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Efficacy and adverse effects of sotalol in adults with congenital heart disease

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ABSTRACT

Introduction: Adults with congenital heart disease (CHD) are predisposed to arrhythmias, which can often be refractory to medical therapy. Sotalol is an attractive alternative antiarrhythmic to amiodarone in this younger patient population, given the latter's toxicity profile, but it may have proarrhythmic effects. We therefore aimed to assess the efficacy and safety of sotalol in adults with CHD.

Methods: We retrospectively assessed our adult CHD database for all patients ≥16 years old, with moderate to highly complex defects, who were prescribed sotalol between 2000 and 2017. Efficacy in treating the clinical arrhythmia was assessed as complete, partial or failure. Adverse effects, including proarrhythmia, were documented.

Results: Sotalol was prescribed in 82 of 902 adult CHD patients reviewed (9%). The mean age at sotalol commencement was 31.8 ± 13.1 years, with a median time on sotalol of 2.8 years. The average prescribed dose was 122 ± 51 mg/daily. Sotalol was completely effective in 48% (n = 39), partially effective in 46% (n = 38) and failed to control the clinical arrhythmia in 6% (n = 5). Fifteen patients (18%) discontinued sotalol due to a side effect, most commonly fatigue or dyspnoea. No episodes of torsades de pointes or sudden cardiac death were observed. Significant bradycardia related to sotalol occurred in 13% (n = 11, with permanent pacing implemented in 4), and was associated with Fontan anatomy.

Conclusions: In moderate to highly complex adult CHD, sotalol was reasonably effective and safe in low doses. Side effects limiting treatment were typically non-life-threatening, with significant bradycardia related to sotalol more likely in Fontan patients.

1. Introduction

Adults with congenital heart disease (CHD), particularly those with more complex subtypes, are at significantly increased risk of both atrial and ventricular arrhythmias [1,2]. Given these patients often have compromised hemodynamics, tachyarrhythmias can be associated with substantial morbidity and mortality [3,4]. Unfortunately, arrhythmia management can prove challenging, with medical therapies often ineffective or contraindicated, due to reasons such as ventricular dysfunction. The most effective antiarrhythmic available, amiodarone, is limited by its broad spectrum of toxicities associated with long-term use [5]. Potential cumulative toxicity is concerning in the younger patient population of adult CHD (ACHD) patients, with an elevated risk of amiodarone-induced thyroid dysfunction reported in this group [6]. Sotalol is an attractive alternative antiarrhythmic, but was given a class IIb indication only in the 2014 PACES/HRS consensus statement on arrhythmias in ACHD [1]. This reflected concerns regarding a possible increased mortality signal in acquired cardiac disease [7,8], acknowledging the limited data in ACHD patients [9–11]. Sotalol use in ACHD patients with significantly impaired ventricular function was not recommended. We aimed to describe the efficacy, safety and adverse effects of sotalol use in a cohort of moderate to highly complex ACHD patients, from a quaternary level ACHD referral centre.

2. Methods

We prospectively defined a group of moderate to highly complex ACHD lesions [12], at increased risk for arrhythmia, and retrospectively reviewed our database records, for patients treated with sotalol. The congenital heart diagnoses included for analysis are listed in Table 1. All patients had been seen at least once in our clinic between 2000 and 2017, and were ≥16 years old at the time of review. Although sotalol was commenced in some patients when they were <16 years old, to be included patients must have been taking sotalol beyond the age of 16 years. Sotalol was typically introduced at either 40 mg bd or 80 mg bd, then titrated to clinical effect, monitoring for bradycardia and QTc prolongation on serial ECGs. Sotalol was initiated in both inpatient and outpatient settings, at the discretion of the treating clinician. Clinical history was extracted, with investigations from the most recent review prior to starting sotalol included for analysis. Ventricles were defined as either systemic or sub-pulmonary, with mild dysfunction defined as an ejection fraction of 40–49%, moderate 30–39% and severe <30% [13].

