ORIGINAL ARTICLE

# Amiodarone-induced thyroid dysfunction in the Hong Kong Chinese population

CME

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**Objective** To determine the frequency, risk factors, clinical features, and management of amiodarone-induced thyroid dysfunctions.

**Design** Retrospective study.

**Setting** A regional hospital in Hong Kong.

**Patients** Patients who had been prescribed amiodarone for at least 6 months from 1 October 2005 to 30 September 2007.

**Results** A total of 390 patients (mean age, 70 years; standard deviation, 9 years; 54% male) with a median follow-up of 43 (interquartile range, 25-69) months were studied. Hypothyroidism developed in 87 (22%) of the patients (mean age, 72 years; standard deviation, 7 years; 56% male) and thyrotoxicosis in 24 (6%) of the patients (65 years; 11 years; 54% male). Increased baseline thyrotropin (thyroid-stimulating hormone) level appeared to be predictive of amiodarone-induced hypothyroidism, in which a thyroid-stimulating hormone level of 4 mIU/L or above was associated with a 4.7-fold increase in the risk (95% confidence interval, 1.9-11.7; P<0.001). Compared with those who remained euthyroid on amiodarone, thyrotoxicosis developed in younger patients. In these patients, the classical symptoms of thyroid dysfunction were frequently absent, although worsening of underlying arrhythmias, their cardiac condition, weight loss, and over-warfarinisation were suggestive of amiodarone-induced thyrotoxicosis. In both amiodarone-induced thyrotoxicosis and hypothyroidism, the disease course was benign. Patients with the former showed a good response to anti-thyroid drugs and steroid therapy.

**Conclusions** Amiodarone-induced thyroid dysfunction is common among our population. As the clinical presentations are usually vague and atypical, regular biochemical monitoring of thyroid function is warranted, particularly in patients with elevated baseline thyroid-stimulating hormone level. The disease course of amiodarone-induced thyrotoxicosis is usually benign and remits with timely administration of anti-thyroid medications, with or without corticosteroids.

## Introduction

Amiodarone is a commonly prescribed anti-arrhythmic drug because of its ability to treat various types of cardiac arrhythmias including ventricular arrhythmias, paroxysmal supraventricular tachycardias, atrial fibrillation, and flutter with minimal negative inotropic and proarrhythmic effects.[1] It is a benzofuran derivative containing 37.5% iodine by weight. Daily maintenance dosages of 100 to 600 mg result in a 35-to-140–fold excess in the recommended daily iodine intake of 100 to 150 mg. Such a high iodine content and the inherent effects of amiodarone and its active metabolite desethylamiodarone are postulated to result in thyroid dysfunction in 14 to 18% subjects after 2 to 3 years of treatment.[2] The relative frequencies of amiodarone-induced thyrotoxicosis (AIT) and hypothyroidism (AIH) are mainly influenced by iodine intake and any underlying thyroid disorder; AIH is about 10 times more common than AIT in areas of sufficient iodine intake, while AIT is twice as common as AIH if iodine intake is deficient.[2]

Although Hong Kong is a coastal city in southern China, iodine insufficiency does exist. Approximately 45% of children, 52% of adults, and 55% of the elderly had urine

**Key words**
Amiodarone; Anti-arrhythmia agents; Hypothyroidism; Thyroid diseases; Thyrotoxicosis

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iodine concentrations below the World Health Organization criteria for iodine sufficiency (<0.79 mmol/L). Therefore, local iodine intake may be considered to be borderline adequate.[3] With this background, in this retrospective study we aimed to assess the prevalence, risk factors, clinical features, and management of amiodarone-induced thyroid dysfunction in a community-based hospital in Hong Kong.

