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Hyperthyroïdies induites par amiodarone : mise au point et revue de littérature

Issues in amiodarone-induced thyrotoxicosis: Update and review of the literature

Authors : Dr. Salwan Maqdasy^{1,2*}, Dr. Thomas Benichou¹, Mrs. Sarah Dallel¹, Dr. Béatrice Roche¹, Dr. Françoise Desbiez¹, Dr. Nathanaëlle Montanier¹, Dr. Marie Batisse-Lignier^{1,2}, Pr. Igor Tauveron^{1,2}

1: CHU Clermont-Ferrand, Service d'endocrinologie, diabétologie et maladies métaboliques, F-63003 Clermont-Ferrand, France.

2: Laboratoire GReD: UMR Université Clermont Auvergne-CNRS 6293, INSERM U1103, BP 10448, 63177 AUBIERE, France.

***Correspondance :** Dr. Salwan Maqdasy

Service d'endocrinologie, diabétologie, maladies métaboliques

CHU Gabriel Montpied

58, rue Montalembert

63000 Clermont-Ferrand

Tél : + (33) 4 73 75 15 29

Fax : + (33) 4 73 75 15 32

E-mail : smaqdasy@chu-clermontferrand.fr

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Résumé

L'hyperthyroïdie induite par l'amiodarone est une thyroïdite iatrogène liée à la surcharge iodée et/ou à la toxicité directe induite par l'amiodarone. La prise en charge de l'HIA représente un enjeu majeur du fait de sa résistance relative au(x) traitement(s) antithyroïdien(s) et du risque accru de récurrence des troubles de rythme. La détermination du type d'HIA est utile non seulement pour la décision thérapeutique, mais également pour permettre le maintien ou l'arrêt de l'amiodarone et pour estimer le risque de récurrence d'HIA. Cette revue a pour but de détailler les particularités liées à l'HIA et le risque de récurrence d'hyperthyroïdie liée au maintien ou à la reprise de l'amiodarone. Une HIA de type 1 « surcharge iodée sur une thyroïde pathologique » nécessite l'arrêt de l'amiodarone lors de la prise en charge de cette hyperthyroïdie. De plus, la reprise de l'amiodarone présente un risque accru d'un deuxième épisode, motivant un traitement ablatif après le premier épisode. Au contraire, dans les cas d'HIA de type 2 « une thyroïdite aiguë survenant sur une thyroïde saine », l'amiodarone pourrait être maintenue ou pourrait être reprise (si interrompu) avec une influence modeste sur le pronostic d'HIA et un risque de récurrence moins important.

Mots clés : Amiodarone, Hyperthyroïdie induite par l'amiodarone, Reprise d'amiodarone, Récurrence

Abstract

Amiodarone, a benzofuranic iodine-rich pan-anti-arrhythmic drug, induces amiodarone-induced thyrotoxicosis (AIT) in 7-15% of patients. AIT is a major issue due to its typical severity and resistance to anti-thyroid measures, and to its negative impact on cardiac status. Classically, AIT is either an iodine-induced thyrotoxicosis in patients with abnormal thyroid (type 1), or due to acute thyroiditis in a "healthy" thyroid (type 2). Determination of the type of AIT is a diagnostic *dilemma*, as characteristics of both types may be present in some patients. As it is the main etiological factor in AIT, it is recommended that amiodarone treatment should be stopped; however, it may be the only anti-arrhythmic option, needing to be either continued or re-introduced to improve cardiovascular survival. Recently, a few studies demonstrated that amiodarone could be continued or re-introduced in patients with history of type-2 AIT. However, in the other patients, it is recommended that amiodarone treatment be interrupted, to improve response to thioamides and to alleviate the risk of AIT recurrence. In such patients, thyroidectomy is recommended once AIT is under control, allowing safe re-introduction of amiodarone.

Keywords: Amiodarone, Amiodarone-induced thyrotoxicosis, Amiodarone re-introduction, Recurrence

Introduction

Amiodarone is largely preferred to other anti-arrhythmic drugs in patients with refractory tachyarrhythmia, especially when associated with myocardial infarction and/or heart failure [1–3]. However, amiodarone frequently induces thyroid dysfunction originating either from excessive iodine overload related to its biochemical structure, or due to its direct cytotoxicity on the thyrocytes [4]. These effects are correlated with the duration and the cumulative dose of amiodarone [5].

