

# A Practical Guide for Clinicians Who Treat Patients with Amiodarone: 2007

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Amiodarone is commonly used to treat supraventricular and ventricular arrhythmias in various inpatient and outpatient settings. Over- and under-use of amiodarone is common, and data regarding patterns of use are sparse and largely anecdotal. Because of adverse drug reactions, proper use is essential to deriving optimal benefits from the drug with the least risk. This guide updates an earlier version

published in 2000,<sup>1</sup> reviews indications for use of amiodarone and recommends strategies to minimize adverse effects. The recommendations included herein are based on the best available data and the collective experience of the member of the writing committee.

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Update to the Practical Guidelines for Clinicians Who Treat Patients with Amiodarone. Goldschlager et al. Practice Guidelines Subcommittee, North American Society of Pacing and Electrophysiology (HRS). Arch Intern Med. 2000 Jun 26;160(12):1741–8.

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## Introduction

Amiodarone is one of the most widely used antiarrhythmic agents, yet precise data regarding its use are largely unavailable. In view of this, and because adverse effects of the drug are not uncommon and can be serious, it was considered prudent to provide this updated guide for all clinicians who treat patients with cardiac arrhythmias.

## Indications for use

### Oral Amiodarone

#### Ventricular Arrhythmias

Amiodarone is an iodinated benzofuran derivative that has class I, II, III and IV antiarrhythmic properties. Oral amiodarone is approved by the Food and Drug Administration (FDA) for the treatment of life-threatening, recurrent ventricular arrhythmias, such as ventricular fibrillation (VF) or ventricular tachycardia (VT) associated with hemodynamic instability.

This indication includes the stipulation that the arrhythmia is not responsive to, or the patient is intolerant of, other antiarrhythmic agents that might be suitable for treatment.

It is the consensus of this committee that amiodarone is the antiarrhythmic drug of choice, in combination with other appropriate therapies such as beta-blocking agents, in patients who have sustained ventricular tachyarrhythmias associated with structural heart disease, especially if associated with left ventricular dysfunction, who are not candidates for an implantable cardioverter-defibrillator (ICD). This recommendation is based on the following observations: 1) efficacy of amiodarone at 2 years to prevent sustained VT/VF or death is approximately 60%<sup>2–4</sup>; 2) amiodarone has minimal negative inotropic effects; 3) amiodarone has low pro-arrhythmic potential<sup>5</sup>; 4) prospective trial data demonstrate long-term neutral effects on survival and safety in patients with post-myocardial infarction left ventricular dysfunction, and in patients with either ischemic and nonischemic dilated cardiomyopathy<sup>6</sup>; 5) the empiric use of amiodarone has been found to be more effective than the use of class I antiarrhythmic drugs even though these drugs had their efficacy guided by serial invasive or noninvasive tests<sup>3</sup>; and 6) the efficacy of amiodarone is similar to ICD therapy in patients with left ventricular ejection fractions greater than 35%.<sup>7</sup>

Several prospective trials such as The Antiarrhythmics versus Implantable Defibrillators Study (AVID), the Cardiac Arrest Study Hamburg (CASH), and the Canadian Implantable Defibrillator Study (CIDS)<sup>7–9</sup> have demonstrated that an ICD is superior to empiric amiodarone in improving survival and preventing sudden cardiac (presumed arrhythmic) death. This finding has been demonstrated in patients with a history of sustained VT/VF, high risk post-myocardial infarction patients (depressed ejection fraction, nonsustained VT and inducible

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sustained VT), and patients with New York Heart Association (NYHA) II/III heart failure and left ventricular ejection fractions  $\leq 35\%$ .<sup>10–12</sup> Despite these observations, 30–70% of ICD patients continue to require concomitant antiarrhythmic drug therapy for suppression of recurrent VT or suppression of or prophylaxis against atrial fibrillation (AF) with rapid ventricular rates. Given that the majority of patients with ICDs have structural heart disease and left ventricular dysfunction, amiodarone is the drug most often used. Because amiodarone may increase the defibrillation threshold as well as slow the slow rate of VT, repeat ICD testing may be helpful to optimally program the ICD. The Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients (OPTIC) study<sup>13</sup> demonstrated that amiodarone, in combination with a beta-blocker, can statistically significantly reduce the number of ICD discharges. Currently, there is disagreement regarding the predictive value of electrophysiologic testing with respect to subsequent arrhythmia outcomes in patients receiving amiodarone therapy.

