 mm Hg (HR = 2.50, p = 0.002) were associated with decreased efficacy (or increased likelihood of stopping). LVEF (HR = 0.99, p = 0.15), gender (HR = 0.65, p = 0.08) and history of sustained VT (HR = 0.58, p = 0.12) were not significantly associated with efficacy.

The probability of remaining on sotalol at 1 year was 74% and 50% at 3 (Figure 1). Sotalol had minimal side effects causing cessation (2.2%). Sotalol was stopped for inefficacy in 27.2% (Table 2). Amiodarone had the lowest rate of discontinuation for inefficacy (8.5%), however 19.1% of patients treated with it had side effects causing discontinuation, confirming the known limits on its use particularly in young patients. Indeed the probability of remaining on amiodarone at 1 year was 51.4% and 29.2% at 3, suggesting that for many patients the side effects are likely not tolerated.

Only a small number of patients treated with disopyramide and dofetilide were included, however the probability of remaining on treatment with disopyramide was 43.7% at 1 year and 35.0% at 3 years, while the probability of remaining on dofetilide at 1 year was 73.0%, 54.4% at 3.

Table 2
Patients whose medications were stopped for documented inefficacy, incidence of safety events and serious side effects, and incidence of side effects causing discontinuation for each medication

Medication (n = number of drug treatments)	Documented inefficacy causing cessation	Safety events and serious side effects	Side effects causing discontinuation
Sotalol (n = 44)	12 (27.2%)	0 (0%)	1 (2.2%): Dyspnea (n = 1)
Amiodarone (n = 46)	4 (8.5%)	0 (0%)	9 (19.1%): Pulmonary (n = 5), Thyroid (n = 1), Visual (n = 1). Other (n = 2)
Disopyramide (n = 17)	5 (22.2%)	3 (17.6%): Anaphylaxis (n = 1), Sustained VT (n = 1), QTc prolongation (n = 1)	4 (22.2%): Anticholinergic (n = 3), Other (n = 1)
Dofetilide (n = 19)	6 (15.8%)	3 (15.8%): Symptomatic bradycardia (n = 1), Syncope (n = 2)	3 (15.0%): Headache (n = 1), GI (n = 1)

Discussion

Given the paucity of available data looking specifically at AADs for AF rhythm control in HC, this data importantly suggests to clinicians that AAD therapy is likely safe for this indication, with only 4.6% of the overall cohort having serious side effects or safety events. In particular, patients treated with amiodarone or sotalol had no serious side effects or safety events causing cessation. Only a small number of patients were treated with disopyramide (17), or dofetilide (19). Disopyramide has previously been seen to be safe in HC patients,[5] but small numbers preclude inference about the safety of disopyramide.

Furthermore, our data suggest these medications may be efficacious in treating symptomatic AF as the probability of remaining on them for control of symptoms at 1 year was 0.62 and at 3 years 0.42. The probability of remaining on sotalol at 1 year was 74.4% and 50.0% at 3. Sotalol had a majority of patients remaining on it at 1 year of follow-up and minimal side effects causing cessation, however it was stopped for inefficacy in 27.2% suggesting there may be many patients for whom Sotalol will not be effective.