## 香港華人服用碘胺酮引致甲狀腺功能異常的研究


**目的** 探討服用碘胺酮引致甲狀腺功能異常的發病率、風險因素、臨床表現及處理方法。

**設計** 回顧性研究。

**安排** 香港一所分區醫院。

**患者** 2005年10月1日至2007年9月30日期間，曾服用碘胺酮不少於6個月的病人。

**結果** 共390位病人（平均年齡70歲；標準差9歲；54%為男性）參與研究，隨訪期中位數為43個月（四分位距：25-69個月）。其中87位病人（22%；平均年齡72歲；標準差7歲；56%為男性）出現因碘胺酮引致的甲狀腺功能不足，24位病人（6%；平均年齡65歲；標準差11歲；54%為男性）出現因碘胺酮引致的甲狀腺功能亢進。碘胺酮引致甲狀腺功能不足的預測因素為服藥前高促甲狀腺素（TSH）水平，當TSH水平≥4mIU/L時，其患病風險增加4.7倍（95%置信區間：1.9-11.7；P<0.001）。碘胺酮引致甲狀腺功能亢進的病人相對正常甲狀腺功能病人較為年輕。碘胺酮引致甲狀腺功能亢進的病人多數沒有典型症狀，但他們的心律失常或心臟病況轉差、體重下降及薄血指數上升可能是甲狀腺功能亢進的提示。碘胺酮引致甲狀腺功能異常皆為良性病例。碘胺酮引致甲狀腺功能亢進的病人對甲狀腺藥及類固醇藥治療均有良好反應。

**結論** 本地的碘胺酮引致的甲狀腺功能異常個案很普遍。由於其臨床症狀一般比較模糊及非典型，必須定期進行甲狀腺功能測試，而測試於高促甲狀腺素的病人尤為重要。碘胺酮引致甲狀腺功能亢進的病例多為良性，及時使用抗甲狀腺藥，必要時加用類固醇藥治療，大多數病情都能受到控制。


## Methods

Patients who had attended the out-patient clinic of the Department of Medicine and Geriatrics of Kwong Wah Hospital, Hong Kong from 1 October 2005 to 30 September 2007, and had received amiodarone from our pharmacy for at least 6 consecutive months were identified through the computer system. Only patients having baseline and at least one thyroid function test 3 months after commencing amiodarone were included in the study. Patients with known thyroid diseases and previous treatment for thyroid were excluded. Demographic, clinical, and biochemical data were retrieved from medical records. The duration of amiodarone therapy was defined as the period between the date of commencement and the date of the latest thyroid function tests, or the date when abnormal thyroid function tests fulfilling the following definitions were checked. Thyroid function tests indicating AIH were defined as follows: serum thyroid-stimulating hormone (TSH) higher than 10 mIU/L in two consecutive samples, with or without subnormal serum-free thyroxine ($FT_4$). While tests indicating AIT were defined as: TSH less than 0.03 mIU/L in two consecutive samples with or without an elevated $FT_4$. Notably, $FT_4$ was not included as an obligatory criterion in the definition because it was not checked consistently in all patients, whereas the less reliable parameter, total thyroxine ($TT_4$), was checked instead. For patients with AIH and AIT, clinical presentations, treatment modalities, and disease progress including time to euthyroidism were also retrieved from medical records. Serum $FT_4$ and ultrasensitive TSH were assayed by the Abbott Axsym system. Normal ranges in our laboratories were as follows: $FT_4$, 9.1-23.8 pmol/L; TSH, 0.29-4.00 mIU/L.

### Statistical analysis

Demographic, clinical, and biochemical characteristics were described for categorical variables by number (%) and for the continuous variables using mean (standard deviation [SD]) or median (interquartile range [IQR]) according to their distribution. Group comparisons of parametric and non-parametric continuous variables were performed by the Student *t*-test or the Mann-Whitney *U* test, respectively. Group comparisons of categorical data were analysed by Chi squared or Fisher's exact tests, where appropriate. A two-tailed P value of less than 0.05 was considered statistically significant. All statistical analyses were performed with Statistical Package for the Social Sciences (Windows version 13.0; SPSS Inc, Chicago [IL], US).

## Results

A total of 462 patients were prescribed amiodarone for at least 6 months during the study period but data analysis was limited to 390 who fulfilled the inclusion criteria. Except for three cases with a history of thyroid disease, all the excluded cases were because their baseline or follow-up thyroid function tests were not checked. The mean (SD) age of this cohort was 70 (9) years with a median follow-up of 43 (IQR, 25-69) months. There were 209 (54%) males and 181 (46%) females. The indications for amiodarone were supraventricular tachycardias in 352 (90%) of the patients and ventricular tachycardias in 38 (10%).

Ischaemic heart disease, congestive heart failure, diabetes mellitus, and chronic obstructive pulmonary diseases were present in 176 (45%), 171 (44%), 86 (22%), and 45 (12%) of the patients, respectively.

