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ORIGINAL ARTICLE

WILEY Congenital Heart Disease

Adverse effects of amiodarone therapy in adults with congenital heart disease

Benjamin M. Moore MBBS[1,2] | Rachael L. Cordina PhD[1,2] | Mark A. McGuire PhD[1,2] | David S. Celermajer DSc[1,2]

[1]Department of Cardiology, Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia

[2]Sydney Medical School, University of Sydney, Camperdown, New South Wales, Australia

Correspondence
David Celermajer, Department of Cardiology, Royal Prince Alfred Hospital, Missenden Rd, Camperdown, NSW 2050, Australia.
Email: David.Celermajer@health.nsw.gov.au

Abstract

Objective: Amiodarone is a highly effective antiarrhythmic therapy, however its toxicity profile often limits treatment. This is particularly relevant in adults with congenital heart disease (CHD), who are often young and in whom other antiarrhythmic agents commonly fail or are contraindicated. We sought to determine incidence and predictors of adverse effects caused by amiodarone in adult CHD (ACHD).

Design: A retrospective review of patients with moderate to complex ACHD treated with amiodarone at our center between 2000 and 2017 was performed. Incidence and predictors of adverse effects were described. Efficacy of amiodarone therapy in controlling the clinical arrhythmia was assessed as complete, partial, or failed.

Results: Amiodarone was prescribed in 57 patients of 902 ACHD patients reviewed (6%), for a mean duration of 2.7 ± 4.3 years. Significant adverse effects occurred in 56%, most commonly thyroid dysfunction, with amiodarone-induced thyrotoxicosis (AIT) in 30% and amiodarone-induced hypothyroidism in 14%. AIT frequently led to arrhythmia exacerbation and occurred most in those with Fontan anatomy. Severe dermatological effects were seen in 7% and bradycardia requiring pacing in 5%. Interstitial lung disease, peripheral neuropathy and alopecia were observed in single cases. Amiodarone toxicity led to discontinuation of the drug in 42%. Amiodarone was highly effective when tolerated, however, achieving complete arrhythmia control in 63%, partial control in 35%, with failure to control in only one patient.

Conclusions: Amiodarone therapy is effective in moderate to complex ACHD patients, but is frequently limited by adverse effects. ACHD patients seem especially vulnerable to thyroid dysfunction, with Fontan patients in particular at increased risk of AIT.

KEYWORDS
adverse effects, amiodarone, arrhythmia, efficacy

1 | INTRODUCTION

Amiodarone is a highly efficacious antiarrhythmic medication for both atrial and ventricular arrhythmias.[1,2] Its toxicity profile however, remains the major limitation to long-term therapy in acquired cardiac disease.[3,4] Adverse effects of chronic amiodarone use in younger patients with congenital heart disease (CHD) are less well described[5]; concerningly there appears to be a substantially increased risk of thyroid dysfunction within this group.[6–8] Adult CHD (ACHD) patients with complex disease are particularly susceptible to arrhythmias and can prove difficult to manage.[9] Arrhythmias are often refractory to other medical therapies, ventricular dysfunction often limits therapeutic choices and

