Trends in Cardiovascular Medicine 29 (2019) 285–295

Contents lists available at ScienceDirect

Trends in Cardiovascular Medicine

journal homepage: www.elsevier.com/locate/tcm

Amiodarone and thyroid physiology, pathophysiology, diagnosis and management☆

Richard G. Trohman, MD, MBA*, Parikshit S. Sharma, MD, MPH, Elizabeth A. McAninch, MD, Antonio C. Bianco, MD, PhD

Divisions of Cardiology and Endocrinology, Diabetes and Metabolism, Department of Internal Medicine, Rush University Medical Center, Chicago, IL, United States

ARTICLE INFO

Keywords:
Amiodarone
Adverse effects
Hypothyroidism
Myxedema
Hyperthyroidism
Thyroid storm
Atrial fibrillation
Ventricular arrhythmia
Electrical storm

ABSTRACT

Although amiodarone is considered the most effective antiarrhythmic agent, its use is limited by a wide variety of potential toxicities. The purpose of this review is to provide a comprehensive "bench to bedside" overview of the ways amiodarone influences thyroid function. We performed a systematic search of MEDLINE to identify peer-reviewed clinical trials, randomized controlled trials, meta-analyses, and other clinically relevant studies. The search was limited to English-language reports published between 1950 and 2017. Amiodarone was searched using the terms *adverse effects, hypothyroidism, myxedema, hyperthyroidism, thyroid storm, atrial fibrillation, ventricular arrhythmia, and electrical storm*. Google and Google scholar as well as bibliographies of identified articles were reviewed for additional references. We included 163 germane references in this review. Because amiodarone is one of the most frequently prescribed antiarrhythmic drugs in the United States, the mechanistic, diagnostic and therapeutic information provided is relevant for practicing clinicians in a wide range of medical specialties.

Introduction

Amiodarone was originally synthesized in 1962 in the pharmacological laboratory of Labaz in Belgium as an antianginal agent [1,2]. It was widely prescribed for angina in Europe and by chance found to suppress arrhythmias. Argentine investigators began using amiodarone to treat resistant arrhythmias in the 1970s [1,3,4]. United States physicians initially obtained amiodarone from Canada [5], Argentina [4,6] and Europe [1]. Under threat of non-shipment from Europe, the US Food and Drug Administration approved amiodarone in 1985 for use in life-threatening ventricular tachyarrythmias when other drugs were ineffective or poorly tolerated [1,7].

Intravenously administered amiodarone significantly improves the number of patients presenting with out-of-hospital cardiac arrests that make it to the hospital and has been shown to be superior to intravenous lidocaine in patients with out-of-hospital and in-hospital cardiac arrest [2,8,9]. The combination of amiodarone and beta blockade is the treatment of choice for electrical storm (VT or VF occurring 2 or more times in 24 h, usually requiring electrical cardioversion or defibrillation) [1,10]. Intravenous amiodarone may also be used to terminate stable monomorphic VT although some evidence suggests that procainamide may be more effective [11,12]. The 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death assigns amiodarone a Class IIb indication for acute management of hemodynamically stable VT [12].

Although implantable cardioverter defibrillators (ICDs) are superior to amiodarone in reducing total mortality in patients at risk for sudden cardiac death (amiodarone's effects are neutral), frequent shocks result in physical and emotional trauma and may increase the risk of death in some patients [1,13–15]. Oral amiodarone reduces shocks from ICDs and is the most commonly prescribed antiarrhythmic drug among ICD recipients at hospital discharge [16].

Although not approved by the Food and Drug Administration for this indication, amiodarone is also the most commonly prescribed antiarrhythmic drug for atrial fibrillation (AF) [17]. AF and atrial flutter occur in 40–60% of patients after cardiac surgery. A meta-analysis provided evidence that amiodarone prophylaxis decreases the occurrence of AF, ventricular tacyarrhythmias, stroke and length of stay after cardiac surgery [18]. While the data for perioperative amiodarone in cardiac surgery is compelling; however, incremental benefit beyond β-blockade alone remains un-

☆ The authors report no relevant conflicts of interest.

* Corresponding author at: Electrophysiology, Arrhythmia and Pacemaker Services Rush University Medical Center 1653 W. Congress Parkway, Suite 301 Kellogg, Chicago, IL 60612, United States.

E-mail address: rtrohman@rush.edu (R.G. Trohman).

https://doi.org/10.1016/j.tcm.2018.09.005
1050-1738/

Table 1
Clinical use of amiodarone.

Rhythm	Clinical scenario	Efficacy/indications
AF	Chemical cardioversion	Limited efficacy
AF	Maintain sinus rhythm	More effective than other antiarrhythmic drugs
AF	Rate control	IV indicated for acute rate control when other measures are unsuccessful or contraindicated
		Oral amiodarone is not appropriate first-line therapy for chronic rate control
AF	AF and CHF	Does not exacerbate CHF; appropriate first-line AF therapy only in symptomatic patients with left ventricular dysfunction and CHF
AF	AF and Wolff–Parkinson–White Syndrome	Use of intravenous amiodarone is limited by its relatively slow onset of action
		Intravenous amiodarone may enhance conduction over the accessory pathway and increase the risk of life-threatening ventricular arrhythmia [161]
		Prevention with oral amiodarone may be considered when other options are exhausted
AF	AF and HCM	Amiodarone is viewed as the most effective antiarrhythmic drug for preventing AF recurrences
Atrial Flutter	Isthmus dependent	Ablation is more effective first-line treatment
Multifocal atrial tachycardia	Hypoxemia	Treating underlying cause preferable; may help restore sinus rhythm
PSVT	Recurrent	Catheter ablation or less toxic drugs are treatments of choice
VT	Hemodynamically stable	Intravenous amiodarone is useful in acute management
VT	Frequent ICD Shocks	Amiodarone plus β-blockers more effective than sotalol or β-blockers alone in prevention of shocks
VF	Cardiac Arrest	Intravenous amiodarone is more effective than lidocaine for out-of-hospital VF resistant to shocks and epinephrine.
VT/VF	Electrical storm	Patients who receive a combination of amiodarone and a β-blocker have the best outcomes
AF/Flutter	Perioperative cardiovascular	May decrease AF/flutter, ventricular tachyarrhythmias, stroke, and length of stay
Frequent ventricular ectopy	CRT	Suppression may facilitate biventricular pacing[a]

AF: atrial fibrillation.
VT: ventricular tachycardia.
VF: ventricular fibrillation.
PSVT: paroxysmal supraventricular tachycardia.
CHF: congestive heart failure.
HCM: hypertrophic cardiomyopathy.
ICD: implantable cardioverter defibrillator.
CRT: cardiac resynchronization therapy.
[a] Optimal response to CRT (the greatest reduction in mortality occurs when biventricular pacing is achieved in >98% of all ventricular beats).

clear [1]. Amiodarone is the most effective agent for long-term maintenance of sinus rhythm in patients with paroxysmal and persistent AF and is considered first line pharmacotherapy for patients with heart failure and symptomatic AF [1,2,19]. A recent multicenter randomized study demonstrated that catheter ablation of AF is superior to amiodarone in achieving freedom from AF at long-term follow-up as well as reducing unplanned hospitalization and mortality in patients with heart failure and persistent AF. Catheter ablation appears to be the treatment of choice for this patient group [20].

Thus, more than 50 years since amiodarone was developed and about 30 years from the date the US Food and Drug Administration approved its use, amiodarone is still considered the most effective antiarrhythmic drug (Table 1) and is one of the most frequently prescribed specific antiarrhythmic drugs in the United States [1,21]. Unfortunately, amiodarone has numerous side effects (Table 2) that may involve the skin, eyes, lungs, liver, central and peripheral nervous system.

The thyroid gland may also be adversely affected by amiodarone. The drug is an iodine-rich compound (37.3% of its molecular weight) [22] with some structural similarity to thyroid hormone. Even low dose oral therapy (200 mg daily) can elevate daily iodine intake by 50–100 times [23,24]. Older estimates have suggested that the overall incidence of amiodarone-induced thyroid dysfunction ranges from 2 to 24% [25,26]. More recent reviews of the literature noted that hypothyroidism occurs in 5–10% and hyperthyroidism afflicts approximately 0.9–10% of amiodarone recipients [1,27]. These differences may reflect the evolution of more conservative dosing regimens employed over time. A meta-analysis suggested that when lower amiodarone doses (152–330 mg daily) were used, the incidence of thyroid dysfunction was 3.7% [28].

Table 2
Amiodarone toxicity [1,162,163].

Adverse effect	Prevalence and/or annual incidence
Corneal microdeposits	> 90%
Optic neuropathy/neuritis	< 1%–2%
Hypothyroidism	5%–10%
Hyperthyroidism	0.9%–10%
Photosensitivity	25%–75%
Blue-gray skin discoloration	4%–9%
Pulmonary toxicity	1%–17%
Elevated liver enzyme levels	15%–30%
Hepatitis and cirrhosis	< 3%; 0.6%/yr.
Tremor and ataxia	3%–35%
Peripheral neuropathy	0.3%/yr.
Bradycardia and AV block	3%–5%
Torsades de Pointes	< 1%
Hypotension (IV formulation)	15–26%

Insomnia, memory disturbances and delirium have also been reported.

This treatise will focus on amiodarone-induced thyroid disease. A discussion of the drug's unique pharmacokinetics, diagnostic surveillance techniques, pathophysiology of thyroid involvement, treatment modalities and clinical outcomes are included.

Pharmacokinetics

The oral bioavailability of amiodarone varies between 22 and 86% (averages about 50%) [29]. Its large volume of distribution (66 L/kg) delays the onset of action (2 days to 3 weeks for oral therapy) and results in a long elimination half-life [1,30]. A 50% reduction in serum concentration is seen 3–10 days after cessation of chronic therapy and is followed by a longer terminal

half-life of 13–142 days as tissue stores slowly deplete [1,29,30]. While amiodarone accumulates in adipose tissue, liver, lung, muscle, and the thyroid gland, it is mostly metabolized by the hepatic cytochrome P4503A (CYP3A). Amiodarone's active metabolite N-desethylamiodarone (DEA),) has an even longer half-life. Most patients will have approximately equivalent concentrations of amiodarone and DEA at steady state, although DEA levels may exceed those of the parent drug [29,31,32]. The "therapeutic" serum range for amiodarone and DEA is 0.5–2.5 μg/mL, respectively [1] however, serum levels do not correlate well with efficacy or adverse effects [1,29,32].

