Amiodarone-induced thyrotoxicosis is associated with a nearly threefold increased risk for major adverse cardiovascular events that must be identified and treated

Yiu KH, Jim MH, Siu CW, Lee CH, Yuen M, Mok M, Shea YF, Fan K, Tse HF, Chow WH, Amiodarone-induced thyrotoxicosis is a predictor of adverse cardiovascular outcome. J Clin Endocrinol Metab 2009;94:109-14.

SUMMARY

BACKGROUND Amiodarone-induced thyrotoxicosis (AIT) is a common clinical condition that is notoriously difficult to manage; however, the risk for subsequent adverse cardiovascular events in patients with AIT is largely unknown. The aim of this study was to assess the clinical characteristics of major adverse cardiovascular events, including ventricular tachycardia and death, in patients with AIT as compared with euthyroid patients.

METHODS This is a retrospective study of patients treated at the Cardiac Medical Unit, Grantham Hospital, Hong Kong, from January 2000 through December 2005. The study subjects were stable cardiac patients treated with amiodarone for at least 3 months. Excluded from the study were patients with end-stage heart failure or incessant ventricular tachyarrhythmias not controlled by medical therapy, or uncorrected severe valvular abnormality, complex congenital heart disease, or cancer. The study patients were retrospectively evaluated for major adverse cardiovascular events, defined as cardiac death, myocardial infarction, stroke, and heart failure, or ventricular arrhythmias that required hospitalization, as compared with the baseline clinical characteristics, laboratory parameters, and outcomes in euthyroid patients.

RESULTS The study subjects were 354 patients (mean age ±SD, 61.8±14.1 yr), the majority of whom (64.7%) were male. The overall duration of follow-up was 48.6±26.7 months. Among the various groups of patients, there were neither significant differences in the prevalence of underlying heart disease and baseline left ventricular ejection fraction nor significant differences in the indications, duration, cumulative dose, or average daily dose of amiodarone (P>0.05) (Figure 1). However, patients with AIT were younger (56.7± 14.6 vs. 62.3±13.7 years; P = 0.01) as compared with euthyroid patients, while those with amiodarone-induced hypothyroidism were more likely to be female (47.9% vs. 33%; P = 0.03) and to have hyperlipidemia (28.8% vs. 12.9%; P = 0.03) as compared with those who remained euthyroid (Figure 1). After 28.2±23.3 months of amiodarone therapy, AIT developed in 57 patients (16.1%), 224 (63.3%) remained euthyroid, and after a mean duration of 27.2±23.3 months, amiodarone-induced hypothyroidism developed in 73 (20.6%) (Figure 2). Among the 57 patients with AIT, 5 had suspected type I or II AIT (1 with a history of Graves' disease and 4 with diffuse goiter with increased ultrasound Doppler flow) and 13 had suspected type II AIT (5 with negative thyroglobulin antibodies and 8 with diffuse Doppler flow by ultrasound); in 35 patients, the diagnosis of AIT type I or II was uncertain.

Ischemic heart disease was the most common underlying cardiac abnormality, and atrial fibrillation was the most common indication (75%) for amiodarone therapy, followed by ventricular tachycardia (19%) (Figure 4). The left ventricular ejection fraction was less than 45% in one third of the patients (mean, 51.2±16.8),. As compared with euthyroid patients, those with AIT had a higher rate of major adverse cardiovascular events (31.6% vs. 10.7%; P<0.01), which was mainly caused by a higher rate of ventricular arrhythmias that required hospital admission (7.0% vs. 1.3%, P = 0.03) (Figure 3). Cox regression multivariate analysis revealed two independent predictors of major adverse cardiovascular events: AIT (hazard ratio, 2.68; confidence interval, 1.53 to 4.68; P<0.01) and left ventricular ejection fraction less than 45% (hazard ratio, 2.52; confidence interval 1.43 to 4.42; P<0.01) Amiodarone was discontinued in most patients (89%), and three were given prednisolone. Antithyroid drug therapy was prescribed