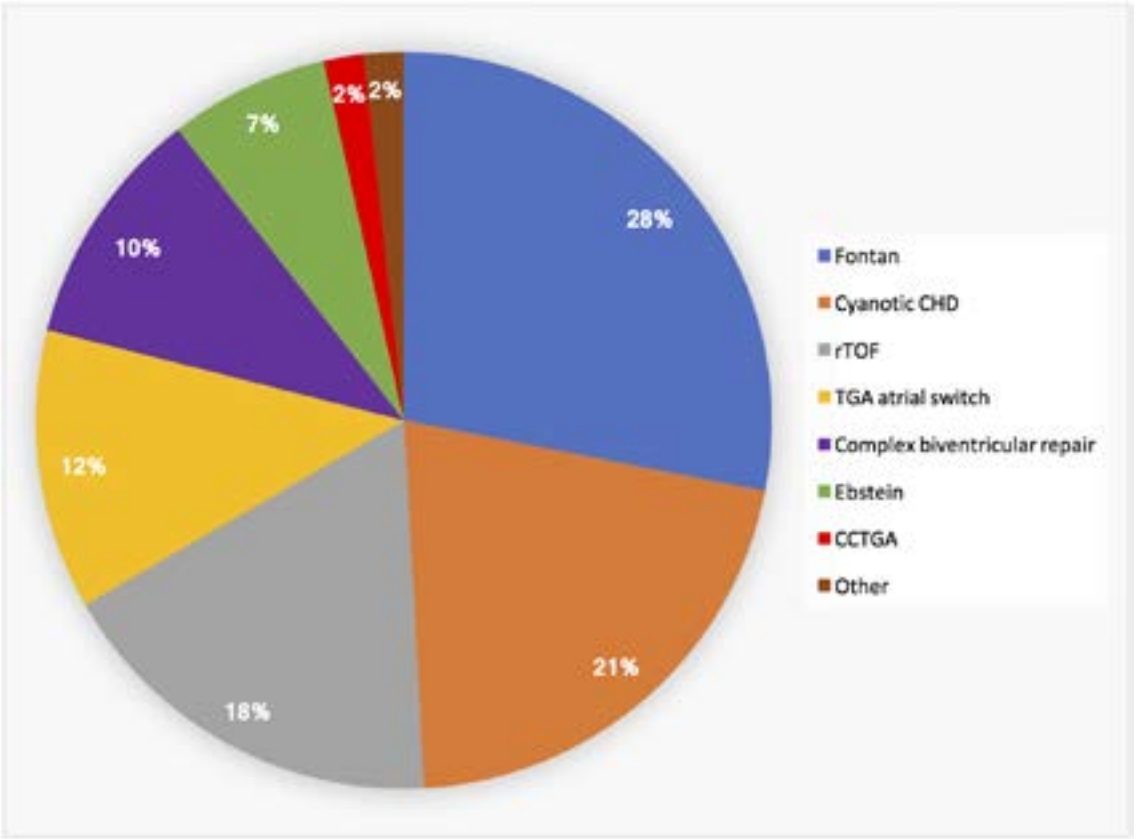


FIGURE 1 Underlying CHD diagnoses in the study population. Abbreviations: CHD, congenital heart disease; rTOF = repaired tetralogy of Fallot; TGA, transposition of the great arteries; CCTGA, congenitally corrected transposition of the great arteries [Colour figure can be viewed at wileyonlinelibrary.com]

catheter ablation is technically more challenging, compared to structurally normal hearts.[9,10] The substantial morbidity, recurrent hospital admissions and increased mortality associated with these arrhythmias frequently necessitates amiodarone when other interventions fail or are contraindicated.[9] Our primary aim was to describe the incidence and predictors of adverse effects due to amiodarone in a cohort of moderate to complex ACHD patients from a quaternary level ACHD referral center. Our secondary aim was to describe the relative efficacy of amiodarone in arrhythmia control.

2 | METHODS

We prospectively defined a group of "high risk" ACHD lesions, with respect to arrhythmia, and retrospectively reviewed our database records, for patients treated with amiodarone. The moderate to complex CHD diagnoses included for analysis are shown in Figure 1. Patients given loading doses only of amiodarone (<1 week) who were then changed to alternative antiarrhythmic treatments were not included. All patients were ≥16 years old and had been seen at least once in our clinic between 2000 and 2017. Using these criteria, 902 complex and moderate ACHD patients were identified, of which 57 had been prescribed amiodarone. Amiodarone loading was typically either 1.2 g intravenously over 24 hours, or if orally loaded 600 mg daily for 1 week, followed by 400 mg daily for 1 week, then 200 mg daily thereafter, depending on the clinical situation. Clinical history was extracted, with investigations from the most recent review prior to starting amiodarone included for analysis. Ventricles were defined as either systemic or subpulmonary, with mild dysfunction defined as an ejection fraction of 40%-49%, moderate 30%-39%, and severe <30%.

The primary outcome was the development of any adverse effect; this was included if deemed to be definitely or probably due to amiodarone by the treating physician *and* the study reviewer. The response to an adverse effect was classified as either discontinuation of amiodarone, dose reduction, or continuation at an unchanged dose. Amiodarone-induced thyrotoxicosis (AIT) was defined as a depressed thyroid-stimulating hormone (TSH) in combination with an elevated free thyroxine (fT4). Hypothyroidism was defined as an elevated TSH with a depressed fT4. Thyroid function derangements *in the first 3 months* of therapy without associated clinical hyper- or hypothyroidism were not included as an adverse event, due to the recognized changes in peripheral metabolism of thyroxine induced by amiodarone during the first few months of therapy.[11] "Significant bradycardia" was defined as symptomatic bradycardia likely due to amiodarone either requiring dose reduction, cessation of amiodarone, or permanent pacing for continuation.

