Amiodarone-induced thyrotoxicosis in heart failure with a reduced ejection fraction: A retrospective cohort study

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Abstract

**Background:** Amiodarone-induced thyrotoxicosis (AIT) is associated with significant morbidity and mortality. We aimed to describe AIT and its clinical outcomes in patients with heart failure with reduced ejection fraction (HFrEF).

**Methods:** We performed a retrospective chart review at a heart failure center in Winnipeg, Canada. We screened 1059 consecutive patients seen over a 12-month period (August 2011 to July 2012) for AIT in patients with HFrEF. Using descriptive and Cox proportional hazard analyses, we explored the association between AIT and mortality.

**Results:** A total of 110 patients with HFrEF who were exposed to amiodarone were included in the analysis. Of these, 13 (11.8%) were diagnosed with AIT. All AIT patients in our cohort were male. Amiodarone was discontinued in nearly half (46.2%) of patients with AIT. All patients were treated with antithyroid medications, and 5 patients (38.5%) also received prednisone. Euthyroidism was achieved in 2 patients (15.4%), hypothyroidism occurred in 6 patients (46.2%), and 5 patients remained thyrotoxic until death or time of chart review (38.5%).

**Conclusion:** Thyrotoxicosis is common in patients with HFrEF on amiodarone and is challenging to treat. Due to the sample size, while no association was found in mortality for patients with HFrEF with AIT, a real association could have been missed.

**KEYWORDS**
amiodarone-induced thyrotoxicosis, amiodarone side effects, heart failure, heart failure-reduced ejection fraction, systolic heart failure, thyroid, thyrotoxicosis

1 | INTRODUCTION

Arrhythmias are a common cause of morbidity and mortality in heart failure (HF), and medical treatment options for these patients are limited. Amiodarone is a type III antiarrhythmic approved for use in ventricular and supraventricular arrhythmias. Amiodarone is the medical treatment of choice for rhythm control of atrial fibrillation in patients with HF with reduced ejection fraction (HFrEF)es.7

Ventricular tachycardia is a leading cause of morbidity and mortality in this patient population. Antiarrhythmic drug therapy is discouraged in HF patients unless symptomatic arrhythmias persist, despite optimal medical therapy and correction of any ischemia or electrolyte and metabolic abnormalities.7 The superiority of the implantable cardioverter defibrillator (ICD) over antiarrhythmic drugs as the primary therapy in the treatment of patients at high risk of life-threatening ventricular arrhythmias, both in primary as well as secondary prevention, has been clearly established.8

Implantable cardioverter defibrillator shocks can lead to significant anxiety and even posttraumatic stress disorder in these patients.9 The concomitant use of antiarrhythmic agents, such as amiodarone, in patients with an ICD, has been shown to be efficacious in reducing appropriate ICD shocks.8 Clinicians managing HFrEF will prescribe...
amiodarone as the antiarrhythmic of choice, to reduce the burden of ICD shocks, both appropriate for ventricular arrhythmias and inappropriate for supraventricular arrhythmias.\(^\text{10}\)

Amiodarone is 37% iodine by molecular weight and is associated with thyroid dysfunction in up to 24% of exposed patients.\(^\text{11}\) Presentations include amiodarone-induced thyrotoxicosis (AIT), hypothyroidism, and asymptomatic changes in thyroid function tests.\(^\text{11,12}\) There are 2 main recognized types of AIT. Type 1 AIT is secondary to the iodine load and typically occurs in patients with an underlying predisposition, such as positive antibodies for Graves’ disease or a multinodular goiter. Type 2 is a destructive thyroiditis.\(^\text{11}\) Amiodarone-induced thyrotoxicosis is a serious and potentially life-threatening complication.

To our knowledge, no studies have specifically examined the outcomes of AIT in patients with HFrEF. We designed and conducted a retrospective study examining the clinical outcomes associated with AIT in individuals with HFrEF.

2 METHODS

2.1 Study design and data source

We performed a retrospective cohort study, examining the medical records of all patients seen at the St. Boniface Hospital Heart Failure Clinic (Winnipeg, Manitoba, Canada) from August 1, 2011 to July 31, 2012. We included all patients within that period that met the study criteria. Thus, patients who died or were lost to follow-up prior to the enrollment date were not included in our study cohort. This study was approved by the University of Manitoba Bannatyne Campus Research Ethics Board, Research Ethics Board Registry Number: H2013:149(H516298).

The St Boniface Hospital Heart Failure Clinic is 1 of 2 Canadian Heart Failure Network Centers in Manitoba, servicing a population of 1.2 million persons. Clinical information from each encounter is recorded in the Canadian Heart Failure Network database. This database is prospectively populated with clinical variables such as demographic data, detailed drug information, past medical history, laboratory data, and pertinent information related to the care of HF.