Efficacy of sotalol in controlling the clinical arrhythmia was assessed as either complete, partial or failure [9]. Complete efficacy was defined as either no recurrence of the

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[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Table 1
Baseline clinical characteristics.

Characteristic	
Congenital heart diagnosis	
Fontan	26 (32%)
rTOF	16 (20%)
TGA atrial switch	13 (16%)
Cyanotic CHD	10 (12%)
Complex biventricular repair	8 (10%)
Ebstein's anomaly	5 (6%)
CCTGA	2 (2%)
Other[a]	2 (2%)
Weight (kg)	74 ± 18
BMI (kg/m^2)	25 ± 5
Average daily dose (mg, range)	122 ± 51 (40–320)
Cyanotic (n, %)	11 (13%)
Eisenmenger (n, %)	3 (4%)
Pacemaker (n, %)	10 (12%)
Defibrillator (n, %)	11 (13%)
Prior DCCV (n, %)	42 (51%)
Prior ablation (n, %)	9 (10%)
Prior stroke (n, %)	10 (12%)
Prior CCF admission (n, %)	12 (15%)
Prior syncope (n, %)	10 (12%)
Creatinine (μmol/L, range)	79 ± 20 (37–140)
Anticoagulation	
Warfarin (n, %)	31 (38%)
NOAC (n, %)	4 (5%)
QRS (ms)	125 ± 28
QTc (ms)	443 ± 35

rTOF = repaired Tetralogy of Fallot, TGA = transposition of the great arteries, CHD = congenital heart disease, CCTGA = congenitally corrected transposition of the great arteries, BMI = body mass index, DCCV = direct current cardioversion, CCF = congestive cardiac failure, SV = systemic ventricle, PV = subpulmonary ventricle, NOAC = non-vitamin K oral anticoagulant.

[a] Including 1 non-cyanotic patient with atrioventricular septal defect, RVOT obstruction and left supra AV valve stenosis, and 1 patient with left atrial isomerism and repaired coarctation.

arrhythmia, or brief and occasional (<5 min) episodes not causing significant symptoms or hemodynamic compromise. Partial efficacy was defined as improvement in symptoms and/or reduction in arrhythmia burden, but not abolition of the arrhythmia. Failure was defined as either minimal effect of sotalol therapy on the arrhythmia, or the development of a very early adverse effect (within the first 72 h of therapy), that prohibited further treatment. If an adverse effect leading to discontinuation of sotalol occurred at a later stage, efficacy was classified based on arrhythmia control up until the point of discontinuation.

Adverse effects were attributed to sotalol if deemed to be definitely or probably due to sotalol by the treating physician *and* the study reviewer. If there was disagreement, a third opinion from a congenital heart specialist was sought to reach consensus. The response to an adverse effect was classified as either discontinuation of sotalol, dose reduction, or continuation at an unchanged dose. "Significant bradycardia" was defined as symptomatic bradycardia either requiring dose reduction, cessation of sotalol or permanent pacing for continuation.

Continuous variables are presented as mean ± standard deviation, or median with interquartile range (IQR). Categorical variables are presented as frequencies with percentages. Survival free from "significant bradycardia" and from "side effect leading to discontinuation" were assessed by the Kaplan-Meier method. The complete efficacy group was compared to the partial efficacy and failure groups, analysing for predictors of complete control. Patients who developed a specific adverse event were compared to those who did not develop that adverse effect, as a comparator group. Univariate comparison of categorical variables was performed using either Chi-squared or Fischer's exact test, and of continuous variables with the *t*-test. Predictors of outcomes were assessed via binary logistic regression. A two-tailed p-value of <0.05 was considered statistically significant. Statistical analysis was performed using Statistical Package for Social Services V.22.0 (SPSS, Chicago, Illinois).