The inhibitory and inactivation effects on cytochrome P450 provide insight into amiodarone's interaction with other drugs. Amiodarone inactivates CYP3A4, while desethylamiodarone inactivates CYP1A1, CYP1A2, CYP2B6, and CYP2D6. Amiodarone weakly inhibits CYP2C9, CYP2D6, and CYP3A4-mediated activities. Desethylamiodarone competitively inhibits the catalytic activities of CYP2D6 and noncompetitively inhibits CYP2A6, CYP2B6, and CYP3A4. The catalytic activities of CYP1A1, CYP1*A*2, CYP2*C*9, and CYP2*C*19 are also inhibited by desethylamiodarone. The inhibitory effects of desethylamiodarone on each CYP activity are stronger than amiodarone [33]. Amiodarone and DEA are also potent inhibitors of P-glycoprotein-mediated transport [34].

Effects of amiodarone on thyroid hormone economy

Patients on amiodarone exhibit alterations in serum TSH, thyroxine (T4) and 3,5,3-triiodothyronine (T3) concentrations. Most commonly there is decreased serum T_3, increased serum T_4 and reverse T_3 levels while serum thyrotropin (TSH) is normal or mildly elevated. Early (dose-and time-dependent) elevations in serum TSH usually return to normal within a few months (Table 3) [23,32]. The high iodine content in amiodarone, while central, is insufficient to explain the entire spectrum of thyroid-related abnormalities seen in patients started on this drug. Amiodarone's effects on thyroid function can be divided into those effects that are intrinsic drug properties and those effects that are due to iodine [35,36]. The effects of amiodarone on thyroid hormone economy are, at least, partially due to interference with the iodothyronine deiodinases, which metabolize thyroid hormones [37]. These are thioredoxin-fold like containing selenoenzymes that can activate outer ring deiodination (ORD) or inactivate inner ring deiodination (IRD) thyroid hormone via sequential removal of iodine atoms [38]. For example, T4 can be activated to T3 via ORD; T4 and T3 can be inactivated by IRD to rT3 and T2, respectively. The type 1 deiodinase (D1) catalyzes both ORD and IRD whereas the type 2 deiodinase (D2) catalyzes ORD only [39]. D2 is thought to be the major source of plasma T3 in humans and also plays a critical role as a source of intracellular T3 in a number of cell types. Lastly, type 3 deiodinase (D3) is restricted to IRD and terminates thyroid hormone action in the brain, placenta and fetal tissues [40].

Multiple studies indicate that D1 activity is decreased in tissue homogenates of animals treated with amiodarone, in a dose-dependent fashion [23,41–48]. Similar observations have been made in cultured cells exposed to amiodarone [41]. It has been proposed that amiodarone and/or DEA inhibit D1directly via a competitive mechanism [49], which is supported by the observation that D1 mRNA levels are not affected by amiodarone treatment [50]. D1 inhibition may persist for several months after amiodarone therapy is discontinued. More is known about the effects of amiodarone/DEA on D2 activity. Earlier studies had shown that amiodarone is a weak D2 inhibitor [51,52]. More recent studies using animal models and cultured cells confirmed amiodarone as a weak noncompetitive inhibitor of D1 and D2, while showing that its metabolite, DEA, strongly inhibits both enzymes via a similar mechanism. Thus, for amiodarone to exhibit significant inhibitory effects on deiodinase activity it must be added to live cells or injected in live animals, allowing for its conversion to DEA. It is currently not known whether amiodarone/DEA interfere with D3 activity.

Given the fundamental role played by D2 in determining the plasma levels of TSH [53] and TSH releasing hormone (TRH) [54] secretion, as well as plasma T3 [55], it is expected that amiodarone/DEA-mediated D2 inhibition explains a substantial component of these drugs' effect on thyroid economy. Indeed, patients and experimental animals that have been placed on amiodarone tend to have a transient elevation in serum T4 and TSH concentrations that lasts for several months [56–58]. This would be unexpected given that T4 acts in a negative feedback loop, via D2 in the pituitary and hypothalamus, to decrease TSH and TRH production, respectively. However, a similar phenotype is also observed in the D2 knockout mouse (D2KO) [59]. It is also compatible with inhibition of D2 in the hypothalamic median eminence tanycytes and/or pituitary thyrotropes by amiodarone and/or DEA. By inhibiting D2 activity, amiodarone weakens the T4-mediated feedback at the pituitary gland, thus elevating plasma TSH. TRH expression does not seem to be involved in this mechanism.

Cardiac expression of deiodinases modulates thyroid hormone signaling

Some of the cardiovascular effects of amiodarone/DEA have been attributed to their ability to decrease thyroid hormone signaling in the myocardium, resulting in less thyroid hormone action [60]. The chemical structures of amiodarone and DEA are very similar to T3, and both have been shown to inhibit thyroid hormone transport across the plasma membrane [61], and/or direct binding to the thyroid hormone receptors, TRα and TRβ [62,63] and possibly even TR-dependent gene transcription [64].

The healthy human (but not rodent) myocardium expresses D2 and thus is capable of generating T3 inside the muscle fiber. Locally generated T3 combines with the T3 incoming from plasma to strengthen local thyroid hormone signaling. In fact, inhibition of T_4 deiodination to T_3 has been proposed as a contributory mechanism to the antiarrhythmic efficacy of amiodarone [1].

To better understand the role played by D2 in the myocardium, a transgenic mouse was created that expresses the human D2 gene in the myocardium under the α-myosin heavy chain (α-MHC) promoter [65]. This mouse has normal thyroid function tests but exhibits a discrete increase in myocardial T3 content and a gene expression profile compatible with increased thyroid hormone signaling, i.e. increased mRNA levels of HCN2 (an ionic channel that

Table 3
Effects of amiodarone on euthyroid subjects.

Thyroid hormone	Acute effects ≤ 3 mos.	Chronic effects ≥ 3 mos.
Total and free T4	↑ 50%	Remains ↑ 20–40% of baseline
T3	↓ 15–20% remains in low-normal range	Remains ↓ 20%. Remains in low-normal range
rT3	↑ 200%	Remains ↑ 150%
TSH	↑ 20–50%, transient, generally remains <20 mU/L	Normal

Reproduced from reference 35 with permission.

is key to the cardiac pacemaker) and decreased mRNA levels of β-MHC [66]. In perfused *ex vivo* studies, the α-MHC-D2 heart has about a 20% higher heart rate and decreased levels of phosphocreatine and ADP, indicating accelerated metabolic rates. This is supported by *in vivo* studies in which glucose uptake is increased by about 2.5-fold in the α-MHC-D2 heart [65]. These "thyrotoxic" effects are associated with an increased capacity of the α-MHC-D2 heart to generate cAMP in response to catecholamine stimulation [66]. Cardiac-specific increase in thyroid hormone signaling was confirmed in a second α-MHC-D2 mouse model conditionally expressing human D2 in the myocardium [67]. This model further demonstrated that myocardial D2 expression provides a functional advantage such as increased fractional shortening, velocity of circumferential fiber shortening, peak aortic outflow velocity and aortic velocity acceleration [67]. Thus, by virtue of accumulating in the myocardium and being a noncompetitive D2 inhibitor, amiodarone/DEA can potentially decrease thyroid hormone signaling in the heart.

Role of myocardial deiodinases in cardiac remodeling

Severe illness that is associated with ischemia/hypoxia results in ectopic cardiac expression of D3, which inactivates thyroid hormone and causes localized hypothyroidism [68,69]. D3 expression has also been observed in animal models of adverse remodeling such as myocardial infarction [70] and chronic pulmonary hypertension with right ventricular hypertrophy and ventricular failure (treatment with monocrotaline) [71,72]. While it is not clear if, under these circumstances, D3 expression is beneficial or maladaptive, these data beg the question of whether ectopic D2 expression in the heart protects against adverse myocardial remodeling. In fact, studies in both animal models of humanized myocardium showed that D2 activity in the myocardium protects against adverse myocardial remodeling caused by pressure overload (aortic banding) [59] or chemical injury (treatment with doxorubicin) [73]. At face value, these data suggest that by inhibiting the D2 pathway in the heart, amiodarone could have a positive role and prevent adverse remodeling. This is in agreement with clinical studies indicating that the use of amiodarone reverses left ventricular dilatation and other structural changes in patients with chronic tachycardia such as occurs in poorly controlled atrial fibrillation [74]. Amiodarone has also been reported to improve left ventricular ejection fraction in mild to moderate heart failure without improving total mortality [75]. Further studies should address whether these benefits are due solely to the antiarrhythmic properties of amiodarone or if D2 inhibition plays a role (even if minor).

Cytoxic potential of amiodarone

Amiodarone has direct, dose-dependent cytotoxic effects on the thyroid in a variety of animal models [23]. These findings have been confirmed in human post-operative pathologic specimens. DEA is even more cytotoxic for thyroid cells than the parent drug [23,76]. Although iodide excess may induce apoptosis, amiodarone administration is associated with ultrastructural changes indicative of thyroid cytotoxicity distinct from those induced by excess iodine alone. These changes include marked distortion of thyroid architecture, apoptosis, necrosis, inclusion bodies, lipofuscinogenesis, macrophage infiltration, and markedly dilated endoplasmic reticulum (ER) [23,77]. Amiodarone is amphiphilic and strongly binds to intralysosomal phospholipids, making them indigestible by phospholipases, which may also contribute to subcellular alterations [23,78]. In fact, exposure of human thyroid ML-1 cells and human primary thyrocytes to amiodarone, but not iodine, induces the expression of ER stress markers including Ig heavy chain-binding protein (BiP), phosphoeukaryotic translation initiation factor 2α (eIF2α), CCAAT/enhancer-binding protein homologous protein (CHOP) and spliced X-box binding protein-1 (XBP-1). Notably, amiodarone-induced ER stress is prevented by the pretreatment with the chemical chaperone 4-phenylbutyric acid, both molecules are known to minimize ER stress [79].

Thyroid autoimmunity and amiodarone

It is unlikely that thyroid autoantibodies appear in subjects who have negative tests before starting amiodarone treatment [23]. However, amiodarone treatment may be associated with an increase in certain lymphocyte subsets suggesting that, in susceptible individuals, amiodarone may precipitate or exacerbate preexisting organ-specific autoimmunity [23,25,80,81]. While this increase may be involved in the pathogenesis of thyrotoxicosis, it may be more important in amiodarone-induced hypothyroidism (AIH) [81]. The concomitant presence of thyroid autoantibodies and female gender is associated with 13.5 times the risk of AIH compared to men without thyroid autoantibodies [27,82]. While some authors contend that the presence of thyroid antibodies increases the risk of hypothyroidism, it is important to recognize that some authors have reported that the majority of AIH patients have circulating thyroid autoantibodies before amiodarone treatment is initiated, whereas others have found no increase in the incidence of previous thyroid dysfunction (including antithyroid antibodies) in patients who developed amiodarone-induced hypothyroidism [23,25,83]. Elevated antithyroid antibody titers occur in up to 40% of patients who become hypothyroid after amiodarone administration [25,81,82].

