

Prescribing Amiodarone

An Evidence-Based Review of Clinical Indications

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AMIODARONE, CONSIDERED THE most effective antiarrhythmic drug, was originally developed in the 1960s as an anti-anginal agent. It was widely prescribed in Europe for angina but serendipitously found to suppress arrhythmias. Argentinian physicians began using amiodarone to treat resistant arrhythmias in the 1970s.^{1,2} United States physicians initially obtained amiodarone from Canada and Europe. Under threat of nonshipment from Europe, the US Food and Drug Administration approved amiodarone in 1985 for use in life-threatening ventricular tachyarrhythmias when other drugs are ineffective or poorly tolerated.^{3,4} Despite limited indications, amiodarone is one of the most frequently prescribed specific antiarrhythmic drugs in the United States.⁵

In this article, we review amiodarone's clinical pharmacology and evaluate evidence supporting amiodarone for treatment and prevention of various arrhythmias, with the goal of motivating clinicians to rigorously evaluate how they prescribe amiodarone.

EVIDENCE ACQUISITION

We performed a systematic review of peer-reviewed literature using MEDLINE. We searched amiodarone using the terms *adverse effects, atrial fibrillation, atrial flutter, congestive heart failure, electrical storm, hypertrophic cardiomyopathy, implantable cardioverter-defibrillator, surgery, ventricular*

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Context Although amiodarone is approved by the US Food and Drug Administration only for refractory ventricular arrhythmias, it is one of the most frequently prescribed antiarrhythmic medications in the United States.

Objective To evaluate and synthesize evidence regarding optimal use of amiodarone for various arrhythmias.

Evidence Acquisition Systematic search of MEDLINE to identify peer-reviewed clinical trials, randomized controlled trials, meta-analyses, and other studies with clinical pertinence. The search was limited to human-participant, English-language reports published between 1970 and 2007. Amiodarone was searched using the terms *adverse effects, atrial fibrillation, atrial flutter, congestive heart failure, electrical storm, hypertrophic cardiomyopathy, implantable cardioverter-defibrillator, surgery, ventricular arrhythmia, ventricular fibrillation, and Wolff-Parkinson-White*. Bibliographies of identified articles and guidelines from official societies were reviewed for additional references. Ninety-two identified studies met inclusion criteria and were included in the review.

Evidence Synthesis Amiodarone may have clinical value in patients with left ventricular dysfunction and heart failure as first-line treatment for atrial fibrillation, though other agents are available. Amiodarone is useful in acute management of sustained ventricular tachyarrhythmias, regardless of hemodynamic stability. The only role for prophylactic amiodarone is in the perioperative period of cardiac surgery. Amiodarone may be effective as an adjunct to implantable cardioverter-defibrillator therapy to reduce number of shocks. However, amiodarone has a number of serious adverse effects, including corneal microdeposits (>90%), optic neuropathy/neuritis (≤1%-2%), blue-gray skin discoloration (4%-9%), photosensitivity (25%-75%), hypothyroidism (6%), hyperthyroidism (0.9%-2%), pulmonary toxicity (1%-17%), peripheral neuropathy (0.3% annually), and hepatotoxicity (elevated enzyme levels, 15%-30%; hepatitis and cirrhosis, <3% [0.6% annually]).

Conclusion Amiodarone should be used with close follow-up in patients who are likely to derive the most benefit, namely those with atrial fibrillation and left ventricular dysfunction, those with acute sustained ventricular arrhythmias, those about to undergo cardiac surgery, and those with implantable cardioverter-defibrillators and symptomatic shocks.

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arrhythmia, ventricular fibrillation, and Wolff-Parkinson-White. Studies included all clinical trials, randomized controlled trials, meta-analyses, and other studies with clinical pertinence. Relevant studies compared amiodarone with placebo, other contemporary antiarrhythmic drugs, or nonpharmacological therapies. We limited our search to human-participant, English-language reports published between 1970 and 2007. Bibliographies of identified articles and

guidelines from official societies were reviewed for additional references. The search identified 856 articles; of these,

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92 met the inclusion criteria and were included in the review (FIGURE).

Evidence for amiodarone use was graded using American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) recommendation classes and levels of evidence.⁶ Recommendation class I indicates conditions for which there is evidence, general agreement, or both that a given procedure or therapy is beneficial, useful, and effective; class II, conditions for which there is conflicting evidence, a divergence of opinion, or both about the usefulness or efficacy of the procedure or therapy (with class IIa indicating that the weight of evidence or opinion favors usefulness or efficacy and class IIb indicating that usefulness or efficacy is less well established by evidence or opinion); and class III, conditions for which there is evidence, general agreement, or both that a procedure or therapy is not useful or effective and in some cases may be harmful. Level of evidence A indicates that data are derived from multiple randomized clinical trials or meta-analyses; level B, that data are derived from a single randomized trial or from nonrandomized studies; and level C, that evidence represents only consensus opinion of experts, case studies, or standard of care.