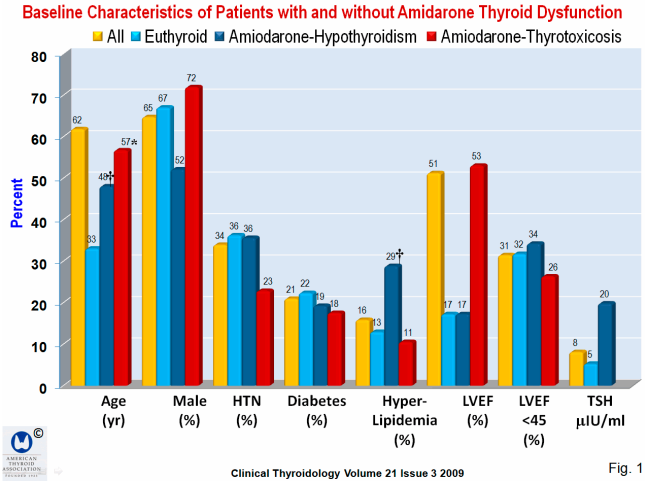

Figure 1. Patients with amiodarone-induced thyrotoxicosis (AIT) were younger (57 yr) than those who remained euthyroid (62 yr). *P = 0.01. Women were more likely to have amiodarone-induced hypothyroidism (48% vs. 33%; †P = 0.03) and greater hyperlipidemia (29.% vs. 12.9%, †P = 0.03) as compared with men. HTN denotes hypertension, and TSH thyrotropin. Here and elsewhere percentages are rounded to integer.

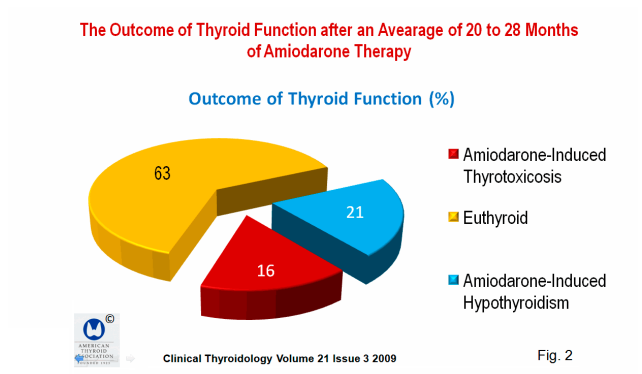

Figure 2. After an average of about 28 months of amiodarone therapy, 16% developed AIT and 63% remained euthyroid, and after a mean duration of about 27months 21% developed hypothyroidism).

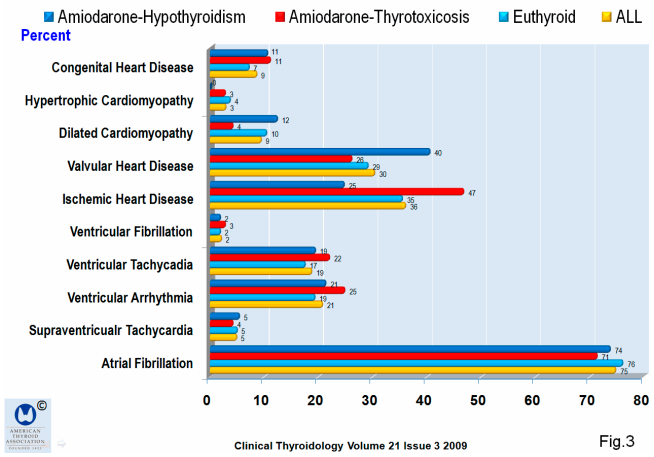

Figure 3. Ischemic heart disease was the most common underlying cardiac abnormality, and atrial fibrillation was the most common indication (75%) for amiodarone therapy, followed by ventricular tachycardia (19%)