The type of thyroid dysfunction is dependent on the usual iodine intake of the patient. Patients with a sufficient iodine intake are mainly exposed to hypothyroidism after amiodarone exposure, while amiodarone-induced thyrotoxicosis (AIT) is more frequent in patients living in zones of iodine deficiency [6,7]. In Europe, amiodarone-induced thyroid dysfunction affects 3 over 100 treated patients per year, and AIT is the major form [8].

In contrary to amiodarone-induced hypothyroidism, management of AIT remains a major challenge. Such hyperthyroidism is frequently resistant to anti-thyroid drugs, usually increases the risk of relapse of tachyarrhythmia, and the morbidity and mortality in such patients [9,10].

To improve the efficacy of anti-thyroid treatment, amiodarone is preferred to be stopped during the management of AIT [11,12]. However, resistant tachyarrhythmia, especially in patients with congenital heart diseases or heart failure, amiodarone stands out as the only option and needs to be continued or re-introduced. These decisions are considered as a major *dilemma* in the management of AIT, and could delay the response to anti-thyroid drugs, or could lead to AIT relapse [12–15]. Some recent studies tried to evaluate the impact of amiodarone continuation on the response to anti-thyroid drugs [8,16–18].

This review highlights the recent topics in the management and the prognosis of AIT, especially the risk of AIT recurrence due to amiodarone continuation or re-introduction.

1. Amiodarone-induced thyrotoxicosis (AIT) at a glance

AIT affects about 7 to 15% of patients treated with amiodarone [10]. In Europe, the risk is elevated due to iodine deficiency (12 to 15%), while it is lower in North America (2 to 10%) [19]. Thus, AIT represents 75% and 35% of amiodarone-induced thyroid dysfunction in Europe and USA respectively [6,7].

AIT varies from other types of hyperthyroidism in that it is usually severe, abrupt, and resistant to anti-thyroid treatment. Furthermore, in this type of hyperthyroidism, we are usually dealing with elderly fragile male patients, with pre-existing cardiovascular diseases [11,20,21]. Hyperthyroidism can appear at any moment after amiodarone introduction; it could be early (a month after amiodarone introduction) or late (many years) [15,21,22]. As the drug has a long half-life and is stored in the adipose tissue, AIT can occur even many months after amiodarone interruption [22]. Besides, the clinical manifestations of hyperthyroidism are frequently nonspecific and can be similar to other types of thyrotoxicosis.

The impact of thyroid hormones on the cardiovascular tissue is well known; they act on both systolic and diastolic function leading to tachyarrhythmia and heart failure [23]. AIT increases cardiovascular morbidity and mortality [9,10,20]. Conen *et al.* demonstrated that 46% of patients suffered from recurrent arrhythmia. The mortality was high (19% of patients) in this study and mainly correlated to altered ejection fraction [9]. Yiu *et al.* have also reported cardiac complications in 30% of patients with AIT, and a higher risk of late-onset complications [10].

2. AIT types and management

AIT cases were first described in 1973 [24]. Since then, many studies helped to describe the pathophysiology, management and the prognosis of AIT. Based on the concepts of

pathophysiology, Bartalena et *al.* in 1994, classified AIT into two major categories. AIT is either iodine-induced in an abnormal thyroid gland (type 1), or an inflammatory thyroiditis (type 2). These criteria include thyroid morphology and vascularity on ultrasound study, and radioactive iodine uptake on scintiscan. In contrary to the biological diagnosis of hyperthyroidism, determination of AIT type remains difficult and confounding [12,25]. Even though, this distinction is primordial in the determination of the type of anti-thyroid treatment, in the decision of continuation or interruption of amiodarone, and in the estimation of the risk of AIT recurrence. The major characteristics of types of AIT are summarized in Table 1.

Type 1 AIT is the predominant type in patients with chronic iodine deficiency, who have a pre-existing nodular goiter or Grave's disease. Iodine overload leads to follicular hyperactivity in patients. Although previously more frequent than type 2, its prevalence is declining thanks to improved iodine supply in the last decades and privileged screening of pre-existing biological and morphological thyroid dysfunction before amiodarone initiation [21].