Because amiodarone is effective in suppressing ventricular arrhythmias and has had neutral effects on survival in patients with left ventricular dysfunction, the drug is often used to suppress symptomatic, nonsustained VT in these patients. However, amiodarone adversely affected survival in NYHA III patients in the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT).<sup>12</sup> Thus, amiodarone should be reserved for patients with nonsustained VT that is symptomatic, refractory to beta-blocker therapy, and concerning enough to warrant treatment.

### Atrial Fibrillation

Although amiodarone is not approved for use in the treatment of atrial fibrillation (AF) by the FDA, it is the most commonly used antiarrhythmic drug for this purpose. This is based on 1 year efficacy rates for maintaining sinus rhythm of greater than 60%, compared to 50% or less for other antiarrhythmic agents. The Canadian Trial of Atrial Fibrillation (CTAF) demonstrated that amiodarone was more effective than propafenone or sotalol in preventing AF recurrences; although discontinuation rates due to adverse effects trended higher in the patients treated with amiodarone.<sup>14</sup> In the Sotalol-Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T) amiodarone prolonged the median time to AF recurrence compared to sotalol ( $P < .001$ ) and to placebo ( $P < .001$ ), but not in patients with ischemic heart disease.<sup>15</sup> Maintenance of sinus rhythm with amiodarone improved quality of life and exercise capacity.

It is the consensus of this committee that amiodarone should be used to treat AF based on the recommendations of the American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC), published in 2006,<sup>16</sup> in the following patient groups: 1) patients post-myocardial infarction who are not candidates for sotalol or dofetilide; 2) patients with congestive heart failure and left ventricular dysfunction who are not candidates for dofetilide; 3) patients with significant left ventricular hypertrophy, and 4) antiarrhythmic drug-refractory, symptomatic patients as a medical alternative to catheter ablation. Because of the end-

organ toxicity, the drug should be considered after sotalol and/or dofetilide have been tried in the post-myocardial infarction setting, after dofetilide in patients with left ventricular dysfunction, and only in drug-refractory idiopathic AF. Although amiodarone can be used to control ventricular rate in AF, it should be considered only in circumstances in which digoxin, beta-blockers and calcium channel blockers are ineffective, contraindicated or not tolerated. In most of these refractory patients, a more appropriate approach is atrioventricular (AV) junction ablation and permanent cardiac pacing, or AF ablation in appropriate patients.

Although several studies,<sup>17</sup> most recently the Prophylactic Amiodarone for the Prevention of Arrhythmias that Begin Early After Revascularization, Valve Replacement, or Repair (PAPA BEAR),<sup>18</sup> have demonstrated that loading with oral amiodarone prior to aortocoronary bypass surgery can decrease the incidence of postoperative AF, this approach should be considered only in high risk patients (prior history of AF, valve replacement surgery) in whom beta-blockers alone might be expected to still be associated with a high post-operative AF occurrence rate. The use of preoperative prophylactic amiodarone has not been universally accepted because of the widespread use of beta-blockers, logistical preoperative loading dose issues, concerns for potential toxicity and cost.

### Intravenous (IV) Amiodarone

Intravenous (IV) amiodarone is commonly used to treat atrial and ventricular arrhythmias.<sup>19</sup> Even though tissue levels rise rapidly with IV infusion effective suppression and prevention of these arrhythmias can take days. Sinus node suppression, AV nodal blockade, and very rarely, torsades de pointes VT can occur within minutes to hours after IV loading.

### Ventricular Arrhythmias

IV amiodarone is approved by the FDA for treatment and prophylaxis of recurrent VF and hemodynamically unstable VT in patients who are refractory to other antiarrhythmic therapy. IV amiodarone is also approved to treat (suppress and prevent) VF or VT in patients who are candidates for oral amiodarone but are unable to take the oral preparation.

IV amiodarone has a “class IIb” indication in the Advanced Cardiac Life Support (ACLS) guidelines.<sup>20</sup> Based on 2 prospective randomized parallel dose-response studies,<sup>21,22</sup> IV amiodarone is now the antiarrhythmic drug of first choice for persistent VF or pulseless VT if standard (non-antiarrhythmic) resuscitative measures are ineffective.