3. Results

The study population comprised 82 patients (52% male), aged 31.8 ± 13.1 years (range 10–67) at the time of sotalol commencement. Mean follow-up post commencement of sotalol was 8.0 years, of which the median time on drug therapy was 2.8 years (IQR 8.2). Table 1 shows baseline clinical characteristics of the study population. Prior to sotalol commencement, the systemic ventricle contracted well in 46 patients (56%), was mildly impaired in 29 (35%) and moderately impaired in 7 (9%). The subpulmonary ventricle contracted well in 35 (43%), was mildly impaired in 15 (18%), moderate-severely impaired in 3 (4%), and not assessable in 35% (in a univentricular heart for example). The indication for sotalol was atrial tachycardia/flutter (AT) in 52 patients (63%), atrial fibrillation (AF) in 13 (16%), ventricular tachycardia (VT) in 6 (7%), AT + VT in 5 (6%), AT + AF in 4 (5%) and supraventricular tachycardia in 2 patients. Medical therapy had previously failed in 29 patients (35%), including amiodarone, other beta blockers and digoxin in 11% each respectively, and calcium channel blockers and flecainide in 2 patients each. Seven patients were concurrently taking digoxin, whilst on sotalol.

3.1. Efficacy of sotalol

Fig. 1 summarises the clinical progress of patients once sotalol was commenced. Complete control of the clinical arrhythmia was achieved in 48% of patients (n = 39), for an average of 5.0 years on-drug treatment. In 21/39 patients with complete control, sotalol was nevertheless discontinued. The most common reasons for discontinuation in this group were side effects in 8 patients, trial off sotalol with no significant arrhythmia exacerbation in 6, and resolution after catheter ablation in 4. Partial control of the clinical arrhythmia was achieved in 46%, for an average of 6.1 years on-drug treatment. In this group, sotalol was eventually discontinued in 28/38 patients, most commonly due to a change in antiarrhythmic medication aiming for improved efficacy (14 patients). Twelve patients in the "partial control" group underwent adjunctive catheter ablation whilst on sotalol, and continued therapy post ablation. Surgical intervention for hemodynamic reasons was performed in 5/82 patients on sotalol (ASD closure, total cavopulmonary circulation conversion, tricuspid valve repair and 2 percutaneous pulmonary valve replacements). In 3 of these 5 patients, sotalol had achieved good arrhythmia control for >2 years prior to surgical intervention. In 7 patients, moderate-severe unrepaired valvular regurgitation was present and may have predisposed to arrhythmia (systemic AV valve, subpulmonary AV valve or pulmonary valve); despite this sotalol achieved complete arrhythmia control in 4/7 and partial control in 3/7.

Freedom from first episode of recurrent arrhythmia after starting sotalol is seen in Fig. 2a. Recurrent arrhythmia was typically the same as the initially documented arrhythmia, apart from 2 patients with AF who represented with AT. There were no significant predictors of complete efficacy, compared to partial efficacy. Specifically, outcomes were similar irrespective of the initial arrhythmia indication (AT, AF or VT) for sotalol.

Sotalol failed to deliver any clinical benefit in 5 patients (6%). Two of these patients suffered a severe side effect within 24 h and were unable to continue sotalol (bronchospasm and severe vomiting). Three patients did not achieve any clinical arrhythmia control. The first patient had repaired Tetralogy of Fallot (rTOF) and proceeded to early atrial tachycardia ablation, when sotalol was ineffective. The second patient had complex unrepaired CHD, and when low dose sotalol was ineffective for AF, amiodarone was substituted. In the third patient sotalol was ineffective for recurrent VT, in the setting of Rastelli repair and moderate systemic ventricular impairment, with mexilitene subsequently used. Overall 21 patients (25%) were eventually changed to amiodarone following sotalol, with 11/21 achieving good control with no significant side effects, and 10/21 developing severe treatment-limiting side effects on amiodarone.