Type 1 AIT appears usually early after amiodarone exposure (3 to 20 months after exposure) [15,21,22,26]. It is characterized by a normal or elevated blood flow on color Doppler reflecting a functional thyroid tissue [27,28]. Furthermore, thyroid tissue fixes either on 24-hour ^{123}I -scan, or on $^{99\text{m}}\text{Tc}$ -SestaMIBI radio-isotope scan despite iodine overload (Table 1) [29–32].

Unfortunately, despite amiodarone interruption, spontaneous regression of hyperthyroidism is extremely rare, thus anti-thyroid treatment by thioamides is mandatory in most cases. Usually, iodine overload blocks the effect of thioamides and Potassium or Sodium perchlorate are needed to be added to thioamides to improve their efficacy by removing iodine from thyroid tissue [33]. Therefore, thyroid function tests need few months in order to be normalized.

In contrary, type 2 AIT is a destructive thyroiditis induced by drug toxicity. This type of AIT appears in patients with an apparently normal thyroid morphology, and is due to massive release of thyroid hormones due to cellular destruction, a mechanism similar to sub-acute thyroiditis. Bogazzi *et al.* in 2007 demonstrated an increased prevalence of this type in the last decades in comparison with type I AIT (89% of new cases of AIT are type 2) [21]. The main characteristics of type 2 AIT are summarized in table 1. This type of AIT is usually less severe and could spontaneously resolve in 20% of cases [16,34]. If necessary, glucocorticoids (prednisone 0.5 mg/kg/day) are the only effective drugs and response to treatment is more rapid than type 1 AIT [26,35,36].

Sometimes, an association of thioamides, perchlorate and glucocorticoids is necessary to control severe hyperthyroidism [37,38]. Failure of either anti-thyroid strategy indicates that such patients suffer from a “mixed type” AIT [28,39]. A study showed that only 58% of type 2 AIT and 36% of type 1 AIT respond to glucocorticoids and thioamides respectively [39]. Such patients could have a nodular goiter with an extinctive fixation on scintigraphy. Indeed, some studies abandoned this classification to minimize bias related to this distinction [8,20,40]. AIT management strategies are summarized in Fig.1.

Beyond AIT types and their anti-thyroid strategies of management, amiodarone is usually recommended to be interrupted during the management of AIT [6,7,41]. However, this decision could be impossible in the absence of other anti-arrhythmic options. Thus, the drug is either maintained or re-introduced, rendering the management of AIT more challenging and increasing the risk of AIT recurrence. Such particular issues are discussed separately.

3. Pending issues in AIT management

3.1. Can AIT be prevented?

AIT could be a late complication of amiodarone and revealed after many years [21,26,28,34]. Its prevention is primordial in patients with a severe underlying heart disease. In North

America, improved iodine supplementation reduced the risk of AIT and favored amiodarone-induced hypothyroidism. Moreover, patient selection led to reduce the risk of type 1 AIT; amiodarone could be privileged in patients with a normal thyroid [21]. A baseline TSH, anti-thyroid antibodies and ultrasound study are thus necessary before starting amiodarone. Otherwise, an ablative strategy with radioactive iodine could be considered before amiodarone introduction. Unfortunately, amiodarone introduction is usually an urgent decision and thyroid preventive strategies are not considered. In such patients, thyroid investigations should be considered early after amiodarone introduction to adopt a follow up or ablative strategy.

3.2. How should patients on amiodarone treatment be followed up?

To-date, there is no consensus statement about the follow up of patients under amiodarone treatment. Long term regular follow up of TSH every 6 months is reasonable. Indeed, “subclinical” AIT is observed in about 1/3 of patients before the diagnosis of hyperthyroidism [42]. American Thyroid Association and American Association of clinical Endocrinologists recommend evaluation of thyroid function tests before, 3 months after amiodarone initiation and every 3 to 6 months [43]. Indeed, studies confirmed that amiodarone-induced thyroid dysfunction affect about 7 to 15 % of patients treated with amiodarone [6,7,44]. Furthermore, AIT could be a late complication [18,21,26,28]. Consequently, regular long term follow up should be maintained.