### Prevalence and risk factors of amiodarone-induced thyroid dysfunction

Of 390 patients, 87 (22%; 49 males, 38 females) developed AIH after a median follow-up of 26 (IQR, 14-62) months, while 24 (6%; 13 males, 11 females) developed AIT after a median follow-up of 37 (IQR, 24-50) months. As shown in the Figure, more patients developed AIH than AIT (37 or 43% vs 6 or 25%, P<0.001) within 2 years of amiodarone therapy. A comparison of baseline characteristics in patients with normal and abnormal thyroid function is shown in Table 1. Compared with those who remained euthyroid on amiodarone, those who developed thyrotoxicosis were younger (65 vs 70 years; P=0.01), whereas patients with higher baseline TSH were more likely to develop AIH. If the baseline TSH level was higher than 4.0 mIU/L, there was 4.7-fold increase in the risk (95% confidence interval, 1.9-11.7, P<0.001) compared with those with lower TSH levels. Female gender did not increase the risk of amiodarone-induced thyroid dysfunction.

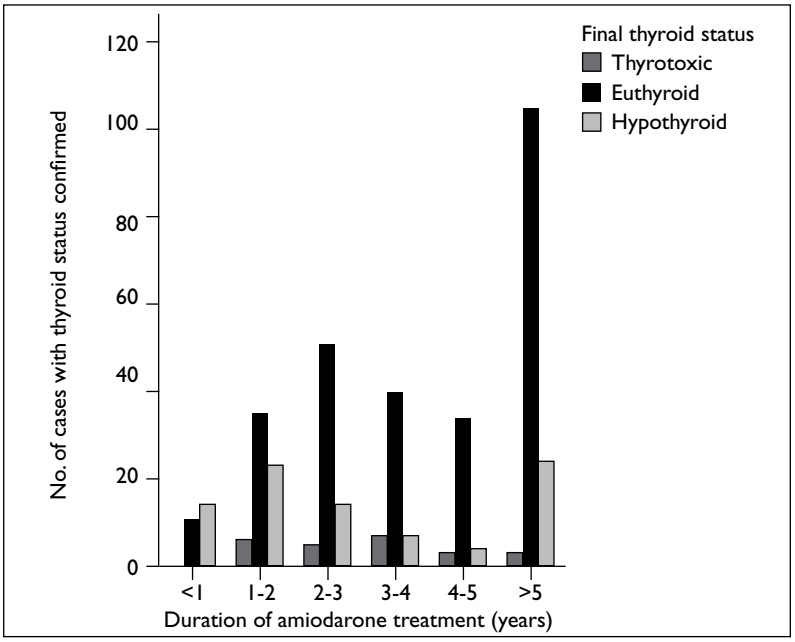


FIG. Thyroid status in patients receiving long-term amiodarone treatment in relation to the duration of amiodarone treatment

TABLE 1. Baseline characteristics of patients with amiodarone-induced thyroid dysfunction compared with euthyroid patients on amiodarone*

| Characteristic | AIT (n=24, 6%) | Euthyroid (n=279, 72%) | AIH (n=87, 22%) |
|---|---|---|---|
| Mean (± SD) age (years) | 65 ± 11† | 70 ± 9 | 72 ± 7 |
| Male (%) | 13 (54) | 147 (53) | 49 (56) |
| IHD (%) | 11 (46) | 111 (40) | 39 (45) |
| CHF (%) | 11 (46) | 113 (41) | 40 (46) |
| COPD (%) | 4 (17) | 31 (11) | 10 (11) |
| DM (%) | 2 (8) | 57 (20) | 22 (25) |
| Duration of amiodarone therapy (months) | 37† (24-50) | 48 (30-78) | 26‡§ (15-63) |
| Cumulative dosage of amiodarone (g) | 168.5† (112.5-233.4) | 258.1 (160.9-423.4) | 157.8† (87.6-377.4) |
| Baseline TSH (mIU/L) | 1.4 (0.6-2.0) | 1.1 (0.8-2.0) | 1.7‡ (1.2-3.0) |
| Patients with baseline TSH ≥4 mIU/L (%) | 0 (0) | 8 (2.9%) | 12 (14.1%)‡ |
| Baseline $FT_4$ (pmol/L) | 16.2 ± 3.0 | 15.8 ± 3.2 | 15.7 ± 3.1 |

* AIT denotes amiodarone-induced thyrotoxicosis, AIH amiodarone-induced hypothyroidism, CHF congestive heart failure, COPD chronic obstructive pulmonary disease, DM diabetes mellitus, $FT_4$ free thyroxine, IHD ischaemic heart disease, SD standard deviation, and TSH thyroid-stimulating hormone
† P<0.05 vs euthyroid patients
‡ P<0.001 vs euthyroid patients
§ P<0.05 vs AIT