The secondary outcome of efficacy was classified as either complete, partial, or failure.[12] Complete efficacy was defined as either no recurrence of arrhythmia, or brief and occasional (<5 minute) 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 arrhythmia. Failure was defined as minimal effect of amiodarone therapy on the arrhythmia.

Continuous variables are presented as mean ± standard deviation. Categorical variables are presented as frequencies with percentages. Survival free from AIT and from "adverse effect causing discontinuation" were assessed by the Kaplan-Meier method. Patients who developed a specific adverse effect were compared to the other patients prescribed amiodarone in the cohort who did not develop that adverse effect, as a comparator group. Univariate comparison of categorical variables was performed with either Chi-square or Fischer's exact test, and of continuous variables with the two-tailed *t* test. Predictors of events were assessed via binary logistic regression. A two-tailed *p* value of <.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 57 patients (63% male), with a mean age of 36.3 ± 12.6 years (range 16-65) at the time of amiodarone commencement. Mean follow-up postcommencement of amiodarone was 5.8 years, of which the average time on amiodarone was 2.7 ± 4.3 years. Figure 1 shows the types of congenital heart disease in our cohort, with Table 1 displaying baseline clinical characteristics of the patients. The indication for amiodarone was atrial tachycardia or flutter (AT) in 34 (60%), atrial fibrillation (AF) in 8 (14%), AF + AT in 4 (7%), supraventricular tachycardia (SVT) in 2 (4%), ventricular tachycardia (VT) in 8 (14%), and AT + VT in 1 patient. Thirty-eight patients (67%) had previously failed other medical therapy, including sotalol in 24 (42%), digoxin in 8 (14%), other beta-blockers in 5 (9%), flecainide in 4 (7%), and calcium channel blockers in 2 patients. Six patients were concurrently taking digoxin and five were also taking beta-blockers.

TABLE 1 Baseline clinical characteristics of the study population

Characteristic	
Average dose amiodarone (mg)	204 ± 63
Average duration of treatment (years)	2.8 ± 4.4
Weight (kg)	72.8 ± 22.6
BMI (kg/m^2)	25.6 ± 6.1
Cyanotic	13 (23%)
Eisenmenger	4 (7%)
Pacemaker	8 (14%)
ICD	7 (12%)
Previous ablation	
AT/flutter/AF	15 (26%)
VT	1 (2%)
Surgical	1 (2%)
Prior DCCV	35 (61%)
Prior stroke	8 (14%)
NYHA	
I	18 (32%)
II	37 (65%)
III	2 (4%)
Prior syncope	9 (16%)
Prior CCF admission	18 (32%)
Anticoagulation	
Warfarin	25 (44%)
NOAC	4 (7%)
QRS (ms)	129 ± 34
QTc (ms)	455 ± 39
At least moderate SV impairment	8 (14%)
At least moderate PV impairment	4 (7%)

Abbreviations: BMI, body mass index; ICD, implantable cardiac defibrillator; AT, atrial tachycardia; AF, atrial fibrillation; VT, ventricular tachycardia; DCCV, direct current cardioversion; NYHA, New York Heart Association; CCF, congestive cardiac failure; NOAC, nonvitamin K antagonist oral anticoagulant; SV, systemic ventricle; PV, subpulmonary ventricle.

3.1 | Clinical progress on amiodarone

Figure 2 shows the clinical progress of patients once amiodarone was commenced. Amiodarone achieved complete control of the underlying arrhythmia in 63%, with partial control in 35%. One patient with severe tricuspid regurgitation and right ventricular impairment due to unrepaired Ebstein's anomaly failed to obtain any benefit on 2 months of amiodarone therapy for AF. Sinus rhythm was achieved in this patient after valve repair plus Star procedure. Amiodarone therapy was discontinued in 39 patients (68%) during the course of the study. The reason for discontinuation was most commonly an adverse effect (42%, n = 24), followed by resolution of the arrhythmia postablation (9%, n = 5), resolution postsurgery (5%, n = 3), or physician concern re long-term side effects (4%, n = 2). In single cases only amiodarone was discontinued for the following reasons: loss of efficacy and change in rhythm control medication, change to rate control strategy, pregnancy planning, and subclinical thyroid dysfunction.