3.3. Is total thyroidectomy indicated in the management of AIT?

In severe AIT resisting to combined therapeutic strategies (thioamides, perchlorate and glucocorticoids) or in cases of drug contraindications, total thyroidectomy is recommended (low level of evidence) [6,43]. Surgery controls hyperthyroidism and consequently improves the cardiac status of patients with known severe left ventricular dysfunction [45]. Nevertheless, surgery and general anesthesia in such patients are highly hazardous with a

potential risk of « thyroid storm » and tachyarrhythmia during surgery [20,46]. Few case studies of operated patients despite hyperthyroidism did not show any over-risk of morbidity or mortality [45,47–49]. By contrast, Mayo Clinic series of 34 patients demonstrated an elevated morbidity and mortality (29% and 9% of patients respectively) [50]. Surgery could be reserved to patients suffering from severe type 1 AIT and resisting to anti-thyroid drugs, especially when amiodarone should be continued. Experienced team of anesthetists is mandatory. If possible, thyroid hormones should be normalized before surgery to minimize the peri-operative complications [45,51,52]. Some teams suggested plasmapheresis to remove excessive thyroid hormones and restore euthyroid status shortly before surgery [51,53–55]. Nevertheless, such experience in AIT is extremely limited and the efficacy is debated [53,56].

3.4. Can radioactive iodine be considered in the management of AIT?

In AIT, an ablative treatment by radioactive iodine ^{131}I , after stimulation by recombinant thyrotropin alfa TSH (Thyrogen[®]), has been tried [57,58]. The efficacy of this option is questionable due to thyroid saturation with iodine, minimizing ^{131}I capture. Although Thyrogen[®] increased iodine capture, this option was associated with thyroid storm and new episodes of tachyarrhythmia, limiting the utility of this method [58].

3.5. Should amiodarone be stopped during an AIT episode?

Severe, resistant tachyarrhythmia, or tachyarrhythmia in patients with congenital heart diseases would need either amiodarone continuation or its re-introduction if interrupted despite the risk of AIT aggravation or recurrence.

One of the arguments in favor of amiodarone continuation is its lipo-solubility. The drug is accumulated within the adipose tissue and should be interrupted for at least 6 months to be eliminated [12]. Thus, one can suggest that its interruption or continuation might not influence AIT management. In this direction, the onset of AIT could be after amiodarone interruption; type 1 and 2 AIT occurred in 5% and 20% of patients respectively while

amiodarone was previously stopped [22]. Despite some spontaneous remissions of type 2 AIT despite amiodarone continuation [59], an Italian study demonstrated that amiodarone continuation delays the response to glucocorticoids and consequently AIT remission [18]. In another study including type 2 AIT, amiodarone continuation was responsible for AIT recurrence in 3 patients over 22 included [26]. Furthermore, Osman *et al.* reported AIT recurrence in 5 of 10 patients who continued amiodarone [16]. ATA recommendations take in consideration the cardiologists' decision, whether an alternative to amiodarone is possible [43]. To-date, amiodarone interruption in patients with type 2 AIT is not compulsory [6,7]. Meanwhile, its interruption in type 1 AIT is recommended to improve the response to thioamides.

3.6. Should thyroid be definitely ablated after an episode of AIT?

Ablation after an AIT episode is controversial. Of thyroid specialists, only 34 and 8% recommend an ablative treatment after type 1 and 2 AIT respectively [6,7]. Indeed, the risk of AIT recurrence was not well known and such recommendations were based on expert opinions. Theoretically, type 2 AIT recurrence is supposed to be low and hypothyroidism could be the fate of this type, and ablative therapy is not indicated [15,60,61]. Though, type 2 AIT recurrence is reported and could be either spontaneous or after amiodarone re-introduction [15,18,22]. We have published a retrospective study revealing the risk of AIT recurrence after amiodarone re-introduction. The risk is relatively low for type 2 AIT and logically elevated in patients with a history of type 1 AIT [15]. We consider that thyroid ablation is crucial in the latter group, especially when hyperthyroidism was resistant to anti-thyroid drugs or when amiodarone is crucial and will be potentially re-introduced. Meanwhile, ablation is optional in patients with type 2 AIT.

Surgery is the option of choice and usually successful in patients with normalized thyroid hormones. If patients cannot undergo surgery, ¹³¹I could be suggested. These modalities

prevent AIT recurrence and give the opportunity to re-introduce amiodarone if needed [13,14].