3.2. Adverse effects due to sotalol

Overall, 30 patients (37%) experienced an adverse effect on sotalol, with 15 patients (18%) discontinuing sotalol as a result. Adverse effects on sotalol, with clinical responses to each adverse effect, are shown in Table 2. The Kaplan-Meier curve for freedom from "major side effect leading to discontinuation" is seen in Fig. 2b. Older age at sotalol

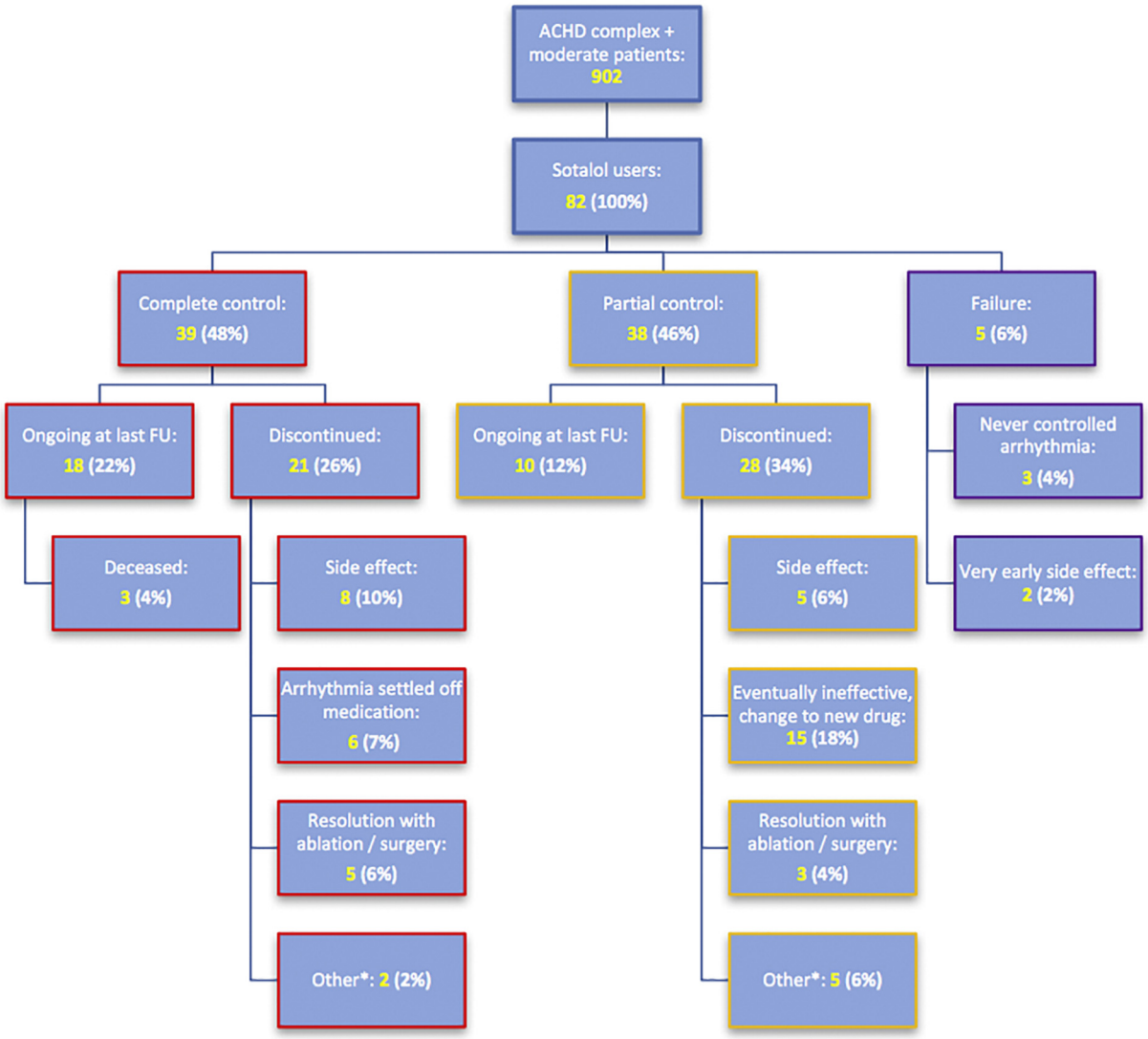


Fig. 1. Clinical progress on sotalol. *"Other" reasons for discontinuation include patient preference, pregnancy planning or worsening renal failure.