### Clinical features and management of patients with amiodarone-induced thyrotoxicosis

Most patients with AIT were diagnosed in the out-patient setting; only three (13%) out of 24 were hospitalised at diagnosis (patients No. 7 and 9 because of breakthrough arrhythmias, and patient No. 11 who presented with a convulsion). Classical thyrotoxic symptoms (palpitation, tremor, and heat intolerance) were not present, though documentation might have been inadequate. Weight loss of more than 2 kg in the past 6 months occurred in 10 (42%) of the 24 patients. Five (63%) out of the eight patients taking warfarin revealed excessive international normalised ratios (INRs) of more than 4 when AIT was biochemically confirmed.

Only four (17%) of the cases were referred to an endocrinologist for further management. Radiological and biochemical differentiation of AIT into type 1 (on top of a nodular goitre) or type 2 (due to amiodarone thyroiditis) was not performed in all cases. Anti-microsomal and anti-thyroglobulin antibodies were checked in 19 (79%) of the patients and all were negative. Ultrasonography of the thyroid was performed in 10 (42%) of the cases and no thyroid enlargement or nodule was reported. Table 2 summarises various treatment modalities and patient outcomes with AIT. Sixteen (67%) of the patients had their amiodarone therapy terminated. Anti-thyroid medications were used in 14 (58%) of the patients (carbimazole in 9 and propylthiouracil in 5) and the resulting median time to euthyroidism was similar to that of patients not on anti-thyroid medications: 19 (IQR, 10-25) weeks vs 20 (IQR, 11-62) weeks (P=0.43). Steroids, in addition to anti-thyroid drugs, were used in four (17%) of these cases and resulted in a similar remission time to those taking anti-thyroid drugs only

TABLE 2. Treatment modalities and outcomes in patients with amiodarone-induced thyrotoxicosis

| Patient No. | Sex | Age (years) | Free thyroxine (pmol/L) at diagnosis | Stop amiodarone | Anti-thyroid drugs (weeks) | Steroid (weeks) | Time to euthyroidism* (weeks) |
|---|---|---|---|---|---|---|---|
| 1 | M | 67 | 23.9 | Yes | No | No | 12 |
| 2 | M | 66 | 23.1 | No | No | No | 100 |
| 3 | M | 82 | 24.1 | No | No | No | 142 |
| 4 | F | 67 | 48.4 | Yes | Yes (19) | No | 18 |
| 5 | F | 68 | 42.0 | Yes | Yes (183) | No | 21 |
| 6 | M | 68 | 39.8 | No | Yes (30) | No | 10 |
| 7 | F | 84 | 28.0 | Yes | Yes (42) | Yes (28) | 37 |
| 8 | F | 73 | 43.0 | Yes | No | No | 17 |
| 9 | F | 64 | 63.6 | Yes | Yes (52) | Yes (50) | 9 |
| 10 | M | 65 | 36.9 | Yes | Yes (55) | Yes (15) | 11 |
| 11 | M | 81 | 27.1 | No | Yes (24) | No | 14 |
| 12 | F | 64 | 47.7 | Yes | Yes (59) | No | 24 |
| 13 | F | 69 | 34.1 | Yes | No | No | 49 |
| 14 | M | 64 | 34.3 | Yes | Yes (62) | No | 23 |
| 15 | F | 83 | 23.8 | No | No | No | 7 |
| 16 | F | 63 | 49.2 | Yes | Yes (34) | No | 29 |
| 17 | M | 57 | 49.0 | No | Yes (18) | No | 7 |
| 18 | M | 48 | 38.2 | Yes | Yes (3) | Yes (9) | 19 |
| 19 | F | 50 | 33.6 | Yes | No | No | 19 |
| 20 | M | 43 | >77.2 | Yes | Yes (84) | No | 31 |
| 21 | M | 46 | 29.3 | No | No | No | 9 |
| 22 | M | 69 | 24.4 | No | No | No | 46 |
| 23 | M | 67 | 23.5 | Yes | Yes (77) | No | 7 |
| 24 | F | 59 | 30.5 | Yes | No | No | 20 |

* Euthyroidism defined as both free thyroxine and thyroid-stimulating hormone are within normal range

(15 [IQR, 10-33] weeks vs 20 [11-31] weeks; P=0.67). All the patients had a benign disease course and there was no fatality. Potassium perchlorate, lithium, or thyroidectomy were not resorted for any patient. Interestingly, six patients (Nos. 4, 12, 16, 17, 21, 24) had subsequent chronic hypothyroidism treated with long-term thyroxine replacement and one patient (No. 11) developed chronic hypothyroidism when amiodarone was re-administered 2 years after AIT remission.