Two prospective double blind studies evaluated IV amiodarone for shock-resistant arrest due to VT or VF in individuals experiencing out-of-hospital cardiac arrest.<sup>23,24</sup> Compared to placebo, a 300 mg IV bolus was associated with a greater chance of survival to hospital admission (44% vs 34% in the placebo group;  $P = .03$ ) but there was no survival benefit to hospital discharge (13.4% vs 13.2% survival in the placebo group).<sup>24</sup> Similarly, compared to lidocaine, a 300 mg IV bolus of amiodarone was associated with a greater chance of survival to hospital admission (22.8% vs. 12.0%,  $P = .009$ ),<sup>24</sup> but

overall survival was poor and no survival benefit to hospital discharge existed.

Amiodarone has also been advocated for treatment of VT/VF refractory to lidocaine after acute myocardial infarction<sup>25</sup> and as an adjunct for “electrical storm,” defined as multiple episodes of recurrent rapid poorly tolerated VT or VF requiring multiple defibrillation attempts over a short period of time (24 hours or less) in which recurrent VT/VF can be only transiently terminated.<sup>25</sup>

Although not tested prospectively, IV amiodarone has been used to suppress recurrent, symptomatic, non-sustained ( $\leq 30$  seconds) VT and recurrent episodes of VT in patients with ICDs who have frequent device activations (shock or anti-tachycardia pacing therapies).<sup>26–29</sup>

### **Atrial Fibrillation and Other Supraventricular Arrhythmias**

IV amiodarone is used to treat various supraventricular tachyarrhythmias, most commonly AF in acute settings, including during and after cardiovascular surgery (despite lack of robust evidence), in intensive care units, and in emergency departments.<sup>30–32</sup>

IV amiodarone can help control ventricular rate control during AF of acute onset,<sup>31</sup> especially in critically ill patients, through its short-term calcium channel-blocking and sympatholytic effects; it is not FDA-approved for this use. Acutely administered, IV amiodarone has little effect on atrial refractory periods, possibly explaining why, in placebo-controlled trials, it has not been shown to convert AF to sinus rhythm more effectively, compared to placebo.<sup>32</sup>

IV amiodarone can help to maintain sinus rhythm after electrical or spontaneous cardioversion and, even then, in many instances, only after 24–48 hours. IV loading increases myocardial tissue levels within hours, but an electrophysiologic effect can take days. The effective loading dose and time to effect are highly variable.

Several trials have addressed the potential benefits of IV amiodarone in the cardiovascular surgical setting. One recent study suggests that the drug may reduce the occurrence of AF in patients undergoing aortocoronary bypass graft surgery.<sup>31</sup> Another investigation<sup>33</sup> showed a 37% relative risk reduction in postoperative AF after 2 g IV amiodarone given prophylactically over 2 days following surgery (35% vs 47% in the control group), but the clinical impact (length of hospital stay or reduction in adverse outcomes) was not different.

Benefits seen with IV amiodarone are related to the loading regimen, patient selection, and other, undefined factors. IV amiodarone may be more effective at higher doses and given for acute episodes of AF, but the risks, including hypotension, liver function abnormalities, sinus bradycardia and AV block, are dose-dependent and depend on infusion rate.<sup>34</sup>

Data supporting the use of IV amiodarone to reduce the risk of AF and to decrease length of hospital stay in the perioperative cardiac surgical period are not consistent. Some reports suggest benefit at low doses,<sup>35</sup> others support the use of relatively large doses, and others suggest no real

benefit. Doses as high as 4500 mg over 5 days may achieve a small 1.4 day mean decrease in length of hospital stay.<sup>36</sup>

Double-blind, randomized studies (10 trials involving 1744 patients) comparing oral and/or IV amiodarone with placebo have found that prophylactic amiodarone decreases length of hospital stay and mortality after cardiac surgery.<sup>37</sup> Data in patients with recent onset AF suggest that IV amiodarone, at a dose of 5 mg/kg over 30 minutes followed by 10 mg/kg over 20 hours, was associated with significantly higher conversion rate of AF to sinus rhythm<sup>38</sup>; high doses such as this are, however, only rarely used in clinical practice.