2.2 Patient population

The institution’s Canadian Heart Failure Network database was reviewed. All patients who had previously consented for enrollment into the database during the study period were considered for inclusion. Consent for enrollment into the Canadian Heart Failure Network database specifies consent for the data to be used for research. Only patients with known dates of amiodarone initiation were included in the analysis.

Using prespecified definitions for the variables of interest, a comprehensive chart review was performed. Each record was systematically examined for the diagnosis of thyroid disease, any medications that could suggest AIT (e.g., amiodarone, propylthiouracil, methimazole, and/or prednisone), as well as any laboratory abnormalities in thyroid function. Charts identified with any of the above were examined further for a possible diagnosis of AIT. If pertinent data were missing from the electronic record, the patient’s hospital chart and clinic chart were also manually reviewed.

Heart failure with reduced EF was defined by clinical evidence of HF with a left ventricular EF <40%.\(^\text{7}\) Amiodarone-induced thyrotoxicosis was deemed to be present if a patient had a suppressed thyroid-stimulating hormone (<0.015 mIU/L), elevated free thyroxine (T4 9.7-25.7 pmol/L), and/or free triiodothyronine (T3 3.7-6.9 pmol/L) in the setting of amiodarone exposure.\(^\text{11}\) When possible, AIT was further classified as either type 1 or type 2,\(^\text{11}\) if a type was indicated by the treating endocrinologist. We combined the 2 types in our analyses and classified patients as having AIT (type 1, type 2, or unclassified) or not. Because AIT is known to be unpredictable in its timing and has been reported to have a sudden onset, we included all patients with thyrotoxicosis who were exposure to amiodarone before diagnosis.\(^\text{13,14}\)

2.3 Data collection

Detailed chart review was performed on those patients identified as having both a diagnosis of HFrEF and AIT. Data were collected for baseline clinical characteristics, treatments received, ensuing complications, discontinuation of amiodarone, and mortality. Ascertainment of death was obtained through the HF database, as well as thorough review of local obituaries. The cohort was assembled from all patient encounters from August 1, 2011 to July 31, 2012. Outcome ascertainment was completed on March 5, 2015.

2.4 Statistical analysis

After describing our data with cross-tabulations, means, and medians, where appropriate, we explored the association between AIT and survival, using survival analysis. To examine the association between AIT and survival, we fit our data by using Cox proportional hazard regression models. Covariates were chosen based on clinical reasoning. The presence of AIT was incorporated as a time-varying covariate. Thus, an individual could potentially contribute toward survival time with or without AIT throughout the duration of follow-up. We also incorporated New York Heart Association (NYHA) class and duration of HF as time-varying covariates. We checked for violations of the proportional hazard assumption visually by comparing the survival curve among those with AIT and those without. The risk for death was expressed as a hazard ratio (HR) with 95% confidence intervals (CIs). Those who had not died by the date that their chart was reviewed or the date that they were lost to follow-up at the HF clinic were censored. They were censored on their respective chart extraction date or date of leaving the HF clinic, whichever came first. Analyses were conducted in Stata, version 11.0.

3 RESULTS

3.1 Baseline characteristics

In total, 145 patients received amiodarone, of which 112 were men. Two patients were excluded because the index date of amiodarone initiation was not recorded. An additional 33 patients were excluded because they did not have a diagnosis of HFrEF, thus leaving a total...
Of 110 patients for study inclusion. Of these, 13 (11.8%) had a diagnosis of AIT. Baseline characteristics are summarized in Table 1. All patients with AIT were male. Individuals with AIT tended to be younger (mean age 53.5 vs 62.7 years), were less likely to have ischemic HF (23.1% versus 61.9%), and were less likely to continue amiodarone (53.8 vs 77.3%) in comparison with those without thyrotoxicosis.

3.2 | Clinical presentation and evaluation

Of the 13 people with thyrotoxicosis, 2 (15.4%) had type 1 AIT and 5 (38.5%) had type 2; the remaining 6 individuals (46.2%) were indeterminate. Two patients were diagnosed with subclinical hyperthyroidism (low thyroid-stimulating hormone with normal T4 and T3 measurements) in the setting of amiodarone use. These patients were not included in the AIT group, as they did not meet predefined inclusion criteria. Among those who got AIT, the time from their estimated date of starting amiodarone until they were diagnosed with AIT ranged from 1 day to slightly over 50 months (4.2 years); 31% (4 people) had a duration from start of amiodarone until AIT of 13 months (1.1 years) or less.