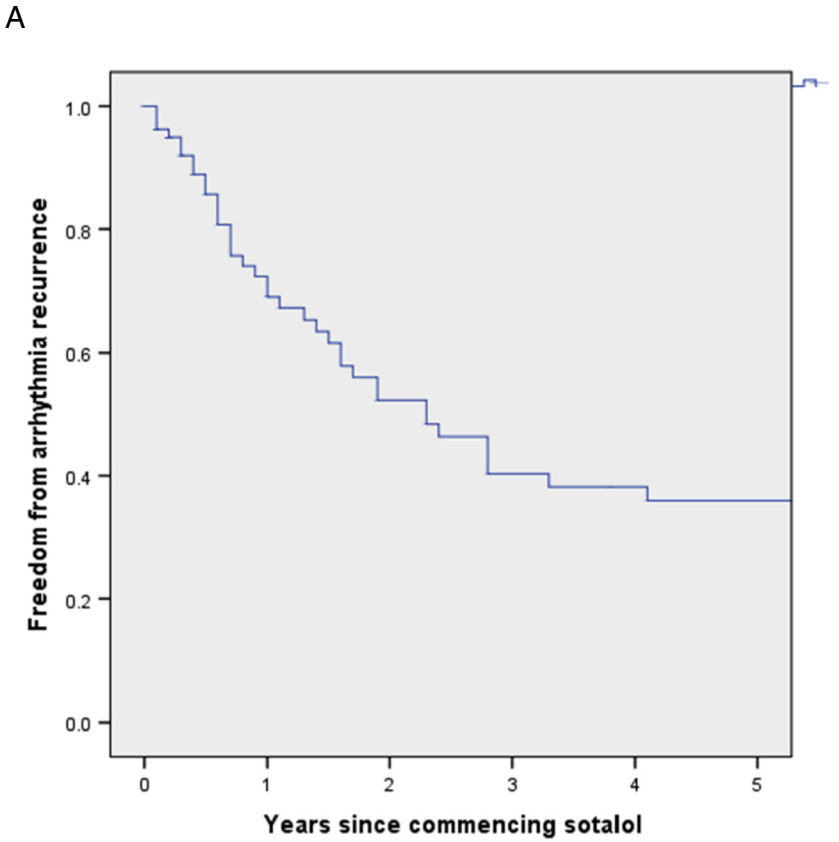
commencement was of borderline significance for developing a treatment-limiting side effect (mean age 38 versus 30 years old, OR 1.04, p = 0.049). The most common side effect was fatigue and/or lethargy in 16% (n = 13), which led to discontinuation of sotalol in 6/13 patients. Bronchospasm and/or dyspnoea, when they occurred, universally led to discontinuation of the drug. Two of the 6 cases of respiratory side effects occurred in patients with mild pre-existing asthma. One case of severe depression was diagnosed 4 years after starting sotalol, albeit with an insidious onset of symptoms over several years. There was a significant improvement in mood symptoms off sotalol.