Amiodarone was not discontinued by the treating physician in 18 patients (32%); 11 continued on amiodarone at last clinic review, and 7 patients died while taking amiodarone. Four of these deaths were due to progressive heart failure in patients with advanced cyanotic heart disease, and one was due to infective endocarditis. Two deaths were due to sudden cardiac death (SCD) with no documented rhythm at time of death in either case. The first SCD patient had complex unrepaired CHD and had been on

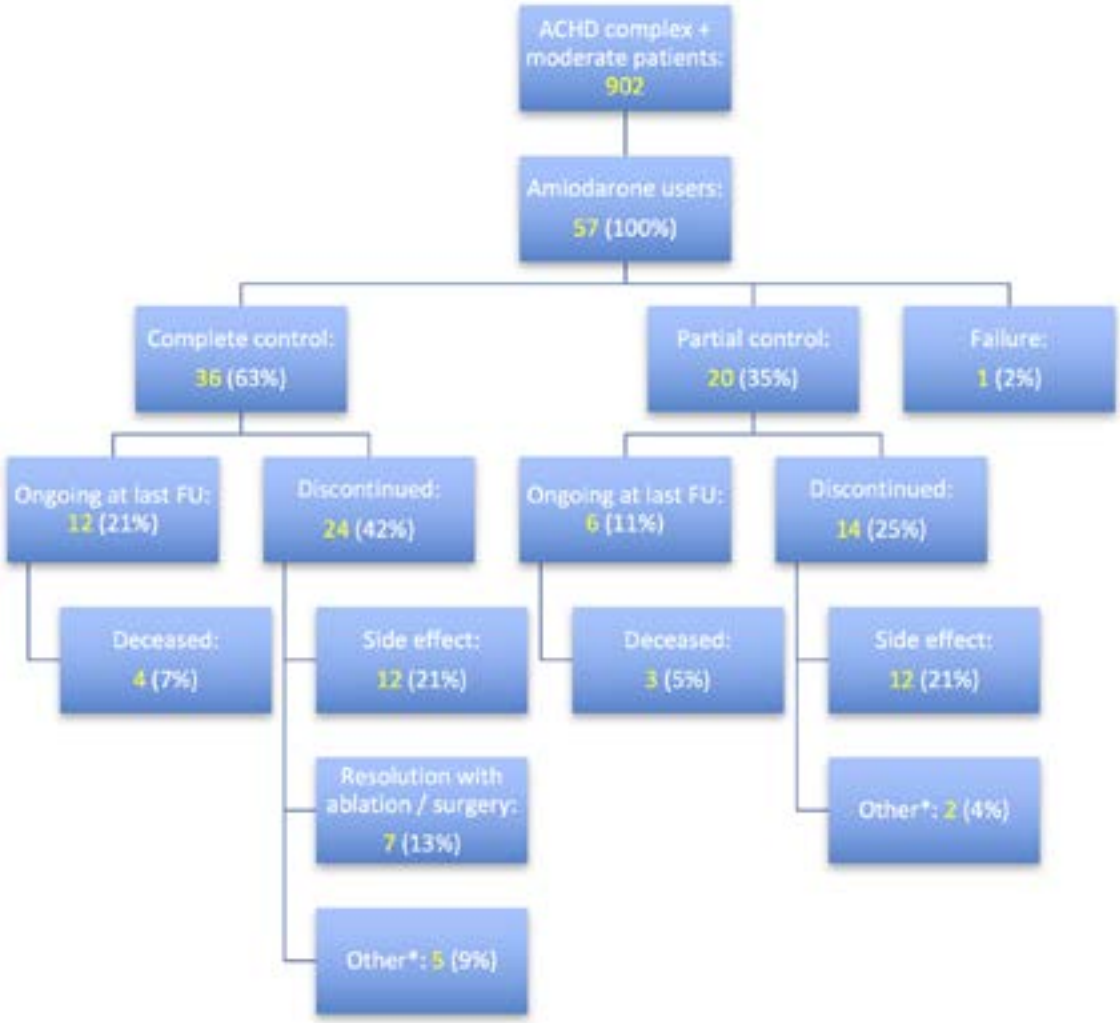


FIGURE 2 Clinical progress on amiodarone. Complete control defined as either no recurrence of arrhythmia, or brief and very occasional episodes (<5 minutes) not causing significant symptoms or hemodynamic compromise. Partial control defined as improvement in symptoms and/or arrhythmia burden, but not abolition of arrhythmia. Failure defined as minimal effect of drug on the arrhythmia. *Other reasons for discontinuation included change in rhythm or rate control medication, pregnancy planning, patient preference, clinician concern re long-term side effects and subclinical thyroid derangement [Colour figure can be viewed at wileyonlinelibrary.com]