3.3 | AIT treatment

All patients with AIT were initially treated with antithyroid drugs, methimazole being most commonly used (11 of 13 patients, 84.6%). Five patients (38.5%) additionally received prednisone. One person underwent thyroidectomy; elevated liver enzymes prompted this while on methimazole therapy.

At the time of chart review or death, 12 of the 13 patients were still actively being followed in the HF clinic. Euthyroidism was achieved in 2 patients (15.4%), hypothyroidism occurred in 6 patients (46.1%), and thyrotoxicosis remained uncontrolled in 5 patients (38.4%). Of the patients remaining thyrotoxic, 1 was recently started on treatment at time of chart review and 3 patients were thyrotoxic at the time of their death. For patients included in our study, the unadjusted mortality was similar between those with AIT and those without, 30.8% versus 28.9%. Of the 4 patients with AIT who died, 3 (75%) were thyrotoxic at the time of their death. All 3 of these patients had continued amiodarone.

3.5 | Survival analysis

We subsequently sought to determine the risk of death from the initiation of amiodarone therapy according to the presence of AIT (Table 2). The unadjusted risk of death was similar between those with AIT compared with those without AIT (HR, 0.99; 95% CI 0.33-3.02). After adjustment for age, NYHA functional class, and duration of HF, those with AIT appeared to be at nearly a 2-fold higher risk of death compared with those who did not develop AIT (HR 1.83; 95% CI 0.55-6.04). This difference was, however, not statistically significant.

4 | DISCUSSION

The risk of developing AIT appears to be related to iodine exposure with 1 study demonstrating rates of AIT in almost 10% of patients in

### TABLE 1

Baseline characteristics of patients with heart failure with reduced ejection fraction (HFrEF) with amiodarone exposure

| Variable                              | Patients With HFrEF and Amiodarone Exposure |
|---------------------------------------|--------------------------------------------|
|                                       | Amiodarone-Induced Thyrotoxicosis (AIT) not Identified (n = 97) | AIT Identified (n = 13) |
| Men n (%)                             | 77 (79.4)                                  | 13 (100)                  |
| Agea (years) mean (SD)                | 62.7 (12.3)                                | 53.5 (12.4)               |
| Ischemic HF n (%)                     | 60 (61.9)                                  | 3 (23.1)                  |
| ICD n (%)                             | 79 (81.4)                                  | 12 (92.3)                 |
| Beta-blocker use n (%)                | 88 (90.7)                                  | 12 (92.3)                 |
| ACE-Ib or ARBc n (%)                  | 83 (85.6)                                  | 12 (92.3)                 |
| Mineralocorticoid antagonist n (%)    | 47 (48.5)                                  | 8 (61.5)                  |
| Amiodarone indication ventricular tachycardia n (%) | 62 (63.9)     | 8 (61.5)                  |
| Amiodarone continued n (%)            | 75 (77.3)                                  | 7 (53.8)                  |

*aAge at start of amiodarone.

*bAngiotensin converting enzyme inhibitor.

*cAngiotensin receptor blocker.

### TABLE 2

Hazard ratios for death in patients with amiodarone-induced thyrotoxicosis (AIT) versus patients without AIT

| Outcome                                                                 | Hazard Ratio (95% Confidence Interval) |
|------------------------------------------------------------------------|----------------------------------------|
| AIT alone                                                              | 0.99 (0.33, 3.02)                      |
| AIT adjusted for New York Heart Association (NYHA) class               | 1.22 (0.41, 3.65)                      |
| AIT adjusted for age and NYHA class                                    | 1.99 (0.62, 6.33)                      |
| AIT adjusted for age and NYHA class and years since heart failure diagnosis | 1.83 (0.55, 6.04)                     |
an area of relative iodine insufficiency compared with rates of 3% in amiodarone treated patients in North America.11,15 Amiodarone-induced thyrotoxicosis is associated with significant morbidity and mortality, with severe left ventricular dysfunction being predictive of an increased mortality, especially in elderly patients.16 Treatment varies between AIT type 1 and type 2.17 Amiodarone-induced thyrotoxicosis is difficult to treat, as patients are iodine saturated and therefore cannot undergo radiiodine ablation.18,19 Furthermore, the literature regarding definitive treatment with thyroidectomy is discordant, with some studies suggesting an associated high morbidity and mortality and others indicating a rapid improvement of left ventricular function in patients with an EF of <40%.19,20

No specific recommendations are provided in HF guidelines regarding amiodarone side effect monitoring for patients with HF requiring amiodarone. The 2010 CCS atrial fibrillation guidelines recommend a clinical exam, with careful history to elicit symptoms of toxicity (eg, sleep disturbance, tremor, gait instability, and constipation), and the measurement of hepatic enzymes and thyrotropin every 6 months in all patients on chronic amiodarone, regardless of symptoms.21 It remains unclear how routinely the above monitoring is implemented in clinical practice.