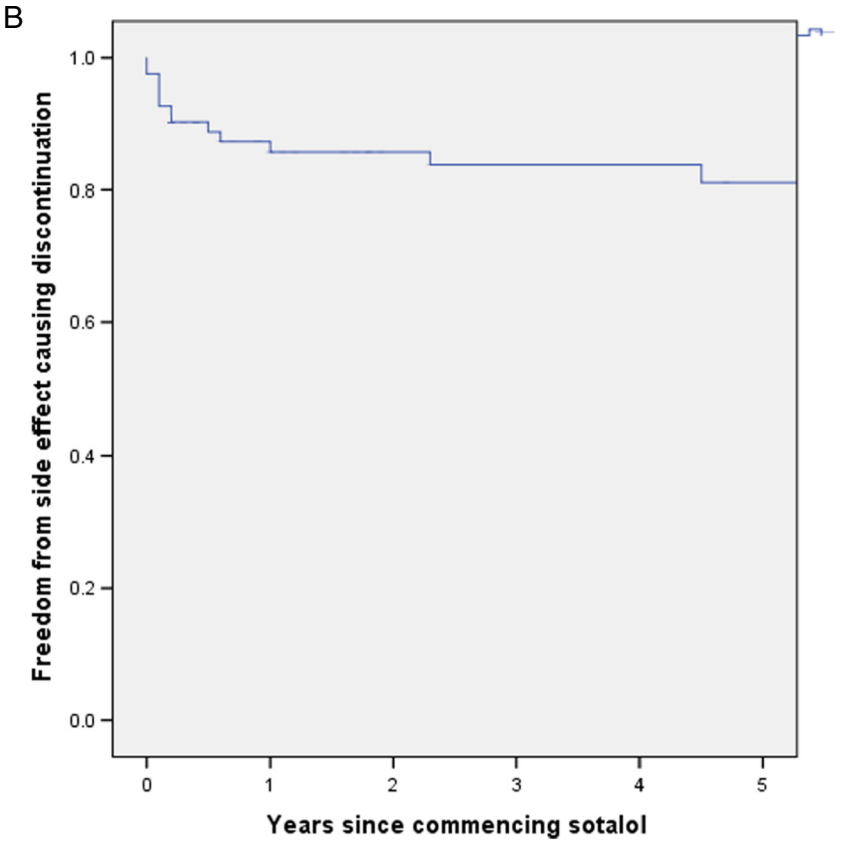
Significant symptomatic bradycardia occurred in 13% (11 patients), with pacemaker implantation required in 4 patients for continuation of sotalol. This was in the context of 12% of patients having a pre-existing pacemaker and 13% having a defibrillator before starting sotalol therapy. No significant increase in pacing percentage was observed for those with pre-existing devices. The underlying diagnoses in those who developed bradycardia were Fontan anatomy in 7 (atrio-pulmonary connection in six, lateral tunnel in one), and in single cases only transposition of the great arteries (TGA) with atrial switch, rTOF, cyanotic palliated TGA with septal defect, and Ebstein's anomaly). The average time to development of bradycardia was 3.1 years, with only 5 cases occurring in the first 3 months of sotalol therapy. The average dose of sotalol in those who developed significant bradycardia was 130 mg. Fontan patients were more likely to develop bradycardia on sotalol (OR 4.8, 95% CI 1.3–18.2, p = 0.022).

3.2.1. Ventricular arrhythmias, heart failure and deaths

No documented cases of torsades de pointes (TdP) or severe QTc prolongation from baseline were observed in our study. Mean increase in QTc on drug was 12 msec; QTc change from baseline did not correlate with efficacy or adverse effects. The only episode of an appropriate ICD shock occurred in the aforementioned Rastelli patient with moderate systemic ventricular impairment, in whom sotalol was prescribed for VT, but was ineffective. A repeat echocardiogram on sotalol was performed in 59 patients (72%). The systemic ventricle contracted well in 29 (49%), was mildly impaired in 20 (34%), moderately impaired in 8 (14%) and severely impaired in two patients. This corresponded to a decline in systemic ventricular function on sotalol in 10 patients (17%). All 10 patients had complex underlying defects, most commonly Mustard or Fontan operations. Subpulmonary ventricular function worsened in 3 patients, 2 with Ebstein's anomaly and one with rTOF. Eight patients (10%) were admitted with heart failure whilst on sotalol.

Three deaths occurred during the study period. The first patient had underlying lateral tunnel Fontan anatomy, and achieved complete arrhythmia control for AT on sotalol for 15 years. She died due to progressive heart failure and protein-losing enteropathy. The second patient with complex cyanotic CHD eventually died from cardiorenal failure,





Years post commencement	0	1	2	3	4	5
Number at risk	82	55	45	40	35	29

Years post commencement	0	1	2	3	4	5
Number at risk	82	55	45	40	35	29

Fig. 2. a: Freedom from arrhythmia recurrence on sotalol. b: Freedom from side effect leading to discontinuation of sotalol.

Table 2
Adverse effects on sotalol.