amiodarone for 2.7 years for AF. The second SCD patient had Eisenmeneger's syndrome and passed away in their sleep after 2.4 months of amiodarone therapy for atrial tachycardia. Both patients had a mildly prolonged QTc in the setting of a wide QRS (QTC 479 ms with QRS 125 ms, QTc 459 ms with QRS 140 ms). In the course of amiodarone therapy 10 patients had a catheter ablation (9 AT/flutter, 1 AF).

3.2 | Adverse effects

Table 2 displays the incidence of adverse effects due to amiodarone. Figures 3A and 3B show freedom from major adverse effects leading to discontinuation of amiodarone. At 3 and 6 months of therapy, 10% and 20% of patients, respectively, had developed a side effect. A major side effect leading to discontinuation of amiodarone had occurred in 20% of patients by 20 months of therapy. Thyroid dysfunction was common, occurring in 42%. AIT was the single most common adverse effect, occurring in 17 patients (30%), at a mean duration of 2.6 ± 3.1 (0.1-13.4) years therapy, resulting in discontinuation in all cases. AIT was associated with Fontan anatomy (OR 3.4, 95% CI 1.1-11.8, $P = .04$). The Kaplan-Meier curve for freedom from AIT is shown in Figure 3C. Antithyroid medications were prescribed in 71%. Six patients required steroid therapy; three of these with prolonged steroid courses developed significant steroid-induced side effects. These included Cushingoid appearance, proximal myopathy, adrenal suppression, and reactivation of retinal toxoplasmosis. Acute exacerbations of underlying arrhythmia occurred in seven of the AIT patients (41%), and catheter ablation was common in the years following diagnosis. AIH occurred in eight patients (14%) at a mean duration of therapy of 2.4 ± 2.4 (0.4-7.8) years. This led to discontinuation of amiodarone in one patient, dose reduction in three and continuation at the same dose in four (with thyroid replacement therapy in 6/8 patients). No patients had arrhythmia exacerbations. There were no significant predictors of AIH.

TABLE 2 Side effects on amiodarone

Side effect	Frequency	Percentage	Amiodarone discontinued?
Any side effect	32	56	
SE causing discontinuation	24	42	
Thyroid dysfunction[a]	24	42	
AIT	17	30	17/17
AIH	8	14	1/8
Skin[b]	4	7	4/4
Significant photosensitivity	3	5	
Blue-gray discoloration	1	2	
Rash	1	2	
Significant bradycardia[a]	3	5	0/3
ILD	1	2	1/1
Peripheral neuropathy	1	2	1/1
Keratopathy with visual symptoms	1	2	0/1
Alopecia	1	2	0/1
Severe nausea	1	2	0/1

Abbreviations: SE, side effect; AIT, amiodarone-induced thyrotoxicosis; AIH, amiodarone-induced hypothyroidism; ILD, interstitial lung disease.
[a]One patient had both AIT and AIH.
[b]One patient had both significant photosensitivity and blue-gray discoloration.
[c]Defined as symptomatic bradycardia likely due to amiodarone either requiring dose reduction, cessation of amiodarone, or permanent pacing.

A single case of amiodarone-related interstitial lung disease (ILD) was diagnosed in a patient with congenitally corrected transposition on an average dose of 200 mg/daily for 2.1 years. This manifested as a severe restrictive lung function defect with patchy ground-glass changes on a CT scan. The patient was commenced on high dose steroids, with a mild improvement in symptoms at 2-month postcommencement. A Fontan patient on amiodarone for 3.2 years (mean dose 100 mg/daily) developed a peripheral neuropathy with features in keeping with amiodarone toxicity. At 4-month postdiscontinuation of therapy, the symptoms have not resolved. Four patients needed to discontinue amiodarone due to severe dermatological side effects; one rash early after commencement, two with severe photosensitivity and one with both blue-gray discoloration and marked photosensitivity. Three patients required permanent pacemakers for symptomatic bradycardia on amiodarone; prior surgical interventions were Mustard, Rastelli and Tetralogy repair (noting that eight of our ACHD patients had already had pacemakers inserted prior to commencement of amiodarone therapy). In all cases, amiodarone was continued once pacing was established. The only predictor on multivariate analysis of "major side effect leading to discontinuation" was complex underlying CHD (as compared to moderate), with an odds ratio of 6.3 (95% CI 1.3-31.5, P = .03).