3.7. Can amiodarone be re-introduced after an episode of AIT?

Amiodarone reintroduction is debated to avoid a second episode of AIT [6,7]. Amiodarone, *per se*, remains one of the most effective anti-arrhythmic [2]. Amiodarone re-introduction is considered usually in patients with either congenital, ischemic heart diseases, or with heart failure, when the other anti-arrhythmic options fail [15]. But, AIT is a dangerous situation and a second episode would be poorly tolerated [9,10].

As we discussed previously, thyroid ablation before amiodarone re-uptake could be preventive [13,62]. Indeed, 2/3 of specialists recommend thyroid ablation before amiodarone re-introduction in patients with a previous history of type 1 AIT. Hence, amiodarone re-introduction will be without challenges [6,7,18,26]. Unfortunately, not all the patients are prepared and amiodarone could be re-introduced urgently in intensive care units. We studied in our center the prognostic influence of amiodarone re-introduction in a small cohort of patients. Indeed, amiodarone re-introduction was necessary in 30% of patients who previously suffered from an AIT, and only 4% had an ablative therapy prior to this decision [15].

3.8. Can the risk of AIT recurrence be estimated?

The risk of AIT recurrence is not well known. In our study, 14 patients (30%) over 46 suffered from AIT recurrence after amiodarone re-introduction. The risk is maximal in patients who previously suffered from type 1 AIT. In such patients, 70% will suffer from a second episode of AIT if no ablative procedure is considered. Indeed, AIT recurrence could occur early after amiodarone re-introduction (within the first two months of treatment). On the other side, 20% of type 2 AIT experienced a second episode of AIT [15]. About 50% of them, especially those with anti-thyroperoxidase antibodies, will suffer from hypothyroidism.

These results confirm the importance of AIT typing to determine the prognosis of thyroid function evolution.

Historically, thioamides are not recommended in the prevention of AIT [6,7]. Nevertheless, in our study, small doses of thioamides introduced in conjunction with amiodarone re-introduction were effective to prevent AIT recurrence. Only 18% of patients with a history of type 1 AIT suffered from a second episode when thioamides were used as a preventive measure. Besides, they had no efficacy in patients with type 2 AIT history [15]. Therefore, thioamides could be considered in patients with type 1 AIT history, in whom amiodarone should be re-introduced urgently. Thioamides will give the opportunity for such patients to remain in euthyroid status and to be prepared for surgery. Such option could be also considered for patients who cannot be operated. We summarize the optimal attitude in cases of amiodarone reintroduction in Fig.2.

Conclusions

Amiodarone-induced thyroid dysfunction is frequent and motivates regular thyroid hormone monitoring. Thyroid “workup” is necessary before amiodarone prescription to minimize type 1 AIT risk. AIT classification is useful to determine the management strategy. Furthermore, it predicts the response to the anti-thyroid therapeutic strategy, simplifies the decision of amiodarone continuation-interruption, and estimates the risk of AIT recurrence if amiodarone is re-introduced. Amiodarone could be continued or re-introduced (if interrupted) only in patients with type 2 AIT. To prevent AIT recurrence, especially when AIT recurrence risk is high (AIT type 1), thyroid ablation is recommended prior to amiodarone re-uptake. If impossible or amiodarone re-introduction is urgent, low doses of thioamides could be suggested in such patients while pending for surgery.

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Figures and tables

Table 1: Characteristics of both types of amiodarone-induced thyrotoxicosis.

Figure 1: Algorithm for management of amiodarone-induced thyrotoxicosis.

Figure 2: Preventive strategies if amiodarone should be re-introduced in patients with a history of AIT.