Amiodarone-induced hypothyroidism

As noted above, amiodarone is iodine-rich. Large amounts of iodide released during amiodarone metabolism inhibit thyroid hormone biosynthesis (the Wolff–Chaikoff effect) and release [25,84]. The acute Wolff–Chaikoff effect lasts for a few days and then, through the so-called "escape" from the Wolff–Chaikoff effect, the organification of intrathyroidal iodide resumes and the normal synthesis of thyroxine (T4) and triiodothyronine (T3) returns [85]. Persistent amiodarone-induced hypothyroidism is attributed to a subtle defect that results in enhanced susceptibility to the inhibitory effect of iodine on hormonal synthesis, a failure to escape from the Wolff–Chaikoff effect, or both [25,86].

Hypothyroidism may resolve or persist after cessation of amiodarone therapy. Although patients with or without underlying disease may resolve (the typical time frame is 2–4 months consistent with amiodarone's long half-life), persistent hypothyroidism despite amiodarone withdrawal is nearly always associated with underlying autoimmune thyroid disease (the most likely pathogenic mechanism is preexisting Hashimoto thyroiditis and an inability to escape from the Wolff–Chaikoff effect) [23,25]. AIH is slightly more frequent in females, with a female to male ratio of 1.5:1 [23,27]. Hashimoto's thyroiditis is also the most common risk factor for the development and persistence of AIH and is the likely reason for the female preponderance (women are seven times more likely to have Hashimoto's thyroiditis) [87]. As noted above, women with preexisting thyroglobulin or microsomal antibodies have a relative risk of 13.5 for developing AIH compared with men without thyroid antibodies [27,82]. Enhanced autoimmunity may account for this difference. Anti-TPO antibodies (AKA antithyroid microsomal antibodies) are the most common anti-thyroid autoantibody. Women have a higher prevalence of thyroid peroxidase antibody (TPOAb) positivity [88]. Anti-TPO antibodies are present in 99% of cases when thyroglobulin antibodies are present, but only 35% of anti-TPO antibody positive cases will demonstrate thyroglobulin antibodies [89].

While it is tempting to assume that amiodarone's iodine enhances the autoimmune response and unmasks previously subclinical thyroid disease the data should be considered inconclusive. It is equally reasonable to speculate that excess iodine may induce nonspecific thyroid injury which adds to the damage caused by underlying autoimmune disease [25].

Clinical manifestations and treatment of AIH

Hypothyroidism may develop as rapidly as two weeks or as late as 39 months after amiodarone therapy is initiated [90]. Although, serum TSH concentration rises transiently within a few days of starting amiodarone, it gradually returns to baseline concentrations, or even slightly below, over the next one to three months. Despite having (on average) twice the bioavailability of oral amiodarone, it is unlikely that a short course of intravenous amiodarone can induce AIH [1,91].

AIH patients frequently have vague signs and symptoms which are similar to those encountered in spontaneous hypothyroidism. Cool pale, dry skin, fatigue, cold intolerance, slow speech and mental sluggishness are common. Notably, many cardiac patients treated with amiodarone have impaired left ventricular function [1]. Slow movement, dyspnea on exertion and decreased exercise capacity induced by hypothyroidism may be difficult to distinguish from baseline or progressive cardiopulmonary abnormalities.

Amiodarone produces noncompetitive β-blockade that can cause substantial sinus bradycardia within several days (peak, 3 months), which may be exacerbated by hypothyroidism. Although both amiodarone and hypothyroidism prolong the QT/QTc interval, the risk of potentially lethal Torsade de Pointes is likely lower than the risk associated with antiarrhythmic drugs such as ibutilide, dofetilide and sotalol [1].

Given its high degree of efficacy, amiodarone is often the only available antiarrhythmic option for the patient and administration is usually continued in association with levothyroxine (L-T4) replacement. T4 is the drug of choice, particularly in patients with cardiac problems, because it requires once-daily administration and is not associated with the spikes in serum thyroid hormone concentrations observed in patients given L-T3 or desiccated thyroid (a mixture of T4 and T3) [23,92]. Amiodarone recipients often require relatively larger doses of L-T4 to normalize their serum TSH because of amiodarone's inhibitory effects on T4 conversion to T3. In view of the fact that these patients often have severe underlying cardiac disease, maintaining the serum TSH concentration in the upper half of the normal range is advisable [23].

Although lithium may be used for treatment of hyperthyroidism (see below), hypothyroidism is common in lithium treated patients. In a review of 11 reports (including > 1700 patients), the prevalence of hypothyroidism ranged from 6 to 52% [93,94]. The combination of amiodarone and lithium is, however, primarily contraindicated because of the risk of QT prolongation and Torsade de Pointes.

AIH and myxedema coma have been described in case reports [95,96]. Myxedema coma is an endocrine emergency and warrants aggressive treatment. Mortality rates range from 30 to 40% [97–99], with elderly patients and those with cardiac complications (the most common recipients of amiodarone therapy), reduced consciousness, persistent hypothermia, and sepsis having the greatest risk [1,100]. Management of myxedema coma involves replacement of thyroid hormone and supportive therapy. Respiratory support including intubation, controlled mechanical ventilation and supplemental oxygen therapy is pivotal [75].

Although the severity of the hypothermia is related to mortality (the lower the temperature, the more likely a patient is to die), external warming of the hypothermic patient may lead to peripheral vasodilatation with circulatory collapse and should be avoided. The presence of pre-existing cardiac disease (particularly heart failure) seems likely to make amiodarone recipients particularly vulnerable. Covering the patient with blankets at room temperature is preferable [96].

There is considerable disagreement about the optimal method for thyroid hormone replacement in myxedema coma. Intravenous administration is initially preferable as gut absorption is unpredictable [96]. It is important to remember that increasing serum thyroid hormone concentrations rapidly carries some risk of precipitating myocardial infarction or tachyarrhythmias, but the high mortality associated with myxedema coma justifies the risk. Some authorities favor administration of T4; others favor T3, while some prefer a combination of T4 and T3. High T3 serum concentrations during treatment have been correlated with mortality [97,100]. Intermediate replacement doses appear to be more effective than very high or very low doses [100].

Treatment of amiodarone-induced myxedema is associated with a risk of secondary adrenal insufficiency. This may be due to enhanced peripheral metabolism of cortisol after T4 supplementation or associated hypopituitarism [96,100]. Treatment with stress doses of glucocorticoids is requisite until the possibility of coexisting adrenal insufficiency has been excluded [100].

Amiodarone-induced hyperthyroidism

Amiodarone-induced hyperthyroidism is a much more complex entity than AIH. There are two main forms of amiodarone-induced thyrotoxicosis (AIT). Type I AIT usually occurs in abnormal thyroid glands and is the result of excessive iodine-induced hormone synthesis and release. Autoregulatory mechanisms modulate the thyroid gland's iodine handling according to its iodine content [25,101]. Disruption of these autoregulatory mechanisms is suggested by the high glandular iodine content associated with AIT compared with euthyroid amiodarone recipients [25,102,103] and by return of iodine content to normal during resolution of thyrotoxicosis [25,104]. Toxic nodular goiter and Graves' disease are the most common causes of Type I AIT in patients with preexisting or "latent" thyroid disease.

Type II AIT is a destructive thyroiditis leading to release of preformed (stored) thyroid hormones from damaged thyroid follicular cells. Type II AIT typically occurs in patients without underlying thyroid disease [105]. Humoral thyroid autoimmunity seems to play little, if any, role in the development of AIT in patients without underlying thyroid disorders [25]. The relative prevalence of the two forms of AIT is unknown, but may depend on the ambient iodine intake. Type II AIT persists for 1–3 months, until thyroid hormone stores are depleted, but resolves more quickly after glucocorticoid therapy [23,103].

A risk prediction index for Amiodarone-induced thyrotoxicosis has been developed in adults with congenital heart disease. The model includes age at amiodarone initiation, body mass index and the presence or absence of cyanosis. Its applicability has not been validated in other patient populations [106,107].

Clinical manifestations and treatment of AIT

Clinical features such as unexplained weight loss, proximal myopathy, exacerbation of arrhythmia or angina pectoris, or heat intolerance may prompt diagnosis of this complication, however, classical thyrotoxicosis symptoms may be absent due to the antiadrenergic action of amiodarone and impairment of conversion of T_4 to T_3 [23,104]. Goiter may be present or absent, with or without pain in the thyroid region. Goiter and ophthalmopathy are usually absent, unless AIT occurs in a patient with Graves' disease [23,27].

It has been the authors' experience that sudden recrudescence of previously controlled atrial and/or ventricular tachyarrhythmias is the most common clinical presentation. Electrical storm defined as ventricular tachycardia or ventricular fibrillation occurring 2 or more times in 24 h (usually requiring electrical cardioversion or defibrillation) may ensue [1,108]. Angina may also be provoked [25].

In patients with recurrent atrial fibrillation, prevention of thromboembolic events may be particularly tricky. Although thyrotoxicosis modifies the balance between coagulation and fibrinolysis and exerts a procoagulant effect increasing the risk of thromboembolism; in patients receiving warfarin, thyrotoxicosis has been associated with increased warfarin sensitivity (regardless of the thyroid disorder's etiology). Hyperthyroid patients exhibit an exaggerated depression in functional clotting factors (II, VII. IX and X) [27] in response to warfarin and accentuation of their prothrombin times. Importantly, amiodarone inhibits the plasma clearance of warfarin, thereby increasing its anticoagulant action. This effect appears to be mediated by competitive inhibition of hepatic cytochrome P450, family 2, subfamily C, polypeptide 9 gene (CYP2C9) and the vitamin K epoxide reductase subunit 1 gene (VKORC1) [109].

Laboratory features of AIT include low serum thyroid stimulating hormone (TSH), increases in thyroxine, free thyroxine and free thyroxine index. Some patients may also demonstrate high serum levels of triiodothyronine, free triiodothyronine and free triiodothyronine index. Serum levels of triiodothyronine can be normal in as many as 80% of patients [25,110].

As previously noted, amiodarone therapy is often reserved for treatment of life-threatening tachyarrhythmias such as ventricular tachycardia or fibrillation resistant to other pharmacological options [1,23]. Exacerbation of thyrotoxicosis has been reported after temporary amiodarone cessation [25,111,112]. This likely results from loss of amiodarone-induced myocardial intracellular hypothyroidism [25,46,113–115]. In addition, amiodarone's lipophilicity results in tissue storage for prolonged periods of time. Thyrotoxicosis may take as long as 8 months to subside after amiodarone is discontinued. If amiodarone has been effective in managing life-threatening arrhythmias we recommend continuing it while treating the hyperthyroidism. If an alternative drug can be chosen, a switch is reasonable, but the drug's long half-life prevents any immediate benefit [36]. Therefore, discontinuing amiodarone is often not a practical treatment option for AIT.