### Clinical features and management of patients with amiodarone-induced hypothyroidism

All the patients were diagnosed in an out-patient setting. No classical symptoms and signs of hypothyroidism were documented. Baseline anti-microsomal and anti-thyroglobulin antibodies were not checked in all cases, but were positive in 10 (29%) of the 34 patients who had the test performed when AIH was diagnosed biochemically.

Of the 87 patients with AIH, 70 (80%) received thyroxine replacement and amiodarone was discontinued in 36 (41%). Seventeen (47%) of the 36 patients were weaned off thyroxine replacement after amiodarone cessation. There was no fatality.

## Discussion

The reported frequency of AIT varies from 2 to 24%, with overall rate ranging from 1 to 23%. Corresponding reported AIH frequencies varied from 1 to 32%.[2] These wide reported ranges may be due to differences in iodine intake, gender, definition of thyroid dysfunction and the presence of underlying autoimmune thyroid diseases. While amiodarone is commonly used because of its all round anti-arrhythmic properties, the extent and severity of its adverse effect on thyroid function have been infrequently studied in our community.

The rate of AIH encountered in our relatively old cohort was 22%, which was comparable to rates encountered in areas of sufficient iodine intake.[2] However, when we refined our definition of AIH to include patients with TSH levels of higher than 10 mIU/L and suppressed $FT_4/TT_4$, the rate was 12%. By

contrast, about 19% of our patients had persistent subclinical hypothyroidism with normal $FT_4/TT_4$ and elevated TSH levels (≥4 mIU/L). The possibility of an acute physiological effect of amiodarone on the thyroid gland was minimised by excluding patients with abnormal thyroid function test results within 3 months of starting the treatment.[4] The rate of AIT was 6%, which was slightly higher than that encountered in areas of sufficient iodine intake but lower than in areas with moderate-to-low iodine intake.[2] We believe the rate is likely to be underestimated because amiodarone might have been discontinued before the study period due to thyroid dysfunction. Another local study reported a higher rate of AIT (16%), which may have been due to differences in the definition of AIT (defined as elevated $FT_4/TT_4$ and suppressed rather than undetectable TSH). Patients with subclinical hyperthyroidism or non-thyroidal illness may have been classified as AIT in their study. In contrast, comparable rate of AIH was found in both studies (22% vs 21%).[5]

Similar to previous studies,[6,7] the occurrence of AIH in our study was earlier than AIT. According to a long-term prospective study,[7] AIH typically occurs after 6 to 12 months of treatment with amiodarone and rarely later than 1 year. The late occurrence of AIH in some of our cases was likely due to a late diagnosis, as thyroid function was not monitored regularly. Depending on the type of AIT, it can occur early or after many years of amiodarone treatment.[7]

Baseline serum TSH level was found to be the most important predictor for AIH, as in another study.[8] Patients with baseline TSH level of higher than 4 mIU/L had a 4.7-fold increase in the risk of developing AIH. This may be related to underlying autoimmune thyroid disease or limited thyroid reserve due to previous damage. Baseline anti-thyroid antibodies, not checked in most of our cases, have also been shown to confer a 7.3-fold risk of developing AIH.[6] Moreover, the presence of anti-thyroid antibodies may lead to persistent hypothyroidism even after discontinuing amiodarone in AIH patients.[9] In our study, about half (17 of 36) of the patients who developed AIH were weaned off thyroxine replacement upon amiodarone discontinuation. As suggested in recent reviews,[2,10] it therefore seems advisable to check baseline anti-thyroid antibodies before amiodarone administration. Contrary to other studies,[6,11] other reported risk factors such as female gender and cumulative amiodarone dosage were not predictive for AIH in our study. The clinical presentation of AIH was not studied in details in this study. However, no classical hypothyroid symptoms such as cold intolerance, weight gain, and hoarseness of voice were mentioned in the records and all patients with AIH were diagnosed based on routine thyroid function test screening.