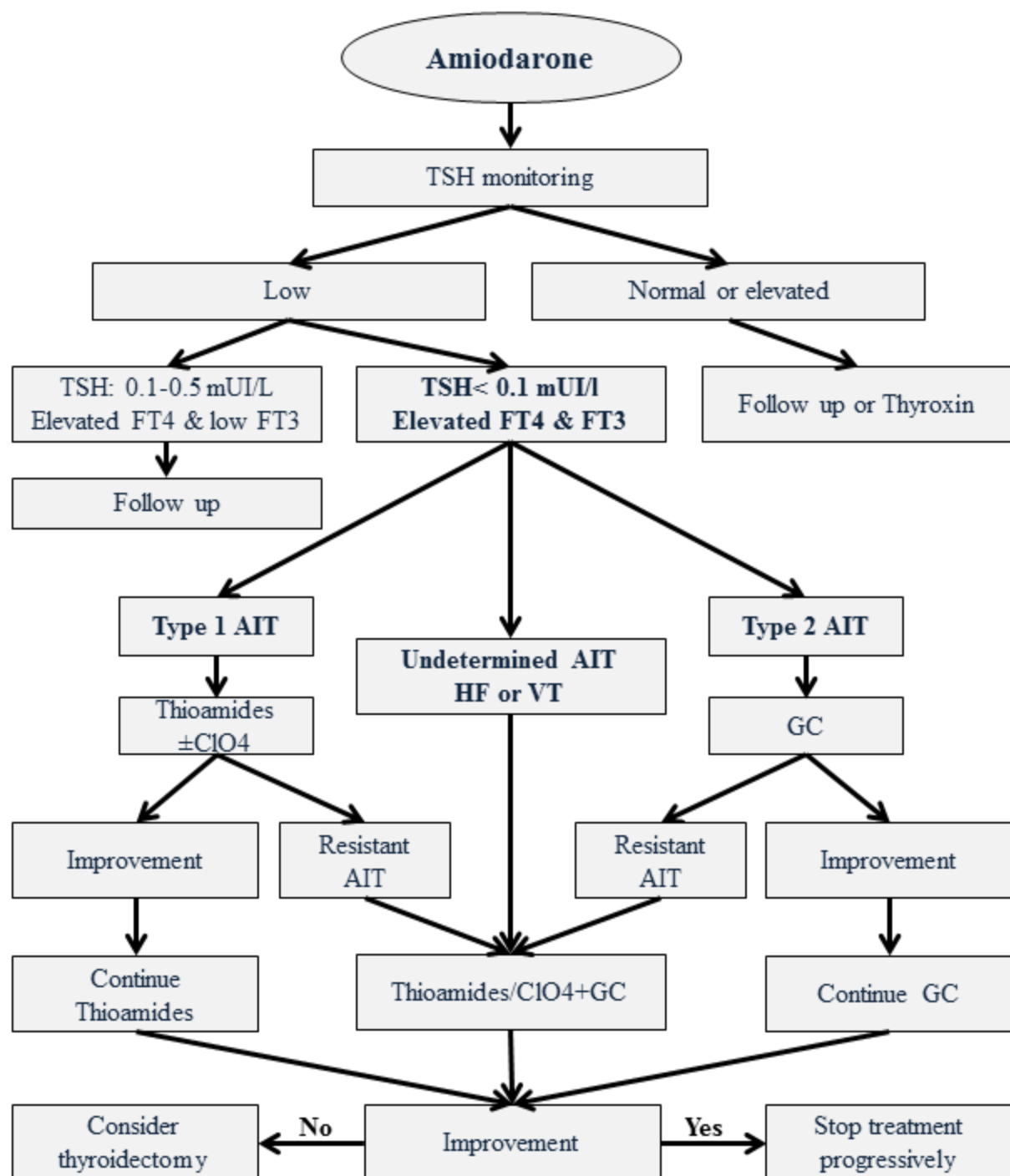


Figure 1 : Characteristics of both types of amiodarone-induced thyrotoxicosis.

AIT: Amiodarone-induced thyrotoxicosis; HF : Heart failure; VT: Ventricular tachyarrhythmia; ClO₄: Perchlorate; GC: Glucocorticoids.