4 | DISCUSSION

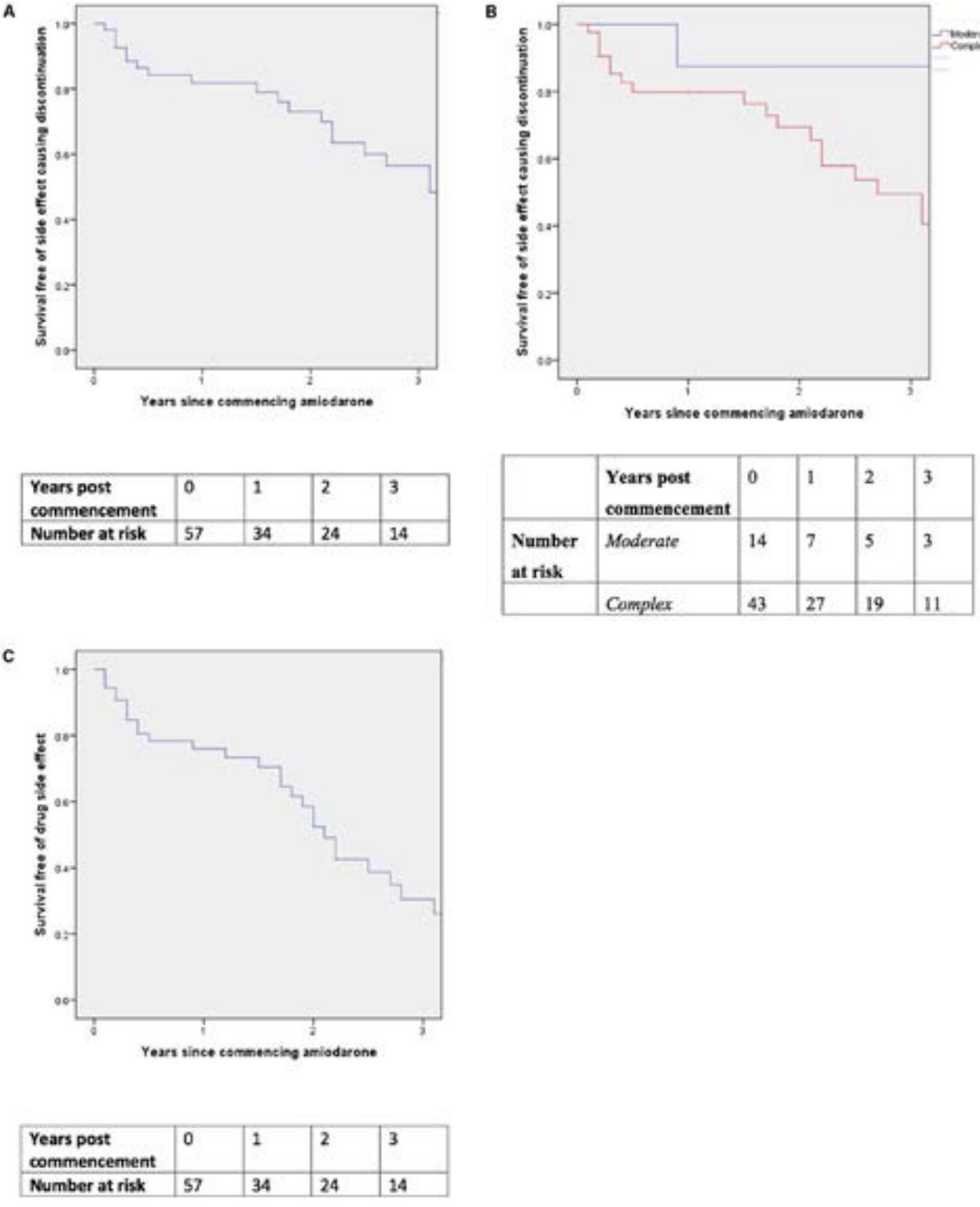
4.1 | Incidence of adverse effects

In our cohort of moderate to complex ACHD patients, adverse effects of amiodarone were strikingly prevalent, affecting 56% of patients, after an average duration of therapy less than 3 years. Furthermore, adverse effects were the single most common reason for drug discontinuation.