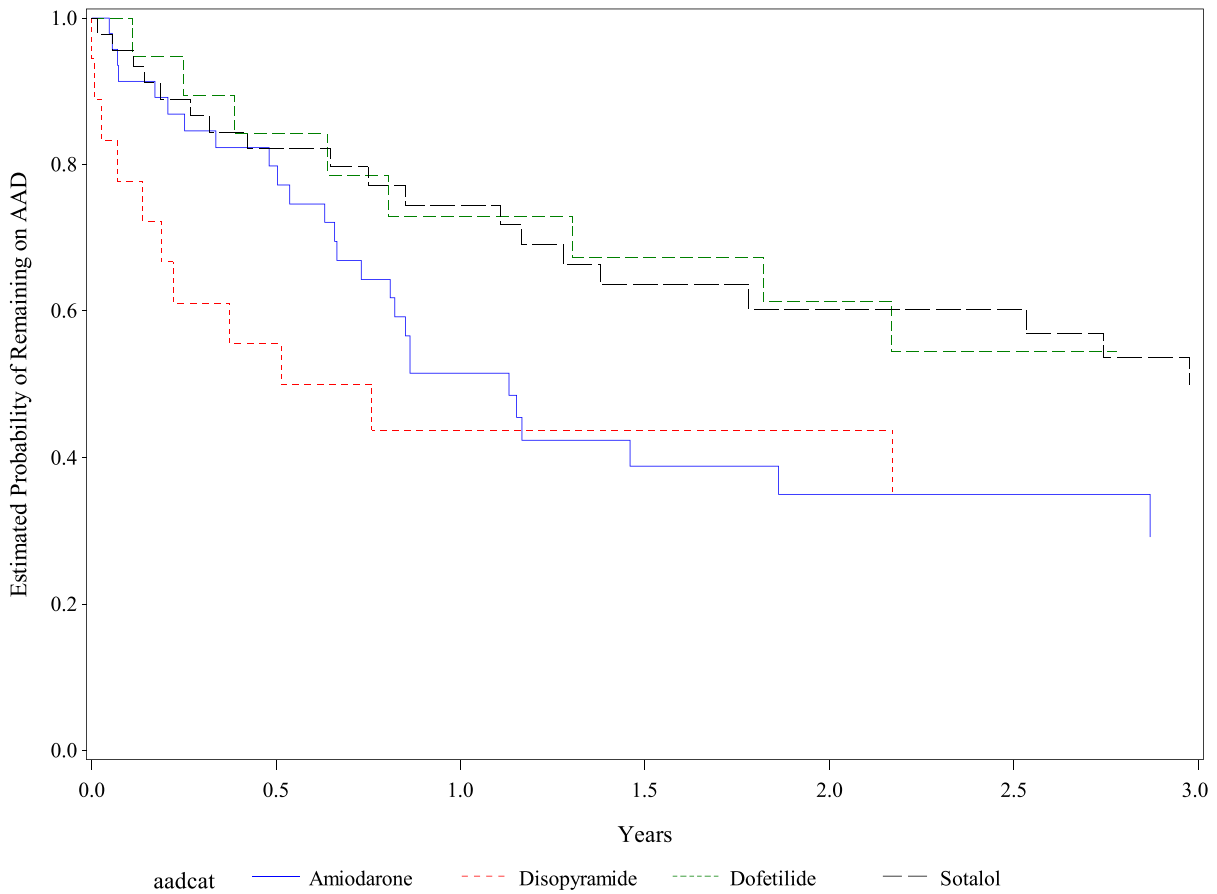

Figure 1. Kaplan-Meier curves illustrating probability of remaining on each medication.

Amiodarone had the lowest rate of discontinuation for inefficacy (8.5%), however 19.1% of patients treated with it had side effects causing discontinuation, and a much lower probability of remaining on the medication at 3 years (29.2%) confirming the known limits on its use particularly in young patients. The small numbers studied preclude significant insight into the efficacy of disopyramide and dofetilide in this population.

This study increases the very limited previous data on the efficacy and safety of AADs for rhythm control in HC. These patients may be both more resistant to maintenance of sinus rhythm and at higher risk of safety issues such as proarrhythmia and arrhythmic syncope. Our data aligns with the limited previously published data on amiodarone[3] suggesting it is relatively efficacious for AF rhythm control in HC, but that patients are exposed to risk from this drug with long-term use of this medication. Data on sotalol for rhythm management of AF in HC patients is very limited,[4] and our study is the largest to date demonstrating that sotalol may be efficacious for AF rhythm control in these patients. Given the absence of safety events or serious safety effects, and the low rate of side effects causing discontinuation, Sotalol may be a good choice for these patients. Our limited results on disopyramide and dofetilide are primarily hypothesis generating, however they suggest that further study of this medication is likely warranted.

Although our study is the largest to date specifically evaluating AAD therapy for rhythm control of AF in HC, we have a relatively small cohort of patients in this retrospective study. As such, the precise risk and benefit of AAD therapy in patients with HC remains incompletely defined and thereby use of these medications should remain a shared decision between clinicians and patients.

In conclusion, this study suggests the relative safety of AAD therapy with amiodarone and sotalol for rhythm control of AF in patients with HC. This data suggest that sotalol may be the medication of choice in this population for this indication given the particularly low incidence of side effects or safety events and given that it was rarely stopped for inefficacy.

Disclosures

None.

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