A meta-analysis evaluating IV amiodarone vs. placebo vs. another antiarrhythmic drug in 18 randomized controlled trials showed a rate of cardioversion with IV amiodarone of 76% vs 72% using other antiarrhythmic drugs vs. 60% with placebo. Adverse events occurred in 17% taking amiodarone vs. 14% taking other antiarrhythmic drugs and 11% taking placebo.<sup>39</sup> Although one meta-analysis suggests that IV amiodarone is effective in suppressing AF after cardiac surgery,<sup>40</sup> one large meta-analysis evaluating new onset AF after cardiac surgery showed consistent evidence favoring beta-adrenergic blockade but little compelling data in favor of IV amiodarone.<sup>41,42</sup> The use of IV amiodarone as a first-line drug for management of AF in this setting may therefore be overstated.

Adverse effects of IV amiodarone include sinus bradycardia or arrest, AV nodal blockade, liver function abnormalities, hypotension, and phlebitis. Very rare cases of fulminant hepatitis and acute respiratory distress syndrome have been reported. The typical long-term side effects seen with oral amiodarone are seen rarely with acute IV dosing.

### **Use in Pregnant Patients**

Amiodarone is not well-studied in pregnant patients. Amiodarone crosses the placental barrier, although fetal serum levels are only 10–25% of maternal levels. Fetal thyroid and congenital malformations have been reported. Given the drug's complex pharmacokinetics, effects on thyroid metabolism and significant end-organ toxicity, the drug should not be used in pregnant patients unless no other option exists. Currently, it has an FDA class “D” rating.<sup>43</sup>

### **Use in Pediatric Patients**

IV amiodarone use in children is not well studied and may be associated with a high incidence of side effects and/or death. In one report of 61 children with various tachyarrhythmias, adverse events were common (87%), leading to drug withdrawal in 10. There were 5 deaths in the 30-day follow-up period (2 possibly related to the drug).<sup>44</sup> However, some tachyarrhythmias in children require rapid control as they may be lethal. Examples include transient tachyarrhythmias after congenital heart disease surgery and tachyarrhythmias that cause cardiomyopathy. Amiodarone is often the antiarrhythmic drug of choice in these settings. Arrhythmias in pediatric patients may change or resolve with time, making long-term amiodarone therapy unnecessary. If the tachyarrhythmias persist, ablation is a possibility

**Table 1** Adverse reactions to amiodarone

Reaction	Incidence (%)	Diagnosis	Management
Pulmonary	2	Cough and/or dyspnea, especially with local or diffuse opacities on high-resolution CT scan and decrease in $D_LCO$ from baseline	Usually discontinue drug; corticosteroids may be considered in more severe cases; occasionally, can continue drug if levels high and abnormalities resolve; rarely, continue amiodarone with corticosteroid if no other option
Gastrointestinal tract	30 15–30 <3	Nausea, anorexia and constipation AST or ALT level greater than 2 times normal Hepatitis and cirrhosis	Symptoms may decrease with decrease in dose If hepatitis considered, exclude other causes Consider discontinuation, biopsy, or both to determine whether cirrhosis is present
Thyroid	4–22 2–12	Hypothyroidism Hyperthyroidism	L-Thyroxine Corticosteroids, propylthiouracil or methimazole; may need to discontinue drug; may need thyroidectomy
Skin	<10 25–75	Blue discoloration Photosensitivity	Reassurance; decrease in dose Avoidance of prolonged sun exposure; sunblock; decrease in dose
Central nervous system	3–30	Ataxia, paresthesias, peripheral polyneuropathy, sleep disturbance, impaired memory and tremor	Often dose dependent, and may improve or resolve with dose adjustment
Ocular	<5  ≤1  >90	Halo vision, especially at night  Optic neuropathy  Photophobia, visual blurring, and microdeposits	Corneal deposits the norm; if optic neuropathy occurs, discontinue Discontinue drug and consult an ophthalmologist
Heart	5 <1	Bradycardia and AV block Proarrhythmia	May need permanent cardiac pacing May need to discontinue the drug
Genitourinary	<1	Epididymitis and erectile dysfunction	Pain may resolve spontaneously

ALT = alanine aminotransferase; AST = aspartate aminotransferase;  $D_LCO$  = diffusion capacity of carbon monoxide.

as the child gets older. The use of amiodarone in children should be supervised by a pediatric electrophysiologist.

### Follow-up of the patient on amiodarone

Issues of importance in follow-up are the continued assessment of drug efficacy, titration of drug dose after achieving a steady state, evaluation of adverse and toxic effects, appropriate management of toxic effects, and attention to important drug–drug and drug–device interactions. To ensure safety, therefore, meticulous follow-up is central to the care of patients taking amiodarone. Especially when used for non–life-threatening arrhythmias for which the drug is not approved, such as AF, the risk–benefit ratio of taking the drug may weigh in favor of risk rather than benefit if adverse effects occur. Our recommendations for follow-up apply to patients treated with amiodarone for either atrial or ventricular arrhythmias.