In the United States and other iodine-sufficient areas of the world, radioactive iodine is also not a viable therapeutic option for AIT. Uptake of radioiodine is inhibited by high intrathyroidal iodine concentrations [105]. Low or suppressed radioactive iodine uptake makes therapeutic administration of radioiodine not feasible [23,25]. Some authors have described its use in Europe, where 24-h radioiodine uptake values in AIT type 1 may be higher [35,116].

Differentiating type I AIT from type II AIT is clinically relevant because it has important therapeutic implications [105]. Serum thyroglobulin is often increased in AIT, but may not be a good marker of thyroid destruction in goitrous patients [23]. Similarly, measurement of erythrocyte sedimentation rate and C reactive protein has been unhelpful in discriminating the 2 AIT subtypes. The presence of thyrotropin receptor antibodies suggests Graves' disease. Interleukin-6 (IL-6) is thought to be a better marker because it has been found to be normal or mildly elevated in patients with Type 1 AIT and significantly elevated in patients with Type 2 AIT [23,117]. Unfortunately, IL-6 may be elevated in heart failure and other non-thyroidal conditions [105].

Color flow Doppler sonography of the thyroid is very useful in distinguishing the type of AIT present. Absence of vascularity and glandular destruction is typical of Type II AIT (other patterns suggest Type I), and 80% of patients can be classified as having Type I or II AIT with color flow Doppler sonography [105]. Technetium-99m sestamibi (99mTc-STS) thyroid scintigraphy has been used to distinguish subtypes of amiodarone-induced thyrotoxicosis. Unfortunately, the information gathered is qualitative and highly subjective. The use of quantitative thyroid-to-background ratios displayed on a time-activity curve has recently been reported to improve interobserver reliability for investigation of different types of AIT [105].

Because it is caused by increased hormonal synthesis Type I AIT is treated with a thionamide [105]. High intrathyroidal iodine content reduces the effectiveness of conventional thionamide drug therapy and higher than average doses are often required [23,105]. Thionamide drug therapy (methimazole, carbimazole, propylthiouracil) works by inhibiting the enzyme thyroid peroxidase and reducing synthesis of T3 and T4.

Potassium perchlorate has been used to treat hyperthyroidism since the 1950 s [118]. Potassium perchlorate inhibits the sodium/iodide symporter and blocks active transport of iodide into the thyroid and helps deplete intrathyroidal iodine stores to improve the therapeutic efficacy of thionamides [23,119]. The time required to achieve euthyroidism is shorter than that in patients responsive to conventional thionamide treatment [120].

Perchlorate is no longer available in the United States [35]. Like amiodarone, the major limitation of potassium perchlorate is toxicity. The main concerns are agranulocytosis, aplastic anemia and renal dysfunction (nephrotic syndrome) [23,25,105]. Daily doses of potassium perchlorate exceeding 1 g, have been associated with a 16–18% incidence of toxicity [23,121]. Hematological toxicity is less likely at lower doses [23,122]. Although short duration perchlorate therapy may result in a high risk of recurrent thyrotoxicosis, it seems wise to discontinue potassium perchlorate once euthyroidism is achieved [23,123]. Agranulocytosis and aplastic anemia are also rare complications of thionamide monotherapy (prevalence of 0.1–0.5%) [124–127].

Lithium carbonate has also been used in a small number of patients to accelerate the time to euthyroidism [23,105,128]. Lithium increases intrathyroidal iodine content, inhibits coupling of iodotyrosine residues to form T4 and T3 [1,23], and inhibits release of T4 and T3 [129–132].

Thionamides (+/−) potassium perchlorate are not appropriate therapy for Type II destructive thyroiditis. Glucocorticoids are effective for Type II AIT because of their anti-inflammatory and membrane-stabilizing effects. Steroids are also beneficial because of their inhibition of 5′-D activity [23,105]. Prednisone is started and tapered over two to three months. Exacerbations may occur during the taper and should be treated by increasing the steroid dose [35,105]. Patients may develop transient hypothyroidism when thyrotoxicosis resolves and may benefit from thyroid hormone replacement.

In patients with mixed forms of AIT or in those in whom differentiation is impossible, a combination of a thionamides plus steroids (and possibly potassium perchlorate), is likely the most beneficial therapeutic regimen [23]. Plasmapheresis may be considered for drug refractory cases [23,35].

Beta blockers relieve thyrotoxicosis symptoms associated with increased beta-adrenergic tone. In the absence of contraindications, a beta-blocker should be started in most patients as soon as the diagnosis is made. Although some beta blockers inhibit the 5′-monodeiodinase that converts T4 to T3, the effect is slow (7–10 days) and contributes little to their therapeutic efficacy [133].

Like myxedema coma, thyroid storm is an endocrine emergency. Thyroid storm may account for 1–10% of hospital admissions for hyperthyroidism; however, most reports estimate an incidence of ≤2%. Thyroid storm is most common in women and is more fre-

quent among patients with underlying Graves' disease. There are a myriad of well-described precipitants of thyroid storm in patients with unrecognized thyrotoxicosis and amiodarone has been implicated [134,135].

Even with early diagnosis, overall mortality from thyroid storm ranges from 10% to 30% [134,135]. Patients in thyroid storm are critically ill and supportive therapy may require reversal of hyperthermia, dehydration, congestive heart failure, tachyarrhythmias, and prevention of adrenal crisis. As in less severe forms of AIT, oral or intravenous β-adrenergic blockade is a cornerstone of treatment strategy. Multi-system organ failure is the most common cause of death, followed by heart failure, respiratory failure, arrhythmia, disseminated intravascular coagulation, gastrointestinal perforation, hypoxic brain syndrome, and sepsis [135].

Thionamides are first-line therapy in the treatment of thyroid storm. As in Type I AIT, these drugs must be used at significantly higher doses than the standard regimen recommended for uncomplicated hyperthyroidism. Critically ill patients may require treatment with rectal formulations or intravenous methimazole (propylthiouracil is relatively insoluble and not suitable for intravenous administration). Nonradioactive iodine administration may transiently decrease thyroid hormone synthesis and may be administered orally, rectally or intravenously. Iodine must be administered at least 30 min after thionamides to avoid serving as a substrate for new thyroid hormone production [135].

Iodine administration also blocks release of preformed hormone by inhibiting the proteolytic release of T3 and T4 from thyroglobulin. This secondary effect of iodine treatment results in a faster onset than propylthiouracil [135–137]. Lithium may be substituted when iodine administration is undesirable or impossible (e.g. history of anaphylaxis) [135].

Thyroid hormones are metabolized in the liver and conjugated products are excreted via bile into the intestine where free hormones are released, reabsorbed, and circulate in a process referred to as enterohepatic circulation of thyroid hormone. Cholestyramine binds the conjugation products, promotes their excretion and decreases thyroid hormone levels [135,138–140].

When clinical deterioration occurs despite conventional therapy, plasmapheresis or plasma exchange rapidly reduces thyroid hormone levels and has been associated clinical improvement. Thyroxine-binding globulin, with bound thyroid hormone, is removed from circulation, and the colloid replacement (usually albumin) provides unsaturated binding sites for circulating free thyroid hormone. Although albumin binds thyroid hormone less avidly than thyroxine-binding globulin, it has a much larger capacity for low-affinity binding, thereby decreasing free thyroid hormone concentrations [135,141].

Thyroidectomy is generally reserved for patients with severe thyrotoxicosis, which is considered to be life-threatening and may include amiodarone-induced thyroid or electrical storm. In many instances, long-term discontinuation of amiodarone is not considered possible from a clinical point of view [23,25,105,114]. Surgical candidates include patients who deteriorate or do not improve despite intensive medical treatment, develop severe side effects such as agranulocytosis or aplastic anemia from treatment or need rapid resolution of their hyperthyroidism because of severe cardiac or pulmonary comorbidities [135]. In a recent study, 73% of patients (8 of 11) with previous episodes of type 1 AIT, who did not receive preventive thionamide treatment, developed a recurrence after amiodarone reintroduction [142]. Surgery (total or near-total thyroidectomy) results in rapid control of thyrotoxicosis and is the only antithyroid treatment that reliably permits continuation of amiodarone therapy [25,143–145]. Recent data from France suggests that complete thyroidectomy is superior to partial thyroidectomy, but only a small number of patients with AIT (5, 2.5%) were included in the 200 patient cohort [146].

Surgical mortality may approach 10% in thyroid storm [135,147]. In contrast, and in spite of the elevated risk imparted by underlying cardiac disease, surgery seems to be reasonably safe for AIT patients [18,88,148]. Small doses of β-blockers have been used before surgery in some patients [148], with caution that a synergistic effect with amiodarone could cause bradycardia or sinus arrest [1,149].

Monitoring and recommendations for amiodarone recipients

Various algorithms have been suggested to monitor thyroid function in amiodarone recipients. A careful history and physical examination is essential to detect pre-existing thyroid disease. Baseline thyroid function testing is also pivotal to avoid precipitating thyroid storm in a hyperthyroid patient or myxedema coma in a patient with Hashimoto's thyroiditis. Some authors recommend assessment of serum TSH, T4 and T3 [25], others suggest also assessing anti-thyroid peroxidase antibodies (anti-TPO antibodies) which are commonly associated with Hashimoto's thyroiditis [35]. As noted in Table 3, there will be differences in thyroid function tests in the first 3 months of amiodarone therapy compared to values seen after 3 months [35]. Nevertheless, in the presence of normal baseline values, most cardiologists/cardiac electrophysiologists will follow serum TSH levels every 6 months [1]. Suspicion of abnormal thyroid function (an elevated or depressed TSH) should trigger consultation with an expert endocrinologist familiar with the nuances of amiodarone-induced thyroid abnormalities and their management. Fig. 1 illustrates a composite approach to follow-up and management [25,35,105].

Is dromedarone an alternative drug to avoid AIT?

Dronedarone is a non-iodinated benzofuran derivative of amiodarone first approved by the FDA in 2009 for the management of AF. Like amiodarone, dronedarone is a potent blocker of multiple ion currents but lacks the iodine moiety and theoretically should have fewer effects on thyroid function. Dronedarone exerts its antiadrenergic effects by noncompetitive binding to β-adrenergic receptors and inhibition of agonist-induced increases in adenylate cyclase activity [150]. Dronedarone is less lipophilic, has a far shorter half-life and fewer serious side effects than amiodarone. Nevertheless, cases of severe liver injury and interstitial lung disease including pneumonitis and pulmonary fibrosis have been reported in patients treated with dronedarone [151,152].