As in another local study,[5] our study revealed that younger age was a risk factor for developing AIT. An explanation for this observation is difficult, as unlike others we did not classify AIT types by colour-flow Doppler sonography of the thyroid, 24-hour radioactive iodine uptake study, or serum interleukin-6 levels.[2] Unlike a previous report,[8] male gender was not a risk factor in this study. It has been suggested that serum free $T_3$ ($FT_3$) is a more specific marker for AIT, as serum $T_4$ level can be high due to the physiological effect of amiodarone on type 1 5′-deiodinase activity and the combination of elevated $FT_4$ and suppressed TSH can rarely occur in severe non-thyroidal illness.[10] On the other hand, $FT_3$ may not be sensitive enough to detect AIT. Free $T_3$ was not routinely measured in our study. Nevertheless, only three out of 24 patients with AIT were hospitalised and their $FT_4$ levels were grossly elevated and TSH levels were undetectable. As in most studies, classical thyrotoxicosis symptoms (palpitations and tremor) were absent in all but two patients, possibly due to the anti-adrenergic action of amiodarone and its impairment of $T_4$ conversion to $T_3$.[10] The two exceptional patients were hospitalised with increasing symptoms of atrial fibrillation and heart failure that were recognised as heralding signs of AIT.[2] Another possible clue of AIT was significant weight loss (encountered in 42% of our AIT patients). In patients receiving warfarin, an additional clue indicative of AIT was an unexplained increase in INR; an exaggerated decline in functional clotting factors II and VII in response to warfarin in thyrotoxicosis is a possible mechanism.[12] This, however, may be difficult to distinguish from the well-known gradually evolving interaction between amiodarone and warfarin. Five out of eight patients in our study had a sudden increase in INR when AIT was diagnosed biochemically.

Even though management of AIT is said to be notoriously difficult due to a high iodine load, in our patients the disease course was relatively benign. Ten patients underwent spontaneous remission without any treatment, and in five this occurred despite continuation of amiodarone. These were milder cases of AIT (with lower $FT_4$ levels: mean, 29.0 pmol/L) and similar findings have been observed by others.[13] The efficacy of various treatment modalities is difficult to compare as more aggressive treatments were used in severe cases with higher $FT_4$ levels. Whether to discontinue amiodarone is still controversial as paradoxically it may protect the heart from thyroid hormone excess by rendering cardiac tissue hypothyroid. Withdrawal of the drug may precipitate dysrhythmias, especially as most other alternative anti-arrhythmics are seldom as effective.[10] All our patients showed good response to anti-thyroid medications with or without steroids, including one who presented with a very high $FT_4$ level (>77 pmol/L). However, neither treatment seemed to shorten the time to remission, probably due to their selective

use in severe cases. The fact that six of our patients developed post-AIT hypothyroidism, suggests type 2 AIT with destructive thyroiditis as the underlying mechanism. Similar to another study,[14] one of our patients with AIT developed AIH upon re-treatment with amiodarone 2 years after AIT.

Although our study entailed a large cohort, its retrospective design provided only a rough idea of the occurrence of amiodarone-induced thyroid dysfunction in our locality. Incidence rates within pre-defined timeframes as determined by prospectively designed studies provide more reliable data. Lack of a control group also limited the comparison of thyroid dysfunction in our relatively old cohort and their age-matched counterparts with non-amiodarone–induced thyroid dysfunction, particularly hypothyroidism. A considerable number of patients (n=72) were excluded due to incomplete thyroid function monitoring, which might have resulted in inaccurate estimation of rates. Lastly, there was incomplete data capture, inadequate and improper laboratory and radiological investigation for thyroid dysfunction (infrequent testing for $FT_3$ and anti-thyroid antibodies, as well as insufficiently detailed clinical and biochemical assessment) in several patients in our series.

## Conclusion

Amiodarone-induced thyroid dysfunction is not uncommon in our relatively old population. Younger patients and those with elevated pre-treatment TSH level are at increased risk of developing AIT and AIH, respectively. Classical symptoms and signs of thyroid dysfunction are often absent, making regular biochemical monitoring of thyroid function mandatory. Amiodarone-induced thyrotoxicosis may be heralded by a worsening of underlying arrhythmias or cardiac disorders, significant weight loss, and in patients taking warfarin with increased INR. Nevertheless, most patients with AIT and AIH have a benign disease course. Patients with AIT show good response to anti-thyroid medication with or without steroids.

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