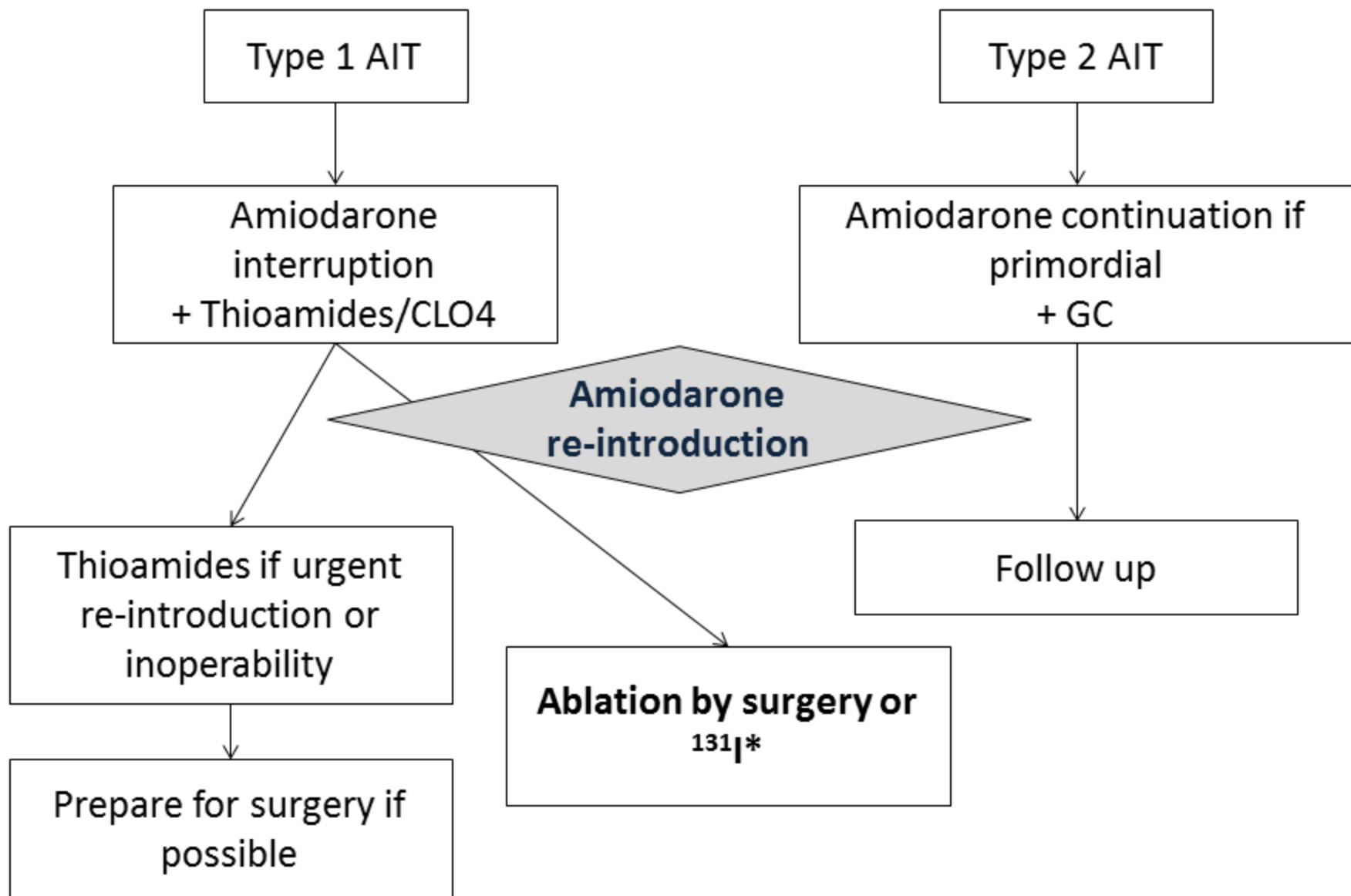


Figure 2: Preventive strategies if amiodarone should be re-introduced in patients with a history of AIT.

* ^{131}I ablative treatment is possible when amiodarone is interrupted for more than 6 months (normal inorganic iodide excretion in the urine/tracer capture on ^{123}I or $^{99\text{m}}\text{Tc}$ -Scan).

GC: Glucocorticoids; CLO4: Perchlorate

Table 1: Characteristics of both types of amiodarone-induced thyrotoxicosis.

	Type 1	Type 2
Pre-existing thyroid disease	Yes	No
Pathophysiology	Iodine overload	Inflammation
Ultrasound study	Goiter/nodule(s) Usually hyperechoic	Normal Hypo echogenic
Color flow Doppler	Increased vascularity Accelerated systolic rate	Reduced vascularity Normal systolic flow
Radio iodine uptake (I^{123}-Scan)	Normal or reduced	Absent
SestaMIBI-Scan tracer uptake	normal	absent
Treatment	Thioamides/CIO4	Glucocorticoids