Adverse effects are common, with a prevalence as high as 15% in the first year of use and 50% during long-term use (Table 1), indicating a cumulative effect with chronic use.<sup>45–47</sup> Furthermore, since the time to steady state on a given dose of drug may exceed 6 months, it may take more than 6 months before an adverse drug effect is reversed. Fortunately, many of these adverse effects are manageable and the need to discontinue amiodarone therapy due to

serious adverse reactions is relatively low, occurring in less than 20% of patients. Nevertheless, evaluation of signs, symptoms, and certain specific test abnormalities helps to identify problems and prevent progression to serious organ toxicity. Early assessment and intervention is required when an adverse effect is suspected. Optimizing therapy with amiodarone entails using the lowest effective dose to minimize adverse effects.

When amiodarone first became available in the United States, it was prescribed only by electrophysiologists because of its potential toxicity. As the drug gained popularity, physicians not specializing in arrhythmia management began both to prescribe and also to follow patients taking the drug. While such physicians have generally been cardiologists, some internists and family practitioners may have enough experience with, and comfort using, the drug to provide follow-up evaluation. This committee recommends that only experienced personnel should direct the follow-up of patients taking amiodarone.

Routine evaluation requires an office visit to assess new symptoms possibly related to the drug (Table 1), recurrence of arrhythmias, the need for upward or downward drug titration, laboratory testing, and changes in drug therapy. Follow-up should be most intensive initially, especially if

dose titration is expected to be necessary or if outpatient oral dose loading is being undertaken. Initial assessment should occur every 3 to 6 months for the first year to assess arrhythmia stability and adverse effects, after which follow-up visits should be scheduled every 6 months. As indicated above, adverse effects increase with time of exposure, and they are partly dose-related. Some adverse effects (neurologic and gastrointestinal tract toxicity) are clearly dose-related, and often occur in the first phases of amiodarone loading. Visual changes, (e.g., "haloes" around lights) are generally, but not always, dose-related. Serious long-term toxicity, especially pulmonary and, less frequently, hepatic toxicity, appears to be in part dose-related.

### Pulmonary Toxicity

Amiodarone-induced pulmonary toxicity is a well-described and highly morbid complication of amiodarone therapy.<sup>6,48,49</sup> Clinical trials have suggested that the overall risk of developing pulmonary toxicity is around 2%, and is more common in older patients and with higher doses of therapy.<sup>5</sup> Specific trials have been largely consistent with this estimate.<sup>13,15,50</sup> Although initially described with higher-dose regimens, amiodarone pulmonary toxicity can occur with low-dose therapy,<sup>6</sup> and can occur as early as the end of the first week of therapy. Patients with preexisting pulmonary disease may be at higher risk of developing pulmonary toxicity, although the available data are discordant.<sup>48,51</sup> Serial pulmonary function testing has been shown to be a sensitive but nonspecific marker of pulmonary toxicity (likely due to a high incidence of heart failure in the population receiving the drug) and is of unclear clinical benefit.<sup>52</sup>

Amiodarone-induced pulmonary toxicity may present at any time during the course of therapy, with data supporting both early and late presentation. The most common scenario is that of acute or sub-acute cough; later manifestations include progressive dyspnea; fever may be present. Pulmonary function testing will show a decreased diffusing capacity ( $D_LCO$ ) and evidence of restriction. Chest computed tomography (CT) will generally reveal diffuse ground glass and reticular abnormalities, evidence of ongoing inflammation, and fibrosis. An increase in lung (as well as liver and spleen) attenuation on CT scan due to parenchymal accumulation of amiodarone is well described but is not predictive of current or future pulmonary toxicity.<sup>52</sup> Surgical lung biopsy should generally be avoided given reports of post-operative acute respiratory distress syndrome (ARDS),<sup>53</sup> but, if performed, reveals a non-specific interstitial pneumonia pattern, with foamy alveolar macrophages filled with amiodarone-phospholipid complexes and focal organizing pneumonia.<sup>54</sup> Bronchoscopy has little role in diagnosing pulmonary toxicity, since the findings are non-specific.