Adverse effect	Frequency	Percentage	Response to adverse effect
Fatigue/lethargy	13	16%	*Discontinue*: 6/13 *Dose reduce*: 3/13 *Continue at same dose*: 4/13
Significant bradycardia[a]	11	13%	*Discontinue*: 2/11 *Dose reduce*: 5/11 *Pacemaker + continue*: 4/11
Bronchospasm/dyspnoea	6	7%	*Discontinue*: 6/6
Nausea/vomiting	2	2%	*Discontinue*: 2/2
Erectile dysfunction	2	2%	*Discontinue*: 1/2 *Dose reduce*: 1/2
Headache/visual disturbance	1	1%	*Discontinue*: 1/1
Dizziness/hypotension	1	1%	*Continue at same dose*: 1/1
Loss of taste	1	1%	*Continue at same dose*: 1/1
Severe depression	1	1%	*Discontinue*: 1/1

Note 3 patients reported significant treatment limiting fatigue and dyspnoea simultaneously, and 1 patient reported both severe fatigue and depression; therefore total "side effects leading to discontinuation" in the above table adds to 19 in 15 patients.
[a] Defined as symptomatic bradycardia either requiring dose reduction, cessation of sotalol or permanent pacing for continuation.

after 10 years of complete AT and VT control on sotalol. The third patient, also with cyanotic CHD, died from cardiorenal failure, after 8 years of complete control on sotalol for AT. Only 1 of these patients had a recent ECG in the 3 months prior to death, with a QTc of 430 ms.

4. Discussion

To the best of our knowledge, this study represents the largest reported experience of sotalol use in adult congenital heart disease. We focused on patients with moderate to highly complex defects, prone to recurrent arrhythmias, and found sotalol was effective at improving arrhythmia burden and symptoms. Non-life-threatening side effects limited treatment in 18%. Reassuringly no sudden cardiac deaths or sustained ventricular arrhythmias due to sotalol were seen, over an average of 5.1 years on-drug treatment.

4.1. Efficacy

Sotalol was effective in improving arrhythmia control in 78% of patients in our study (excluding those who discontinued therapy due to a side effect), with an equal distribution between complete suppression of the clinical arrhythmia, and partial control with reduction in arrhythmia burden. Clinical efficacy was similar between the moderate and complex ACHD subgroups, and in those with moderate-severe systemic ventricular impairment. In acquired cardiac disease, sotalol is an effective antiarrhythmic for both atrial and ventricular arrhythmias, albeit not equal in magnitude to amiodarone's efficacy in maintaining sinus rhythm [14–16]. Studies describing efficacy in ACHD populations, however, are sparse. Miyazaki et al. [9], in a study of 44 paediatric and adult CHD patients found sotalol (at low doses) achieved complete arrhythmia control in 41%, and partial control in 34%. Similarly to our study, adjuvant interventions such as catheter ablation, or surgical intervention for hemodynamic reasons, were not uncommon. Sotalol was safe and effective in maintaining sinus rhythm after a first episode of SVT, in an ACHD population with simple to moderate complexity lesions [10]. Reports in paediatric CHD populations have focussed predominantly on children with accessory pathways, rather than those with structural heart disease [11,17]. Our approach in sotalol dosing was typically cautious, commencing at either 40 mg or 80 mg twice daily, with an average dose of 120 mg / daily across the cohort. At lower doses, the levo isomer of sotalol's racemic mixture with its beta blocking effect predominates, with an increasing contribution of the dextro isomer and class III effect as the dose is increased [18]. Pharmacodynamics vary from patient to patient however, and in some patients antiarrhythmic effect is seen at low dose.

4.2. Safety and adverse effects

In acquired cardiac disease, sotalol appears to be better tolerated than most other antiarrhythmics [19]. Nevertheless, discontinuation due to side effects has been reported (outside the ACHD field) in approximately 15% of patients [18,19], very similar to our observed discontinuation rate in ACHD patients of 18%. In the absence of randomisation, a certain proportion of these limiting side effects are likely to represent placebo effect. Fatigue, asthenia and dyspnoea are the most common specific limiting events in both acquired cardiac disease and our population [19].