Amiodarone's pharmacodynamic and pharmacokinetic profile render it uniquely toxic to multiple organ systems. The drug is iodine rich and lipophilic with a large volume of distribution; half-life is prolonged at approximately 100 days.[11] In older patients with acquired cardiac disease, the incidence of adverse effects may approach 15% in the first year, and be as high as 50% longer term.[11] Discontinuation rates due to severe side effects however, at equivalent low doses, appear to be approximately 20%[3,13]; well below the value seen in our cohort. Toxicity of amiodarone in ACHD is less well described, with patients with complex defects appearing particularly vulnerable in our study. Significant side effects below the age of 10 years in CHD appear to be negligible, and in teenagers appear to be uncommon and mild.[14] This has been attributed to the rapid metabolism of amiodarone in children compared to adults.[5] Our study describes the spectrum of toxicities and tolerability of amiodarone in ACHD. Notably, short-term use of amiodarone may be feasible with a lower incidence of side effects; 80% of our patients were free of any side effect at 6 months of therapy and 80% were free of a major treatment limiting side effect up to 20 months of therapy.

4.2 | Thyroid dysfunction

The suggestion of particular susceptibility of ACHD patients to amiodarone-induced thyroid dysfunction was strongly reinforced by our study. Our incidence of 42% exceeded that reported by Thorne et al.[7] and Takeuchi et al.'s[6] 36% and 30%, respectively, in other ACHD centers. Although these cohorts predominantly included complex ACHD, they did not exclude patients with simple lesions, who may have a reduced risk of thyroid dysfunction. Nevertheless, these observed thyroid toxicity rates well exceed those in acquired cardiac disease of 3%-4% with long-term low dose use.[3] Iodine deficiency of the study population is unlikely to have played a role, due to the widespread use of iodinated salt in foods within Australia. AIT was more than twice as common as AIH, and was associated with Fontan anatomy.



Years post commencement	0	1	2	3
Number at risk	57	34	24	14

	Years post commencement	0	1	2	3
Number at risk	*Moderate*	14	7	5	3
	Complex	43	27	19	11

Years post commencement	0	1	2	3
Number at risk	57	34	24	14

FIGURE 3 (A) Survival free of any major side effect leading to discontinuation of amiodarone. (B) Survival free of major side effect by complexity of underlying ACHD. (C) Survival free of amiodarone-induced thyrotoxicosis (AIT) [Colour figure can be viewed at wileyonlinelibrary.com]

Fontan patients have previously been identified as "high risk" for AIT by Thorne et al.[7] They hypothesized that elevated systemic venous pressures in Fontan patients may alter hepatic metabolism and increase the iodine load on the thyroid gland. Two-thirds of our Fontans with AIT had had atriopulmonary connections, who may indeed be predisposed to systemic venous hypertension compared to extracardiac conduits.[15] We did not find cyanosis was a risk factor for AIT, in contrast to several prior studies.[7,8]

Concerningly AIT has previously been associated with increased "major adverse cardiovascular events" (cardiovascular mortality, myocardial infarct, stroke, heart failure, or ventricular arrhythmias requiring hospitalization), largely driven by arrhythmia hospitalizations.[16] We found arrhythmia exacerbations commonly occurred acutely and longer term post-AIT. Interestingly, we observed an indirect morbidity of AIT, in that 50% of patients (3/6) who required steroids developed significant steroid-induced complications. AIH occurred in 14% of our cohort, in keeping with other ACHD amiodarone thyroid studies.[6,7] Their prognosis appeared more benign than AIT, with the majority continuing amiodarone and maintaining good arrhythmia control.