The diagnosis of amiodarone-induced pulmonary toxicity is often one of exclusion. A high index of suspicion, consistent clinical and chest CT findings and rigorous evaluation to exclude alternative etiologies (in particular infection and heart failure) should suggest the diagnosis. Treat-

ment consists of discontinuing amiodarone and, in more severe cases, starting corticosteroids. There are no good data to guide dosing and duration of corticosteroid therapy. Typically, 40 to 60 mg of prednisone (or equivalent) daily has been prescribed; the response is often rapid. Because the elimination of amiodarone is slow, prolonged therapy, on the order of months, may be required. The dose of steroids can generally be decreased after the first few months to minimize side effects. While mortality from amiodarone-induced pulmonary toxicity has been reported to be as high as 10%,<sup>49</sup> these data likely represent selection for the most severely ill patients; it is therefore likely that the true mortality rate is substantially lower, especially if the diagnosis is made early.

### When to Consult a Pulmonologist:

1. Abnormal chest radiography at baseline or follow-up evaluation.
2. Abnormal pulmonary function test value (particularly forced vital capacity and ( $D_LCO$ )) at baseline or follow-up evaluation.
3. New cough and/or dyspnea, especially if otherwise unexplained or unexpected.

All patients referred for pulmonary consultation for suspected amiodarone toxicity should undergo full pulmonary function testing (spirometry, lung volume determination, and diffusing capacity measurement) and high-resolution CT scanning of the chest.

### Effects on Thyroid Function

Treatment with amiodarone can lead to both hypo- and hyperthyroidism.<sup>55</sup> Acutely, there is an increase in thyroid stimulating hormone (TSH) (although typically it remains  $<20$  mU/L), an increase in both free and total T4, and a decrease in total, and, to a lesser extent, free T3.<sup>56,57</sup> After 3 months, a new equilibrium is reached, and TSH normalizes, again becoming the most reliable marker of thyroid status. T4, however, will remain high normal, or even frankly high, while T3 will remain low normal or, rarely, low.<sup>55,57</sup> Due to these acute changes, it is best to avoid checking thyroid function tests during the first 3 months of treatment, if possible.

In iodine sufficient areas, such as the US, the prevalence of amiodarone-induced hypothyroidism (AIH) is as high as 22%.<sup>55</sup> Both female sex and the presence of anti-thyroid antibodies prior to the initiation of therapy increase the risk.<sup>58,59</sup> Typically, AIH occurs within the first 1–24 months of amiodarone treatment.<sup>58,60</sup> The diagnosis should be suspected in the presence of an elevated TSH (generally  $>20$  mU/L) and a low or low-normal free T4. Symptoms of hypothyroidism, while nonspecific and often subtle, can also aid in the diagnosis. Treatment is accomplished with L-thyroxine, with a goal of normalizing the TSH. The majority of patients who do not have underlying Hashimoto's thyroiditis will have resolution of their hypothyroidism after discontinuation of amiodarone.<sup>59</sup> Consultation with an en-

ocrinologist may be helpful to decide on whether or not subclinical disease (high TSH but normal T4 in an asymptomatic patient) should be treated.

Prevalence of amiodarone-induced thyrotoxicosis (AIT) is much lower than that of AIH in iodine sufficient areas.<sup>55,57</sup> AIT can occur quite suddenly and at any time during treatment. The diagnosis is made based on a suppressed TSH with an elevated free T4. Given the beta-blocking effects of amiodarone, the classic findings of thyrotoxicosis are often absent. Clinically, the most common findings may be weight loss or a required change in warfarin dose. In addition, any change in cardiac status should precipitate a thyroid evaluation. In equivocal cases, a T3 level can be helpful, with an elevated or high normal T3 indicating thyrotoxicosis.

The natural history and treatment of AIT should be guided by the underlying etiology. While attempts to divide AIT into two distinct subtypes<sup>55,57</sup> have provided insight into the pathophysiology of the disease, the practical utility of this division has been limited. Some patients clearly have pre-existing thyroid disease (e.g., Graves' disease or multinodular goiter) aggravated by the iodine load of amiodarone. In other cases, toxicity to the thyroid results in thyroiditis. Unfortunately, many of the criteria proposed to distinguish between these entities do not appear applicable in iodine sufficient areas like the US,<sup>57,61</sup> and, in practice, a large percentage of patients do not clearly fall into either sub-type, and are thought to have mixed disease.<sup>62</sup> Patients who clearly have underlying thyroid disease should have amiodarone discontinued, if possible, and be treated with high doses of antithyroid drugs (propylthiouracil or methimazole). Patients who have unequivocal signs of thyroiditis (tender thyroid gland, fever) can be treated with prednisone with continuation of amiodarone. The thyroiditis is typically self-limited, and patients often eventually become hypothyroid.<sup>63</sup> For the remainder of the patients (perhaps the majority), one strategy is to start both antithyroid drugs and prednisone initially. If there is rapid improvement in 1–2 weeks, the disease is prednisone-responsive and discontinuation of the antithyroid drug can be considered.