Reassuringly, we observed no cases of definite sudden death, TdP or other ventricular arrhythmias attributable to sotalol, despite a relatively long period of drug use and follow up (over 400 patient-years). This was despite the significant complexity of underlying structural heart disease in our cohort, including 17% with moderate to severe systemic ventricular impairment whilst on sotalol. Furthermore, certain CHD lesions are predisposed to bradycardia, and sotalol's reverse use dependence properties may predispose to TdP at slower heart rates [20]. TdP in CHD populations due to sotalol has been limited to case reports only in the literature [9,17]. In a large meta-analysis of trials in acquired heart disease, the incidence of TdP due to sotalol ranged from 1 to 4% [21]. Risk appeared to increase with doses over 320 mg/daily, renal impairment, a history of heart failure or coronary disease, prior sustained VT or female gender. Our conservative dosing, along with relatively preserved renal function in all patients selected for sotalol, may in part explain the absence of any TdP cases. None of the cases of worsening heart failure or ventricular contractility in our series corresponded temporally to sotalol commencement or dose increase. Progression of complex underlying CHD likely played a greater role than negative inotropy of the drug. In the context of acute heart failure admissions, sotalol was often withheld temporarily. In patients with gradual decline of ventricular function, sotalol was continued as long as it remained effective, closely monitoring QTc and renal function.

Significant bradycardia due to sotalol approaches 13% in acquired heart disease [18,19], with 11% of Miyazaki et al.'s [9] CHD cohort requiring pacing after sotalol commencement. The relative contribution of sotalol to bradycardia in complex CHD is difficult to discern from the natural progression of congenital lesions predisposed to conductive disease, such as TGA with atrial switch surgery [1]. The relatively long time until development of bradycardia after sotalol commencement in our study may suggest substrate progression, rather than the drug, was the major culprit. Interestingly, Fontan patients were at higher risk of bradycardia on sotalol. Fontan patients are known to be at high risk of sinus node dysfunction, probably due to either direct trauma to the sinoatrial nodal region, or its blood supply, at the time of operation [22]. Progressive atrial dilatation and fibrosis may further impair sinus node function late after the Fontan operation [1].

Although we note the limited evidence base and potential proarrhythmic tendency of sotalol in CHD, alternative antiarrhythmic medications face their own inherent limitations in this population. Amiodarone is often necessary when other drugs are contraindicated or ineffective, particularly in the setting of significant ventricular impairment. Toxicity of long-term use in younger ACHD patients, however, is substantial, with a significantly increased risk of thyroid dysfunction compared to patients with acquired cardiac disease [6,23]. Mexilitene may have modest efficacy in CHD, but with limited evidence for safety [24]. Catheter ablation is an attractive alternative where possible, to avoid antiarrhythmic drugs, but can be technically challenging in this population [1,2].

4.3. Limitations

This study describes relatively low dose sotalol use in ACHD patients with preserved renal function; results should not be extrapolated to high dose sotalol use, or use in patients with significant renal impairment. Furthermore simple ACHD lesions were excluded and thus are not reflected in our results. Although QTc could be reliably assessed prior to commencing sotalol, due to the retrospective nature of the study, there was no protocol for QTc monitoring on therapy (to analyse for a dose-response relationship). In general, the treating clinicians would monitor the QTc closely once sotalol was commenced. As with any non-randomised drug study, side effects may be overestimated due to the placebo effect. Results however, reflect real world experience in an ACHD population. It is possible sotalol was contributory to ventricular dysfunction in some patients, although there was no temporal correlation observed in any cases. Finally, antiarrhythmic efficacy was assessed in a broad categorical sense by the study reviewers, and not via a clinical arrhythmia scoring system or by arrhythmia recurrence, due to the limitations of retrospective analysis.

5. Conclusions

Sotalol, when used in relatively low doses, appears to be safe and effective in moderate to highly complex ACHD patients. Discontinuation due to side effects typically reflected non-life threatening events such as fatigue or dyspnoea. Significant bradycardia on sotalol was associated with Fontan anatomy.

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Conflicts of interest

The authors report no relationships that could be construed as a conflict of interest.

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