4.3 | Other (nonthyroid-related) adverse effects

A spectrum of other side effects were observed in our study, although unlike thyroid dysfunction, incidences generally did not exceed those seen in acquired cardiac disease.[3] Dermatological effects, predominantly photosensitivity, occurred in 7% and were severe enough to lead to discontinuation in all cases. When prospectively assessed, photosensitivity on amiodarone ranges from 25%-75%[4]; our retrospective assessment is biased to detect more severe cases. Severe dermatological effects occurred in 2% of patients with acquired cardiac disease in a meta-analysis,[3] and only very occasionally in children with CHD.[14] The risk of ILD is thought to be proportional to cumulative dose of amiodarone[4]; our single case occurred after 2.3 years of therapy. Assessing bradyarrhythmias due to amiodarone in CHD is complicated by the predisposition of select lesions (such as transposition with atrial switch repair) to sinus node dysfunction, related to atrial dilatation and fibrosis.[9] Our incidence marginally exceeded that seen in acquired cardiac disease at 3%-5%,[3] but may have reflected substrate progression, rather than drug side effect, in some cases. Amiodarone-related bradyarrhythmia is thought to be relatively benign, rarely causing SCD or collapse, and this was the case in our observed patients. Interestingly alopecia due to amiodarone has been reported occasionally in acquired cardiac disease, but not before in CHD.[17] Typically, this occurs early in therapy and is reversible on discontinuation, as was the case in our patient. Finally, torsades de pointes has only been rarely described in young CHD due to amiodarone,[5] and was not seen at all in a meta-analysis of long-term amiodarone users in acquired cardiac disease.[3] Although we observed no documented cases, we cannot be certain about the exact cause of death in our two SCD cases. Both patients were already at increased risk of SCD, irrespective of amiodarone, due to their severe underlying CHD.

4.4 | Drug efficacy

Despite the high incidence of significant adverse events, amiodarone was very effective in supressing the clinical arrhythmia in our cohort. Its use was often necessitated by the failure of other medical therapy. Sotalol (in limited ACHD series) appears to be safe, but lacks the efficacy of amiodarone and is inherently more arrhythmogenic.[12] Mexilitene may be modestly efficacious in CHD.[18] Dronedarone has been associated with increased mortality in severe heart failure patients with acquired cardiac disease[19]; this raises concerns for use in complex ACHD patients. Catheter ablation is an attractive alternative where possible, to avoid antiarrhythmic therapy. These procedures, however, are technically challenging and require expertise in this area, with repeat ablations not uncommonly required.[9,10] Finally, when considering Fontan patients at elevated risk of AIT, surgical options should be canvassed. This may include conversion surgery in older AP Fontans, bearing in mind a moderate perioperative mortality risk.[20] When amiodarone therapy is absolutely required, it is essential to monitor thyroid and liver function, with chest imaging as clinically indicated.[4] We would advocate 3 monthly thyroid function testing in complex ACHD, particularly for Fontan patients. Furthermore, a nonsignificant trend toward an increased risk of AIT with higher amiodarone doses has been observed in other CHD studies.[6,8] It seems prudent to use the lowest effective dose possible in complex ACHD patients.

4.4.1 | Limitations

This study is retrospective, with a small sample size, and as such can generate hypotheses but not prove causation. Simple ACHD was excluded deliberately, firstly so we could focus on the most arrhythmogenic lesions and secondly as we could not accurately establish the denominator for "simple ACHD patients on amiodarone." Thus, our results should not be extrapolated to simple ACHD patients. We may have underdetected early adverse reactions due to loading amiodarone regimes, given their exclusion from this study. However, on close review of our cohort, no such early side effects were noted. Finally, given the study was retrospective, there was not an established protocol for liver and thyroid function surveillance; it is possible that derangements in either of these parameters may have been underestimated.

5 | CONCLUSIONS

Amiodarone is highly effective for arrhythmia control in moderate to complex ACHD, but is associated with a substantial burden of adverse effects, commonly limiting treatment. ACHD patients, in particular those with Fontan anatomy, are at increased risk of amiodarone-induced thyrotoxicosis. Surveillance of thyroid function is essential when an alternative to amiodarone is not available.

CONFLICTS OF INTEREST

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

AUTHOR CONTRIBUTIONS

BM was responsible for study design, data acquisition, statistical analysis, and drafting of the manuscript. RC was responsible for study design, auditing of data, and critical appraisal of the manuscript. MM was responsible for study design and critical appraisal of the manuscript. DC was responsible for study design, project supervision, auditing of data, and critical appraisal of the manuscript.

ORCID

Benjamin M. Moore http://orcid.org/0000-0003-3645-0890

David S. Celermajer http://orcid.org/0000-0001-7640-0439

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