In the EURIDIS and ADONIS trials, the incidence of clinical hyperthyroidism was 8.4% in the dronedarone group versus 14.1% in the placebo group ($P = 0.002$) and the incidence of hypothyroidism was 5.5% in the dronedarone group versus 3.5% in the placebo group ($P = 0.15$) [153]. The incidence of hyperthyroidism or hypothyroidism did not differ significantly between the placebo and dronedarone groups in the ATHENA trial [153]. These studies suggest that, in contrast to the experience with amiodarone, there is no increase in clinical thyroid disease in patients treated with dronedarone.

Amiodarone is the most effective antiarrhythmic drug for maintaining sinus rhythm in atrial fibrillation patients. Unfortunately, droneradone is clearly less effective in maintaining sinus rhythm than amiodarone [154,155]. Beyond isolated case reports, there is little evidence that dronedarone has significant efficacy in treatment of ventricular arrhythmias [155,156].

In contrast to amiodarone, treatment with dronedarone has been associated with increased early mortality related to heart failure exacerbation in patients with severe heart failure and left

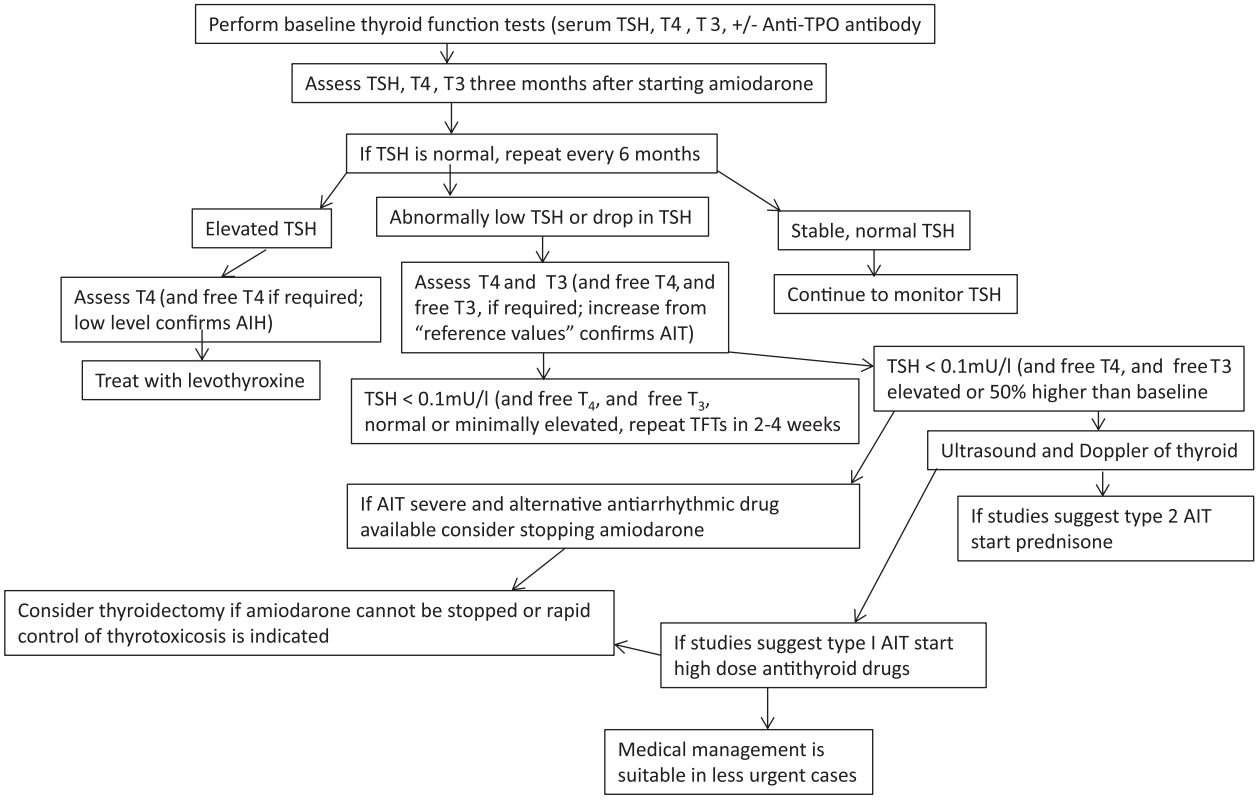

Fig. 1. A composite algorithm for thyroid follow-up and treatment in patients receiving amiodarone.

ventricular systolic dysfunction [157]. Although dronedarone improves ventricular rate control in patients with permanent AF [158], it increased rates of heart failure, stroke, and death from cardiovascular causes in patients with permanent AF at risk for major vascular events [159,160].

Summary and conclusions

Amiodarone is considered the most effective antiarrhythmic drug and is one of the most frequently prescribed antiarrhythmic medications in the United States. Amiodarone has complex pharmacokinetics and pharmacodynamics. It also has significant side effects which include hypothyroidism and thyrotoxicosis. Management of AIH is usually straightforward whereas management of AIT is far more complicated. Most of amiodarone's adverse effects are reversible with dose reduction or discontinuation of therapy; however this option is frequently unavailable in patients with drug refractory (often life-threatening) tachyarrhythmias. Fatal complications (such as pulmonary fibrosis, cirrhosis, and bradycardia leading to cardiac arrest) are well described, but amiodarone-induced thyroid disease is rarely considered among them. Nevertheless, amiodarone may precipitate electrical storm or endocrine emergencies such as myxedema coma and thyroid storm which are associated with significant morbidity and mortality. Amiodarone should be used carefully in patients likely to derive the most benefit. Close follow-up and a high index of suspicion for thyroid disease are requisite to avoid emergencies. Consultation with an endocrinologist is crucial whenever amiodarone-induced thyroid abnormalities are suspected. When life-threatening thyroid complications do occur, a coordinated team effort between endocrinologists, cardiac electrophysiologists, intensivists and surgeons is pivotal to limit mortality.

Acknowledgement

The authors are grateful to Ms. Bruna Pascarelli Pedrico do Nascimento for assistance with the references.

References

[1] Vassallo P, Trohman RG. Prescribing amiodarone: an evidence-based review of clinical indications. JAMA 2007;298(11):1312–22.
[2] Singh BN. Amiodarone as paradigm for developing new drugs for atrial fibrillation. J Cardiovasc Pharmacol 2008;52(4):300–5.
[3] Rosenbaum MB, Chiale PA, Haedo A, Lazzari JO, Elizari MV. Ten years of experience with amiodarone. Am Heart J 1983;106(4 Pt 2):957–64.
[4] Rosenbaum MB, Chiale PA, Halpern MS, Nau GJ, Przybylski J, Levi RJ, et al. Clinical efficacy of amiodarone as an antiarrhythmic agent. Am J Cardiol 1976;38(7):934–44.
[5] Fogoros RN. The Strange History of Amiodarone. Available at https://www.verywellhealth.com/the-strange-history-of-amiodarone-1745987 Last accessed 8/9/18.
[6] Winkle RA. Amiodarone and the American Way. J Am Coll Cardiol 1985;6(Oct (4)):822–4.
[7] Pritchett EL. Evolution and revolution in drug labeling: regulation of antiarrhythmic drugs by the Food and Drug Administration 1962–1996. Pacing Clin Electrophysiol 1998;21(7):1457–69.
[8] Kudenchuk PJ, Cobb LA, Copass MK, Cummins RO, Doherty AM, Fahrenbruch CE, et al. Amiodarone for resuscitation after out-of-hospital cardiac arrest due to ventricular fibrillation. N Engl J Med 1999;341(12):871–8.
[9] Dorian P, Cass D, Schwartz B, Cooper R, Gelaznikas R, Barr A. Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation. N Engl J Med 2002;346(12):884–90.
[10] Nademanee K, Taylor R, Bailey WE, Rieders DE, Kosar EM. Treating electrical storm: sympathetic blockade versus advanced cardiac life support-guided therapy. Circulation 2000;102(7):742–7.
[11] Ortiz M, Martin A, Arribas F, et al. Randomized comparison of intravenous procainamide vs. intravenous amiodarone for the acute treatment of tolerated wide QRS tachycardia: the PROCAMIO study. Eur Heart J 2017;38:1329–35.
[12] Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, Deal BJ, Dickfeld T, Field ME, Fonarow GC, Gillis AM, Hlatky MA, Granger CB, Hammill SC, Joglar JA, Kay GN, Matlock DD, Myerburg RJ, Page RL. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology Foundation/American Heart Association Task Force on

Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2017 Oct 24 pii: S0735-1097(17)41305-2.
[13] Pinski SL, Trohman RG. Implantable cardioverter-defibrillators: implications for the nonelectrophysiologist. Ann Intern Med 1995;122(10):770–7.
[14] Sweeney MO. There are lots of things about implantable cardioverter-defibrillators that should be eliminated: shocks are a good start. Heart Rhythm 2012;9(12):2075–6.
[15] Sweeney MO, Sherfesee L, DeGroot PJ, Wathen MS, Wilkoff BL. Differences in effects of electrical therapy type for ventricular arrhythmias on mortality in implantable cardioverter-defibrillator patients. Heart Rhythm 2010; 7(3):353–60.
[16] Dev S, Peterson PN, Wang Y, Curtis JP, Varosy PD, Masoudi FA. Prevalence, correlates, and temporal trends in antiarrhythmic drug use at discharge after implantable cardioverter defibrillator placement (from the National Cardiovascular Data Registry [NCDR]). Am J Cardiol 2014;113(2):314–20.
[17] Zimetbaum P. Antiarrhythmic drug therapy for atrial fibrillation. Circulation 2012;125(2):381–9.
[18] Aasbo JD, Lawrence AT, Krishnan K, Kim MH, Trohman RG. Amiodarone prophylaxis reduces major cardiovascular morbidity and length of stay after cardiac surgery: a meta-analysis. Ann Intern Med 2005;143(5):327–36.
[19] Kumar K, Zimetbaum PJ. Antiarrhythmic drugs to maintain sinus rhythm in patients with atrial fibrillation: clinical trials. Available at: https://www.uptodate.com/contents/antiarrhythmic-drugs-to-maintain-sinus-rhythm-in-patients-with-atrial-fibrillation-clinical-trials?topicRef=1033&source=see_link Last accessed 8/9/18.
[20] Di Biase L, Mohanty P, Mohanty S, Santangeli P, Trivedi C, Lakkireddy D, et al. Ablation versus amiodarone for treatment of persistent atrial fibrillation in patients with congestive heart failure and an implanted device: results from the AATAC multicenter randomized trial. Circulation 2016;133(Apr (17)):1637–44.
[21] Al-Khatib SM, LaPointe NM, Curtis LH, Kramer JM, Swann J, Honig P, et al. Outpatient prescribing of antiarrhythmic drugs from 1995 to 2000. Am J Cardiol 2003;91(1):91–4.
[22] Cordarone® (amiodarone HCl) TABLETS. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/018972s044lbl.pdf Last accessed 8/8/18.
[23] Martino E, Bartalena L, Bogazzi F, Braverman LE. The effects of amiodarone on the thyroid. Endocr Rev 2001;22(2):240–54.
[24] Gopalan M, Khardori R, Burks J. Thyroid dysfunction induced by amiodarone therapy 11/19/cited; Available from http://emedicine.medscape.com/article/129033-overview.
[25] Harjai KJ, Licata AA. Effects of amiodarone on thyroid function. Ann Intern Med 1997;126(1):63–73.
[26] Albert SG, Alves LE, Rose EP. Thyroid dysfunction during chronic amiodarone therapy. J Am Coll Cardiol 1987;9(1):175–83.
[27] Cohen-Lehman J, Dahl P, Danzi S, Klein I. Effects of amiodarone therapy on thyroid function. Nat Rev Endocrinol Jan 2010;6(1):34–41.
[28] Vorperian VR, Havighurst TC, Miller S, January CT. Adverse effects of low dose amiodarone: a meta-analysis. J Am Coll Cardiol Sep 1997;30(3):791–8.
[29] Singh BN, Wellens HJJ, Hockings BE. Electropharmacological control of cardiac arrhythmias. New York, NY: Futura Publishing Co.; 1994.
[30] Bonow RO, Mann DL, Zipes DP, Libby P. Braunwald's heart disease: a textbook of cardiovascular medicine. 9th ed. Philadelphia, PA: WB Saunders; 2011.
[31] Campbell TJ, Williams KM. Therapeutic drug monitoring: antiarrhythmic drugs. Br J Clin Pharmacol 2001;52(Suppl1):21S–34S.
[32] Goldschlager N, Epstein AE, Naccarelli G, Olshansky B, Singh B. Practical guidelines for clinicians who treat patients with amiodarone. Practice Guidelines Subcommittee, North American Society of Pacing and Electrophysiology. Arch Intern Med 2000;160(12):1741–8.
[33] Ohyama K, Nakajima M, M Suzuki M, N Shimada N, Yamazaki H, Yokoi T. Inhibitory effects of amiodarone and its N-deethylated metabolite on human cytochrome P450 activities: prediction of in vivo drug interactions. Br J Clin Pharmacol 2000;49(Mar (3)):244–53.
[34] Katoh M, Nakajima M, Yamazaki H, Yokoi T. Inhibitory effects of CYP3A4 substrates and their metabolites on P-glycoprotein-mediated transport. Eur J Pharm Sci 2001;12(Feb (4)):505–13.
[35] Basaria S, Cooper DS. Amiodarone and the thyroid. Am J Med 2005;118(7):706–14.
[36] Ross DS. Amiodarone and thyroid dysfunction. Available at: https://www.uptodate.com/contents/amiodarone-and-thyroid-dysfunction Last accessed 8/8/18.
[37] Koenig RJ. Regulation of type 1 iodothyronine deiodinase in health and disease. Thyroid 2005;15(8):835–40.
[38] Sagar GD, Gereben B, Callebaut I, Mornon JP, Zeold A, Curcio-Morelli C, et al. The thyroid hormone-inactivating deiodinase functions as a homodimer. Mol Endocrinol 2008;22(6):1382–93.
[39] Bianco AC, Salvatore D, Gereben B, Berry MJ, Larsen PR. Biochemistry, cellular and molecular biology, and physiological roles of the iodothyronine selenodeiodinases. Endocr Rev 2002;23(1):38–89.
[40] Gereben B, Zavacki AM, Ribich S, Kim BW, Huang SA, Simonides WS, et al. Cellular and molecular basis of deiodinase-regulated thyroid hormone signaling. Endocr Rev 2008;29(7):898–938.
[41] Aanderud S, Sundsfjord J, Aarbakke J. Amiodarone inhibits the conversion of thyroxine to triiodothyronine in isolated rat hepatocytes. Endocrinology 1984;115(4):1605–8.
[42] Hershman JM, Nademanee K, Sugawara M, Pekary AE, Ross R, Singh BN, et al. Thyroxine and triiodothyronine kinetics in cardiac patients taking amiodarone. Acta Endocrinol (Copenh) 1986;111(2):193–9.
[43] Gotzsche LS, Boye N, Laurberg P, Andreasen F. Rat heart thyroxine 5′-deiodinase is sensitively depressed by amiodarone. J Cardiovasc Pharmacol 1989;14(6):836–41.
[44] Ceppi JA, Gonzalez MR, Zaninovich AA. Effect of amiodarone on the conversion of thyroxine to triiodothyronine in the myocardium of rats in vivo and in vitro. Medicina (B Aires) 1988;48(1):29–32.
[45] Balsam A, Ingbar SH. The influence of fasting, diabetes, and several pharmacological agents on the pathways of thyroxine metabolism in rat liver. J Clin Invest 1978;62(2):415–24.
[46] Sogol PB, Hershman JM, Reed AW, Dillmann WH. The effects of amiodarone on serum thyroid hormones and hepatic thyroxine 5′-monodeiodination in rats. Endocrinology 1983;113(4):1464–9.
[47] Pekary AE, Hershman JM, Reed AW, Kannon R, Wang YS. Amiodarone inhibits T4 to T3 conversion and alpha-glycerophosphate dehydrogenase and malic enzyme levels in rat liver. Horm Metab Res 1986;18(2):114–18.
[48] Ceppi JA, Zaninovich AA. Effects of amiodarone on 5′-deiodination of thyroxine to tri- iodothyronine in rat myocardium. J Endocrinol 1989;121(3):431–4.
[49] Ha HR, Stieger B, Grassi G, Altorfer HR, Follath F. Structure-effect relationships of amiodarone analogues on the inhibition of thyroxine deiodination. Eur J Clin Pharmacol 2000;55(11-12):807–14.
[50] Hudig F, Bakker O, Wiersinga WM. Amiodarone-induced hypercholesterolemia is associated with a decrease in liver LDL receptor mRNA. FEBS Lett 1994;341(1):86–90.
[51] Kaplan MM, Pan CY, Gordon PR, Lee JK, Gilchrest BA. Human epidermal keratinocytes in culture convert thyroxine to 3,5,3′-triiodothyronine by type II iodothyronine deiodination: a novel endocrine function of the skin. J Clin Endocrinol Metab 1988;66(4):815–22.
[52] Kaplan MM, Breitbart R. Conversion of thyroxine to triiodothyronine in the anterior pituitary gland and the influence of this process on thyroid status. Horm Metab Res Suppl 1984;14:79–85.
[53] Christoffolete MA, Ribeiro R, Singru P, Fekete C, da Silva WS, Gordon DF, et al. Atypical expression of type 2 iodothyronine deiodinase in thyrotrophs explains the thyroxine-mediated pituitary thyrotropin feedback mechanism. Endocrinology 2006;147(4):1735–43.
[54] Fekete C, Lechan RM. Negative feedback regulation of hypophysiotropic thyrotropin-releasing hormone (TRH) synthesizing neurons: role of neuronal afferents and type 2 deiodinase. Front Neuroendocrinol 2007;28(2-3):97–114.
[55] Abdalla SM, Bianco AC. Defending plasma T3 is a biological priority. Clin Endocrinol 2014;81(5):633–41.
[56] Burger A, Dinichert D, Nicod P, Jenny M, Lemarchand-Beraud T, Vallotton MB. Effect of amiodarone on serum triiodothyronine, reverse triiodothyronine, thyroxin, and thyrotropin. A drug influencing peripheral metabolism of thyroid hormones. J Clin Invest 1976;58(2):255–9.
[57] Melmed S, Nademanee K, Reed AW, Hendrickson JA, Singh BN, Hershman JM. Hyperthyroxinemia with bradycardia and normal thyrotropin secretion after chronic amiodarone administration. J Clin Endocrinol Metab 1981;53(5):997–1001.
[58] Nademanee K, Singh BN, Hendrickson JA, Reed AW, Melmed S, Hershman J. Pharmacokinetic significance of serum reverse T3 levels during amiodarone treatment: a potential method for monitoring chronic drug therapy. Circulation 1982;66(1):202–11.
[59] Schneider MJ, Fiering SN, Pallud SE, Parlow AF, St Germain DL, Galton VA. Targeted disruption of the type 2 selenodeiodinase gene (DIO2) results in a phenotype of pituitary resistance to T4. Mol Endocrinol 2001;15(12):2137–48.
[60] Shi RQ, Lee JK, Hayashi Y, Takeuchi Y, Kambe F, Futaki S, et al. Long-term amiodarone treatment causes cardioselective hypothyroid-like alteration in gene expression profile. Eur J Pharmacol 2008;578(2-3):270–8.
[61] Krenning EP, Docter R, Bernard B, Visser T, Hennemann G. Decreased transport of thyroxine (T4), 3,3′,5-triiodothyronine (T3) and 3,3′,5′-triiodothyronine (rT3) into rat hepatocytes in primary culture due to a decrease of cellular ATP content and various drugs. FEBS Lett 1982; 140(2):229–33.
[62] Bakker O, van Beeren HC, Wiersinga WM. Desethylamiodarone is a noncompetitive inhibitor of the binding of thyroid hormone to the thyroid hormone beta 1-receptor protein. Endocrinology 1994;134:1665–70.
[63] van Beeren HC, Bakker O, Wiersinga WM. Desethylamiodarone is a competitive inhibitor of the binding of thyroid hormone to the thyroid hormone alpha 1-receptor protein. Mol Cell Endocrinol 1995;112(1):15–19.
[64] Bogazzi F, Bartalena L, Brogioni S, Burelli A, Raggi F, Ultimieri F, et al. Desethylamiodarone antagonizes the effect of thyroid hormone at the molecular level. Eur J Endocrinol 2001;145(1):59–64.
[65] Pachucki J, Hopkins J, Peeters R, Tu H, Carvalho SD, Kaulbach H, et al. Type 2 iodothyronine deiodinase transgene expression in the mouse heart causes cardiac-specific thyrotoxicosis. Endocrinology 2001;142(1):13–20.
[66] Carvalho-Bianco SD, Kim BW, Zhang JX, Harney JW, Ribeiro RS, Gereben B, et al. Chronic cardiac-specific thyrotoxicosis increases myocardial beta-adrenergic responsiveness. Mol Endocrinol 2004;18(7):1840–9.
[67] Trivieri MG, Oudit GY, Sah R, Kerfant BG, Sun H, Gramolini AO, et al. Cardiac-specific elevations in thyroid hormone enhance contractility and prevent pressure overload-induced cardiac dysfunction. PNAS 2006;103(15):6043–6048.