The decision to discontinue amiodarone is made based on the cardiac needs of the patient. In patients with subclinical disease (low TSH but normal free T4 in an asymptomatic patient), the decision to discontinue amiodarone can be deferred while the response to antithyroid medication is being assessed with close clinical follow-up during that time. As the drug effects will last for months, discontinuation will not result in immediate improvement. If combination drug therapy does not improve thyroid status, options are limited. Due to the large iodine load, ablation with radioactive I<sup>131</sup> is not possible. Potassium perchlorate, an agent effective in AIT, is no longer available in the US. Thyroidectomy is effective in high-risk patients (for example those being treated for VT) who need rapid treatment.<sup>64</sup> Unfortunately, this has recently become more difficult as iopanoic acid, important for controlling thyrotoxicosis prior to

surgery,<sup>65</sup> is no longer available in the US. In light of these treatment difficulties, AIT should be evaluated and treated aggressively at the first hint of disease. For patients who need to restart the drug after discontinuation for AIT, prophylactic ablative therapy with radioactive I<sup>131</sup> is recommended and has proven successful in preventing recurrence.<sup>66</sup>

Given the significant risk of thyroid side effects, patients should have a TSH, free T4 and total T3 checked prior to initiation of therapy. In addition, obtaining anti-thyroid peroxidase antibodies (TPO) can be useful for predicting subsequent hypothyroidism. These tests, excluding TPO, should be rechecked in 3–6 months to establish a new baseline. Subsequent testing of TSH and free T4 should be conducted every 6 months or sooner based on clinical findings.

### When to Consult an Endocrinologist:

1. Any time hyperthyroidism is suspected (even if suppression of TSH is mild and subclinical disease is possible).
2. An acutely ill patient where interpretation of TFT's will be complicated by euthyroid sick syndrome.
3. When considering treating subclinical hypothyroidism.

### Specific Information To Be Acquired During Follow-up Visits

#### History

Complaints of fatigue (suggesting bradycardia, AV block, or hypothyroidism), dyspnea or cough (suggesting pulmonary toxicity), palpitations (suggesting hyperthyroidism or recurrence of arrhythmias), syncope, visual changes (including loss of vision), skin changes (including photosensitivity), weight change (suggesting hypothyroidism or hyperthyroidism), paresthesias or weakness (suggesting peripheral neuropathy), changes in drug therapy (especially additional antiarrhythmic drugs, warfarin, beta-blockers, and digoxin) that require dose adjustment, newly implanted devices (pacemakers, ICDs, or both), and sleep disturbances should be noted. Notably, amiodarone may change the rates of tachycardias and the defibrillation threshold (the minimum energy to reliably terminate VF) in patients with ICDs such that a VT may occur below the device detection rate and not be recognized and treated, or VF may not be terminated. In these patients, the drug should not be started or the dose changed without the involvement of an electrophysiologist or cardiologist in charge of device follow-up.

#### Physical Examination

Documentation of vital signs, skin color, regularity of pulse, skin color changes, thyromegaly or thyroid nodules and tenderness, dry pulmonary rales, evidence of pulmonary hypertension, left ventricular dysfunction (or both), hepatomegaly, and evidence of neurologic effects (tremor, difficulty with writing, or gait disturbance) should be made. If visual changes are reported, a thorough evaluation by an ophthalmologist, including a slit lamp examination, is required.