Within our cohort of noniodine insufficient patients with HFREF, 11.8% of patients who were exposed to amiodarone developed AIT. This is higher than the reported prevalence of 3% in amiodarone-treated patients in North America.11,15 Around 30% of patients with AIT died, and of these, 75% were thyrotoxic at the time of death despite medical treatment.

All the patients who developed AIT were men; this male predominance is consistent with other reports.11,18 The type of AIT was not indicated in most our patients. This may reflect the difficulty in distinguishing between the types of AIT or could be because the information available in the HF clinic charts was incomplete. Of the patients who did have a type identified, most were diagnosed with type 2 AIT. This is consistent with a study from Italy by Bogazzi et al, which highlighted a predominance of type 2 AIT in their cohort.22

Of the patients who developed AIT, amiodarone was discontinued in about half of cases. The decision as to whether to discontinue amiodarone at diagnosis of AIT is controversial and often dictated by nuanced clinical judgment. Currently, there are no consensus guidelines to help guide standardized management. Interestingly, all of the patients who remained thyrotoxic in this study were continued on their amiodarone. However, this may reflect their continued thyrotoxicosis and arrhythmias, rather than be a predictor of treatment failure. It has been reported that continuation of amiodarone therapy in type 2 AIT patients could delay the restoration of euthyroidism.23 However, in HFREF, sometimes we do not have an option but to continue amiodarone for lack of a better alternative antiarrhythmic in this patient population. Clinicians cannot always differentiate between type 1 and type 2 AIT and will chose to continue the amiodarone, as these patients are at high risk of sudden cardiac arrest and/or ICD shock burden. Prospective, controlled data, and addressing the continuation of amiodarone are currently lacking; a small prospective observational study in France, however, demonstrated no difference in treatment success in patients that continued amiodarone compared with those in which it was discontinued.24

Overall, mortality in this cohort was high (29.1%) for patients with and without a diagnosis of AIT. The mortality associated with AIT in the literature varies, and there are limited data on mortality in patients with HFREF. In 1 study of patients with AIT by O’Sullivan et al, the presence of severe left ventricular dysfunction, as defined by an EF <30%, was significantly associated with death, with a mortality rate of 50% in patients with AIT and severe LV dysfunction.16 A study by Conen et al detailed the predictors of outcomes in their cohort of 84 patients with AIT.25 Overall mortality in their population was 19%; however, this increased to 31% in patients with an impaired EF fraction, defined as an EF <50%.25

Due to the sample size, while no association was found in mortality for patients with HFREF with AIT, a real association could have been missed. Age and NYHA functional class have been implicated as important predictors of mortality in the literature.26 After adjusting for age, NYHA functional class, and duration of HF, we observed a slight increase in mortality between those who developed AIT and those who did not. This difference was not statistically significant and could be a consequence of the severity of underlying heart disease, rather than AIT itself. Our data are consistent with that of Yui et al, who compared patients on amiodarone with and without systolic dysfunction who developed AIT to those who remained euthyroid.27 They identified higher rates of major adverse cardiovascular events but no difference in mortality between the 2 groups.27

Our cohort comprised consecutive patients who are a captive and well-defined population with detailed information regarding cardiac medications and diagnoses. However, there are some study limitations. Because it is an HF database, details regarding the type of thyrotoxicosis and treatment may not have been available, and a remote history of this condition may have been missed. This could have led to an underestimation of the prevalence of AIT in our study. Given the small overall cohort, short follow-up time, and consequently small event rate, we may have lacked sufficient power to determine significant differences between the groups. Lastly, some of our patients started amiodarone up to 10 years before our study start date. This means that our data may have been bias toward the inclusion of long-term survivors, as patients initiated on amiodarone in both groups who died or were lost to follow up prior to this date were not captured.

Our study highlights the need to establish guidelines for screening for thyroid side effects and toxicities in the HF population and the clinical need to review the indication for chronic amiodarone therapy, which may no longer be warranted, in this vulnerable patient population.

In conclusion, AIT is common, occurring in around 1 in 10 people treated with amiodarone in the setting of HFREF, and is difficult to treat. While no association in mortality was found for patients with HFREF with AIT, a real association could have been missed. We believe that further research is necessary to determine the risk factors for AIT to improve outcomes in patients with HFREF who require amiodarone.

**AUTHOR CONTRIBUTIONS**

Conceptualization: Jennifer M. Yamamoto, Pamela M. Katz, Francisco J. Cordova
Data curation: Jennifer M. Yamamoto
Formal analysis: Leigh Anne Shafe
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CONFLICT OF INTEREST

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