[68] Peeters RP, Wouters PJ, Kaptein E, van Toor H, Visser TJ, Van den Berghe G. Reduced activation and increased inactivation of thyroid hormone in tissues of critically ill patients. J Clin Endocrinol Metab 2003;88(7):3202–11.
[69] Ueta CB, Oskouei BN, Olivares EL, Pinto JR, Correa MM, Simovic G, et al. Absence of myocardial thyroid hormone inactivating deiodinase results in restrictive cardiomyopathy in mice. Mol Endocrinol 2012;26(5):809–18.
[70] Olivares EL, Marassi MP, Fortunato RS, da Silva AC, Costa-e-Sousa RH, Araujo IG, et al. Thyroid function disturbance and type 3 iodothyronine deiodinase induction after myocardial infarction in rats a time course study. Endocrinology 2007;148(10):4786–92.
[71] Wassen FW, Schiel AE, Kuiper GG, Kaptein E, Bakker O, Visser TJ, et al. Induction of thyroid hormone-degrading deiodinase in cardiac hypertrophy and failure. Endocrinology 2002;143(7):2812–15.
[72] Simonides WS, Mulcahey MA, Redout EM, Muller A, Zuidwijk MJ, Visser TJ, et al. Hypoxia-inducible factor induces local thyroid hormone inactivation during hypoxic-ischemic disease in rats. J Clin Invest 2008;118(3):975–83.
[73] Hong EG, Kim BW, Young Jung D, Hun Kim J, Yu T, Seixas Da Silva W, et al. Cardiac expression of human type 2 iodothyronine deiodinase increases glucose metabolism and protects against doxorubicin-induced cardiac dysfunction in male mice. Endocrinology 2013.
[74] Tracy CM. Tachycardia-mediated cardiomyopathy. 8/7/2015 cited; Available from: http://www.uptodate.com/contents/tachycardia-mediated-cardiomyopathy.
[75] Singh SN, Fletcher RD, Fisher SG, Singh BN, Lewis HD, Deedwania PC, et al. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. Survival trial of antiarrhythmic therapy in congestive heart failure. New Engl J Med 1995;333(2):77–82.
[76] Beddows SA, Page SR, Taylor AH, McNerney R, Whitley GS, Johnstone AP, et al. Cytotoxic effects of amiodarone and desethylamiodarone on human thyrocytes. Biochem Pharmacol 1989;38(24):4397–403.
[77] Pitsiavas V, Smerdely P, Li M, Boyages SC. Amiodarone induces a different pattern of ultrastructural change in the thyroid to iodine excess alone in both the BB/W rat and the Wistar rat. Eur J Endocrinol 1997;137(1):89–98.
[78] Wiersinga WM. Towards an animal model of amiodarone-induced thyroid dysfunction. Eur J Endocrinol 1997;137(1):15–17.
[79] Lombardi A, Inabnet WB 3rd, Owen R, Farenholtz KE, Tomer Y. Endoplasmic reticulum stress as a novel mechanism in amiodarone-induced destructive thyroiditis. J Clin Endocrinol Metab 2015;100(1):E1–10.
[80] Rani CS. Amiodarone effects on thyrotropin receptors and responses stimulated by thyrotropin and carbachol in cultured dog thyroid cells. Endocrinology 1990;127(6):2930–7.
[81] Amico JA, Richardson V, Alpert B, Klein I. Clinical and chemical assessment of thyroid function during therapy with amiodarone. Arch Intern Med 1984;144(Mar (3)):487–90.
[82] Trip MD, Wiersinga W, Plomp TA. Incidence, predictability, and pathogenesis of amiodarone-induced thyrotoxicosis and hypothyroidism. Am J Med 1991;91(5):507–11.
[83] Foresti V, Parisio E, Scolari N, Carini L, Lovagnini-Scher CA. Amiodarone and antithyroid antibodies. Ann Intern Med 1985;103(1):157–8.
[84] Selenkow HA, Garcia AM, Bradley EB. An autoregulatory effect of iodide in diverse thyroid disorders. Ann Intern Med 1965;62:714–26.
[85] Martino E, Safran M, Aghini-Lombardi F, Rajatanavin R, Lenziardi M, Fay M, et al. Environmental iodine intake and thyroid dysfunction during chronic amiodarone therapy. Ann Intern Med 1984;101(1):28–34.
[86] Markou K, Georgopoulos N, Kyriazopoulou V, Vagenakis AG. Iodine-Induced hypothyroidism. Thyroid 2001;11(5):501–10.
[87] Narayana SK, Woods DR, Boos CJ. Management of amiodarone-related thyroid problems. Ther Adv Endocrinol Metab 2011;2(Jun (3)):115–26.
[88] Amouzegar A, Gharibzadeh S, Kazemian E, Mehran L, Tohidi M, Azizi F. The prevalence, incidence and natural course of positive antithyroperoxidase antibodies in a population-based study: Tehran thyroid study. PLoS One 2017;12(Jan (1)):e0169283.
[89] Ai J, Leonhardt JM, Heymann WR. Autoimmune thyroid diseases: etiology, pathogenesis, and dermatologic manifestations. J Am Acad Dermatol May 2003;48(5):641–59.
[90] Nademanee K, Piwonka RW, Singh BN, Hershman JM. Amiodarone and thyroid function. Progr Cardiovasc Dis 1989;31(6):427–37.
[91] Ursella S, Testa A, Mazzone M, Gentiloni Silveri N. Amiodarone-induced thyroid dysfunction in clinical practice. Eur Rev Med Pharmacol Sci 2005; 10:269–78.
[92] Jackson IM, Cobb WE. Why does anyone still use desiccated thyroid USP? Am J Med 1978;64(2):284–8.
[93] Lazarus JH. Lithium and thyroid. Best Pract Res Clin Endocrinol Metab 2009;23(6):723–33.
[94] Surks MI. Lithium and the thyroid. Available at: https://www.uptodate.com/contents/lithium-and-the-thyroid Last accessed 8/13/18.
[95] Hassan S, Ayoub W, Hassan M, Wisgerhof M. Amiodarone-induced myxoedema coma. BMJ Case Rep 2014;2014.
[96] Chakraborty S, Fedderson J, Gums JJ, Toole A. Amiodarone-induced myxedema coma - a case and review of the literature. Arch Med Sci 2014;10(6):1263–1267.
[97] Hylander B, Rosenqvist U. Treatment of myxoedema coma–factors associated with fatal outcome. Acta Endocrinol 1985;108(1):65–71.
[98] Dutta P, Bhansali A, Masoodi SR, Bhadada S, Sharma N, Rajput R. Predictors of outcome in myxoedema coma: a study from a tertiary care centre. Crit Care 2008;12(1):R1.
[99] Beynon J, Akhtar S, Kearney T. Predictors of outcome in myxoedema coma. Crit Care 2008;12(1):111.
[100] Ross DS. Myxedema coma. 5/31/2015 [cited; Available from: http://www.uptodate.com/contents/myxedema-coma Last accessed 8/13/18.
[101] Ingbar SH. Autoregulation of the thyroid. Response to iodide excess and depletion. Mayo Clin Proc 1972;47(11):814–23.
[102] Leger AF, Fragu P, Rougier P, Laurent MF, Tubiana M, Savoie JC. Thyroid iodine content measured by x-ray fluorescence in amiodarone-induced thyrotoxicosis: concise communication. J Nucl Med 1983;24(7):582–5.
[103] Daniels GH. Amiodarone-induced thyrotoxicosis. J Clin Endocrinol Metab 2001;86(1):3–8.
[104] Newnham HH, Topliss DJ, Le Grand BA, Chosich N, Harper RW, Stockigt JR. Amiodarone-induced hyperthyroidism: assessment of the predictive value of biochemical testing and response to combined therapy using propylthiouracil and potassium perchlorate. Aust N Z J Med 1988;18(1):37–44.
[105] Tsang W, Houlden RL. Amiodarone-induced thyrotoxicosis: a review. Can J Cardiol 2009;25(7):421–4.
[106] Stan MN, Hess EP, Bahn RS, Warnes CA, Ammash NM, Brennan MD, Thapa P, Montori VM. A risk prediction index for amiodarone-induced thyrotoxicosis in adults with congenital heart disease. J Thyroid Res 2012;2012:210529.
[107] Stan MN, Ammash NM, Warnes CA, Brennan MD, Thapa P, Nannenga MR, Bahn RS. Body mass index and the development of amiodarone-induced thyrotoxicosis in adults with congenital heart disease–a cohort study. Int J Cardiol 2013 Aug 10;167(3):821–6.
[108] Credner SC, Klingenheben T, Mauss O, Sticherling C, Hohnloser SH. Electrical storm in patients with transvenous implantable cardioverter-defibrillators: incidence, management and prognostic implications. J Am Coll Cardiol 1998;32(7):1909–15.
[109] Tomisti L, Del Re M, Bartalena L, Tanda ML, Pucci A, Pambianco F, et al. Effects of amiodarone, thyroid hormones and CYP2C9 and VKORC1 polymorphisms on warfarin metabolism: a review of the literature. Endocr Pract 2013;19(6):1043–9.
[110] Harjai KJ, Licata AA. Amiodarone induced hyperthyroidism: a case series and brief review of literature. Pacing Clin Electrophysiol 1996;19(11 Pt 1):1548–54.
[111] Brennan MD, van Heerden JA, Carney JA. Amiodarone-associated thyrotoxicosis (AAT): experience with surgical management. Surgery 1987; 102(6):1062–7.
[112] Leger AF, Massin JP, Laurent MF, Vincens M, Auriol M, Helal OB, et al. Iodine-induced thyrotoxicosis: analysis of eighty-five consecutive cases. Eur J Clin Invest 1984;14(6):449–55.
[113] Singh BN, Vaughan Williams EM. The effect of amiodarone, a new anti-anginal drug, on cardiac muscle. Br J Pharmacol 1970;39(4):657–67.
[114] Franklyn JA, Davis JR, Gammage MD, Littler WA, Ramsden DB, Sheppard MC. Amiodarone and thyroid hormone action. Clin Endocrinol (Oxf) 1985;22(3):257–64.
[115] Marcus FI, Fontaine GH, Frank R, Grosgogeat Y. Clinical pharmacology and therapeutic applications of the antiarrhythmic agent amiodarone. Am Heart J 1981;101(4):480–93.
[116] Bartalena L, Brogioni S, Grasso L, Bogazzi F, Burelli A, Martino E. Treatment of amiodarone-induced thyrotoxicosis, a difficult challenge: results of a prospective study. J Clin Endocrinol Metab 1996;81(8):2930–3.
[117] Bartalena L, Grasso L, Brogioni S, Aghini-Lombardi F, Braverman LE, Martino E. Serum interleukin-6 in amiodarone-induced thyrotoxicosis. J Clin Endocrinol Metab 1994;78(2):423–7.
[118] Godley AF, Stanbury JB. Preliminary experience in the treatment of hyperthyroidism with potassium perchlorate. J Clin Endocrinol Metab 1954;14(1):70–8.
[119] Braverman LE, He X, Pino S, Cross M, Magnani B, Lamm SH, et al. The effect of perchlorate, thiocyanate, and nitrate on thyroid function in workers exposed to perchlorate long-term. J Clin Endocrinol Metab 2005;90(2):700–6.
[120] Martino E, Aghini-Lombardi F, Mariotti S, Lenziardi M, Baschieri L, Braverman LE, et al. Treatment of amiodarone associated thyrotoxicosis by simultaneous administration of potassium perchlorate and methimazole. J Endocrinol Invest 1986;9(3):201–7.
[121] Trotter WR. The relative toxicity of antithyroid drugs. J New Drugs 1962;2:333–43.
[122] Wenzel KW, Lente JR. Similar effects of thionamide drugs and perchlorate on thyroid-stimulating immunoglobulins in Graves' disease: evidence against an immunosuppressive action of thionamide drugs. J Clin Endocrinol Metab 1984;58(1):62–9.
[123] De Weweire A, Unger P, Delwiche F, Unger J. Failure to control hyperthyroidism with a thionamide after KClO4 withdrawal in a patient with amiodarone associated thyrotoxicosis. J Endocrinol Invest 1987;10(5):529–30.
[124] Ross DS. Pharmacology and toxicity of thionamides. Available at: http://www.uptodate.com/contents/pharmacology-and-toxicity-of-thionamides. Last accessed 8/13/18.
[125] Andersohn F, Konzen C, Garbe E. Systematic review: agranulocytosis induced by nonchemotherapy drugs. Ann Intern Med 2007;146(9):657–65.
[126] Watanabe N, Narimatsu H, Noh JY, Yamaguchi T, Kobayashi K, Kami M, et al. Antithyroid drug-induced hematopoietic damage: a retrospective cohort study of agranulocytosis and pancytopenia involving 50,385 patients with Graves' disease. J Clin Endocrinol Metab 2012;97(1):E49–53.
[127] Thomas D, Moisidis A, Tsiakalos A, Alexandraki K, Syriou V, Kaltsas G. Antithyroid drug-induced aplastic anemia. Thyroid 2008;18(10):1043–8.