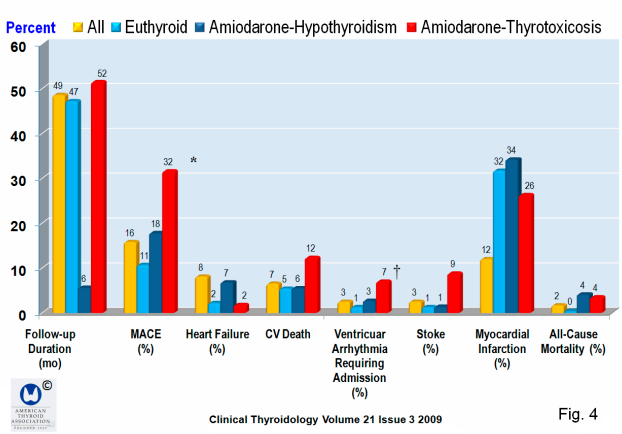

Figure 4. The characteristics and duration of follow-up and the incidence of AIT in patients with and without major adverse cardiovascular events (MACE). CV denotes cardiovascular. *P<0.01, comparing with euthyroid patients. †P = 0.03 comparing patients with AIT with euthyroid patients

for 47 patients (83%) and radioiodine therapy was prescribed for 5 (9%) but none required thyroidectomy.

CONCLUSION Amiodarone-induced thyrotoxicosis is associated with a nearly threefold increased risk for major adverse cardiovascular events including relevant ventricular arrhythmia that required hospitalization and treatment. Cardiovascular mortality was 12%. in the AIT I and II groups, compared with 5% in the euthyroid groups.

COMMENTARY

It has long been recognized that amiodarone, a potent class III anti-arrhythmic agent, can exert profound effects on thyroid function (1, 2). While there are clear structural similarities between the amiodarone molecule and levothyroxine, multiple lines of investigation have demonstrated that these changes in thyroid hormone levels in serum are a result of the high iodine content (33% by weight) of the amiodarone molecule. The widespread use of amiodarone for the treatment of both ventricular and atrial arrhythmias has led to the often observed development of both hypothyroidism and hyperthyroidism in patients with significant coexistent cardiac disease. While the incidence of these findings varies throughout the world, presumably as a result of the differing iodine content in the diet, the development of hypothyroidism is more frequent than that of amiodarone induced thyrotoxicosis (AIT) (2). In contrast, the treatment of AIT is much more challenging as these patients are characteristically resistant to anti-thyroid therapy with thiourea drugs, have insufficient iodine uptake into the thyroid gland to make radioiodine therapy feasible, and respond in an unpredictable way to anti-inflammatory therapy with corticosteroids (3). In the accompanying article we have our clinical impression confirmed with the finding that AIT carries a nearly threefold increased risk for major adverse cardiovascular events. These events, including ventricular tachycardia, cardiovascular hospitalization and cardiovascular death, are almost certainly the result of the underlying cardiac pathophysiology which is worsened by the thyrotoxic state. Yiu and colleagues report a 16% prevalence of AIT over approximately 28 months of amiodarone treatment. This is much greater than would be expected in a North American patient population. The characterization of the type of AIT (type I or II) (4) was uncertain in the majority of cases and although this finding was the basis for amiodarone discontinuation, it is hard to find support for this recommendation in the management of this condition. While the authors do not comment, it would be our recommendation that such patients be treated with beta-adrenergic blockade and that in patients with heart failure, carvedilol be the agent of choice. In our experience the onset of AIT may be heralded by a decrease in Coumadin requirements due to the increase in vitamin K metabolism in patients with atrial fibrillation or alternatively to the increase in defibrillator shocks of patients with ventricular tachycardia who have intracardiac devices. This latter observation is further confirmed by the findings of Yiu et al. While this remains a challenging clinical problem, the recent FDA advisory panel approval of dronedarone, a class III anti-arrhythmic amiodarone analog that has neither iodine nor associated effects on thyroid function (5, Klein unpublished observation), may become the anti-arrhythmic treatment of choice from a thyroidologists perspective.

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