**Table 2** Recommended laboratory testing in patients receiving amiodarone\*

Type of test	Time when test is performed
Liver function tests	Baseline and every 6 mo
Thyroid function tests	Baseline and every 6 mo
Chest x-ray film	Baseline and then yearly
Ophthalmologic evaluation	At baseline if visual impairment
Pulmonary function tests (including $D_LCO$ )	or for symptoms
High-resolution CT Scan	Baseline and for unexplained cough or dyspnea, especially in patients with underlying lung disease, if there are suggestive x-ray film abnormalities, and if there is a clinical suspicion of pulmonary toxicity
Electrocardiogram	If clinical suspicion of pulmonary toxicity
	Baseline and when clinically relevant

$D_LCO$  = diffusion capacity of carbon monoxide; ECG = electrocardiogram.

\*If clinical circumstances warrant, more frequent follow-up will be necessary.

### Routine Laboratory Evaluation

The minimum baseline studies that should be obtained are listed in Table 2: liver function tests (because the drug is hepatically metabolized), thyroid function tests and pulmonary function tests (including the  $D_LCO$ ). A decrease in the  $D_LCO$  from baseline is compatible with amiodarone pulmonary toxicity, but it can be difficult to assess in patients with heart failure and pulmonary edema since the latter increases the  $D_LCO$ , and that itself may falsely normalize the test (see above). A baseline ophthalmologic evaluation should be obtained in any patient who has significant visual abnormalities; it is not required for all patients.

The follow-up evaluation should include, at a minimum, a yearly electrocardiogram and chest x-ray film, and, semi-annually, a thyroid profile (TSH, free T4) and profile of liver enzymes. Amiodarone levels should be obtained if arrhythmias occur or recur or if new symptoms develop, especially after dose titration or a change in drug formulation (to or from generic preparations); amiodarone levels may help determine if the drug can be titrated downward. Such may be the case for patients who experience significant weight loss. Surveillance amiodarone levels as generally obtained are of little use. Drug interactions with amiodarone, especially digoxin, warfarin, and some statins must be recognized and monitored as necessary (Table 3), since dose adjustments of these agents will be required.

### Non-routine Laboratory Evaluation

As indicated above, laboratory tests should be ordered sooner than scheduled if there are symptoms suggestive of

**Table 3** Major drug interactions with amiodarone

Drug	Interaction
Digoxin	Increased concentration and effect with sinus and AV node depression and gastrointestinal tract and neurologic toxicity
Warfarin sodium	Increased concentration and effect
Quinidine, procainamide hydrochloride, or disopyramide	Increased concentration and effect and torsade de pointes ventricular tachycardia
Diltiazem or verapamil	Bradycardia and AV block
$\beta$ Blockers	Bradycardia and AV block
Flecainide acetate	Increased concentration and effect
Phenytoin	Increased concentration and effect
Anesthetic drugs	Hypotension and bradycardia
Cyclosporine	Increased concentration and effect
Simvastatin, atorvastatin	Can promote liver function abnormalities

amiodarone toxicity in a specific organ system, for example, the thyroid or liver.<sup>57</sup> Other testing may be required, depending on changes in drug dose or changes in (or development of) new symptoms. Event monitoring or Holter monitoring may be required if new arrhythmia symptoms occur. Testing of ICDs and pacemakers for threshold changes should be performed if changes in clinical status occur, such as the development of heart failure or intercurrent myocardial infarction.

### When to Refer to an Electrophysiologist:

1. Worsening arrhythmia symptoms
2. Evidence of amiodarone toxicity requiring changes in drug dosing or drug discontinuation. Until the arrhythmia problem stabilizes, the patient may require intensified monitoring, electrophysiologic testing, ablative therapy, or pacemaker or ICD implantation.
3. Repeat defibrillation threshold testing is recommended for patients with an ICD due to the drugs effect of increasing this threshold.
4. Assess amiodarone-induced slowing of VT rate in patients with an ICD such that VT would not be detected by the device and therapy not delivered.
5. Pregnant patients who require amiodarone.
6. Pediatric patients who require amiodarone.

### Conclusion

Although clinical judgment takes precedence over guidelines in clinical practice, it is nevertheless useful to attempt to provide a consensus approach to the management of patients with specific clinical conditions. This guideline provides such an approach. The physician who prescribes amiodarone and observes patients receiving amiodarone incurs a responsibility, outlined herein. Acceptance of this responsibility should lead to improved patient outcomes, cost savings, and more rational patient care.

## Author Disclosures

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†Significant. A relationship is considered to be "significant" if (1) the person receives \$10,000 or more during any 12-month period or 5% or more of the person's gross income; or (2) the person owns 5% or more of the voting stock or share of the entity or owns \$10,000 or more of the fair market value of the entity.

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