[128] Dickstein G, Shechner C, Adawi F, Kaplan J, Baron E, Ish-Shalom S. Lithium treatment in amiodarone-induced thyrotoxicosis. Am J Med 1997; 102(5):454–8.
[129] Bagchi N, Brown TR, Mack RE. Studies on the mechanism of inhibition of thyroid function by lithium. Biochim Biophys Acta 1978;542(1):163–9.
[130] Berens SC, Bernstein RS, Robbins J, Wolff J. Antithyroid effects of lithium. J Clin Invest 1970;49(7):1357–67.
[131] Burrow GN, Burke WR, Himmelhoch JM, Spencer RP, Hershman JM. Effect of lithium on thyroid function. J Clin Endocrinol Metab 1971;32(5):647–52.
[132] Spaulding SW, Burrow GN, Bermudez F, Himmelhoch JM. The inhibitory effect of lithium on thyroid hormone release in both euthyroid and thyrotoxic patients. J Clin Endocrinol Metab 1972;35(6):905–11.
[133] Ross DS. Beta blockers in the treatment of hyperthyroidism. Available at: http://www.uptodate.com/contents/beta-blockers-in-the-treatment-of-hyperthyroidism Last accessed 8/13/18.
[134] Nayak B, Burman K. Thyrotoxicosis and thyroid storm. Endocrinol Metab Clin North Am 2006;35(4):663–86 vii.
[135] Chiha M, Samarasinghe S, Kabaker AS. Thyroid storm: an updated review. J Intensive Care Med 2015;30(3):131–40.
[136] Burch HB, Wartofsky L. Graves' ophthalmopathy: current concepts regarding pathogenesis and management. Endocr Rev 1993;14:747–93.
[137] Wartofsky L, Ransil BJ, Ingbar SH. Inhibition by iodine of the release of thyroxine from the thyroid glands of patients with thyrotoxicosis. J Clin Invest 1970;49(1):78–86.
[138] Kaykhaei MA, Shams M, Sadegholvad A, Dabbaghmanesh MH, Omrani GR. Low doses of cholestyramine in the treatment of hyperthyroidism. Endocrine 2008;34(1-3):52–5.
[139] Tsai WC, Pei D, Wang TF, Wu DA, Li JC, Wei CL, et al. The effect of combination therapy with propylthiouracil and cholestyramine in the treatment of Graves' hyperthyroidism. Clin Endocrinol 2005;62(5):521–4.
[140] Mercado M, Mendoza-Zubieta V, Bautista-Osorio R, Espinoza-de los Monteros AL. Treatment of hyperthyroidism with a combination of methimazole and cholestyramine. J Clin Endocrinol Metab 1996;81(9):3191–3.
[141] Carhill A, Gutierrez A, Lakhia R, Nalini R. Surviving the storm: two cases of thyroid storm successfully treated with plasmapheresis. BMJ Case Rep 2012;2012.
[142] Maqdasy S, Batisse-Lignier M, Auclair C, Desbiez F, Citron B, Thieblot P, et al. Amiodarone-induced thyrotoxicosis recurrence after amiodarone reintroduction. Am J Cardiol 2016;117(7):1112–16.
[143] Solomon B, Glinoer D, Lagasse R, Wartofsky L. Current trends in the management of Graves' disease. J Clin Endocrinol Metab 1990;70(6):1518–24.
[144] Meurisse M, Hamoir E, D'Silva M, Joris J, Hennen G. Amiodarone-induced thyrotoxicosis: is there a place for surgery? World journal of surgery. 1993; 17(5): 622–6; discussion 7.
[145] Mulligan DC, McHenry CR, Kinney W, Esselstyn CB Jr. Amiodarone-induced thyrotoxicosis: clinical presentation and expanded indications for thyroidectomy. Surgery 1993;114(6):1114–19.
[146] Querat C, Germain N, Dumollard JM, Estour B, Peoc'h M, Prades JM. Surgical management of hyperthyroidism. Eur Ann Otorhinolaryngol, Head Neck Dis 2015;132(2):63–6.
[147] Scholz GH, Hagemann E, Arkenau C, Engelmann L, Lamesch P, Schreiter D, et al. Is there a place for thyroidectomy in older patients with thyrotoxic storm and cardiorespiratory failure? Thyroid 2003;13(10):933–40.
[148] Farwell AP, Abend SL, Huang SK, Patwardhan NA, Braverman LE. Thyroidectomy for amiodarone-induced thyrotoxicosis. JAMA 1990;263(11):1526–1528.
[149] Marcus FI. Drug interactions with amiodarone. Am Heart J 1983;106(4 Pt 2):924–30.
[150] Patel C, Yan GX, Kowey PR. Dronedarone. Circulation 2009;120(7):636–44.
[151] Joghetaei N, Weirich G, Huber W, Buchler P, Estner H. Acute liver failure associated with dronedarone. Circ Arrhythmia Electrophysiol 2011;4(4):592–593.
[152] Skaper SD, Di Marzo V. Endocannabinoids in nervous system health and disease: the big picture in a nutshell. Philos Trans R Soc Lond Ser B 2012;367(1607):3193–200.
[153] Hohnloser SH, Crijns HJ, van Eickels M, Gaudin C, Page RL, Torp-Pedersen C, Connolly SJATHENA Investigators. Effect of dronedarone on cardiovascular events in atrial fibrillation. N Engl J Med 2009;360:668–78.
[154] Hernandez Voth AR, Catalan JS, Benavides Manas PD, Avila Martinez RJ, Penalver Paolini CL, Diaz de Atauri Rodriguez MJ. A 73-year-old man with interstitial lung disease due to dronedarone. Am J Respir Crit Care Med 2012;186(2):201–2.
[155] Le Heuzey JY, De Ferrari GM, Radzik D, Santini M, Zhu J, Davy JM. A short--term, randomized, double-blind, parallel-group study to evaluate the efficacy and safety of dronedarone versus amiodarone in patients with persistent atrial fibrillation: the DIONYSOS study. J Cardiovasc Electrophysiol 2010;21(6):597–605.
[156] Exposito V, Rodriguez-Entem F, Gonzalez-Enriquez S, Olalla JJ. Dronedarone for recurrent ventricular tachycardia: a real alternative? Indian Pacing Electrophysiol J. 2012; 12(2): 73–6.
[157] Shaaraoui M, Freudenberger R, Levin V, Marchlinski FE. Suppression of ventricular tachycardia with dronedarone: a case report. J Cardiovasc Electrophysiol 2011;22(2):201–2.
[158] Kober L, Torp-Pedersen C, McMurray JJ, Gotzsche O, Levy S, Crijns H, et al. Increased mortality after dronedarone therapy for severe heart failure. N Engl J Med 2008;358(25):2678–87.
[159] Davy JM, Herold M, Hoglund C, Timmermans A, Alings A, Radzik D, et al. Dronedarone for the control of ventricular rate in permanent atrial fibrillation: the Efficacy and safety of dRonedArone for the cOntrol of ventricular rate during atrial fibrillation (ERATO) study. Am Heart J 2008; 156(3):527 e1–9.
[160] Connolly SJ, Camm AJ, Halperin JL, Joyner C, Alings M, Amerena J, et al. Dronedarone in high-risk permanent atrial fibrillation. N Engl J Med 2011;365(24):2268–76.
[161] Page RL, Joglar JA, Caldwell MA, Calkins H, Conti JB, Deal BJ, et al. 2015 ACC/AHA/ HRS guideline for the management of adult patients with supraventricular tachycardia: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Circulation 2016;133:e506–74.
[162] Giardina EG, Zimetbaum PJ. Amiodarone: monitoring and management of side effects. Available at: https://www.uptodate.com/contents/amiodarone-monitoring-and-management-of-sideeffects?search=amiodarone%20toxicity&source=search_result&selectedTitle=1~48&usage_type=default&display_rank=1.
[163] Cheung AT, Weiss SJ, Savino JS, Levy WJ, Augoustides JG, Harrington A, Gardner TJ. Acute circulatory actions of intravenous amiodarone loading in cardiac surgical patients. Ann Thorac Surg 2003;76(Aug (2)):535–41.