EVIDENCE SYNTHESIS

Pharmacokinetics

Amiodarone has complex pharmacokinetics. It exhibits variable oral bioavailability, averaging approximately 50% (range, 22%-86%).⁷ Amiodarone is highly lipophilic, with a large volume of distribution (66 L/kg) resulting in a delayed onset of action (2 days to 3 weeks for oral therapy) and long elimination half-life.⁸ An initial 50% reduction in plasma concentration 3 to 10 days after cessation of chronic therapy is followed by a longer terminal half-life of 13 to 142 days as tissue stores deplete.^{7,8} Amiodarone is metabolized by the hepatic cytochrome p450 system and excreted in feces. Renal excretion is minimal (<1% unchanged in urine). The active metabolite of amiodarone,

N-desethylamiodarone, has a longer half-life. The "therapeutic" plasma range for amiodarone and desethylamiodarone is 0.5 to 2.5 µg/mL.⁵ Measured levels do not correlate well with efficacy or adverse effects.⁸

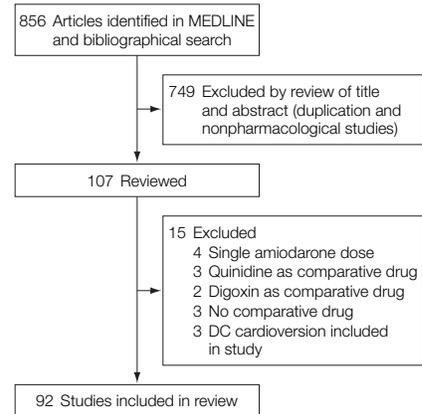
Pharmacodynamics/Cellular Electrophysiology

The pharmacodynamics of amiodarone also are complex. Electrophysiological properties differ when amiodarone is used acutely (intravenous administration) and chronically (oral administration).^{7,9,10} Effects are more pronounced after chronic therapy. Amiodarone prolongs myocardial repolarization homogeneously (reducing dispersion of refractoriness, reentry, and proarrhythmia) via potassium channel blockade (class III effect). Chronic oral therapy prolongs refractory periods in most cardiac tissues. There is little or no prolongation after intravenous use except in AV nodal fibers. Unlike other class III agents, amiodarone causes "use-dependent" potassium channel blockade in the sinus node, atria, AV node, and ventricles (less in Purkinje fibers), incrementally prolonging refractoriness as heart rate increases.⁷

Amiodarone also has class I, II, and IV antiarrhythmic effects. It decreases conduction velocity by blocking sodium channels (class I effect), produces noncompetitive β-blockade (class II effect) that can cause substantial sinus bradycardia within several days (peak, 3 months),⁷ and reduces inward L-type (slow) calcium channel activity (class IV effect) in a use-dependent fashion. Inhibition of thyroxine (T₄) deiodination to triiodothyronine (T₃) may contribute to antiarrhythmic efficacy. Expected thyroid function tests include normal or mildly increased levels of thyrotropin, decreased levels of T₃, and increased levels of T₄ and reverse T₃.¹¹ These changes usually occur without relevant clinical effects.

Although amiodarone prolongs the QT/QTc interval, torsade de pointes is uncommon (incidence, <1%).^{12,13} The

Figure. Study Selection



DC indicates direct current.

multifaceted electrophysiological effects of amiodarone likely contribute to both safety and efficacy. Desethylamiodarone has similar effects and may be more potent than amiodarone.¹⁴

Adverse Effects

Potential adverse effects include corneal microdeposits (>90%), optic neuropathy/neuritis (≤1%-2%), blue-gray skin discoloration (4%-9%), photosensitivity (25%-75%), hypothyroidism (6%), hyperthyroidism (0.9%-2%), pulmonary toxicity (1%-17%), and hepatotoxicity (elevated enzyme levels, 15%-30%; hepatitis and cirrhosis, <3% [0.6% annually]). A range of neuropsychiatric adverse effects also can occur. The most common are tremor and ataxia (3%-35%, depending on dose and duration of therapy). Peripheral neuropathy is uncommon (0.3% annually) but may be severe, requiring dose reduction or discontinuation of therapy. Insomnia, memory disturbances, and delirium also have been reported.^{8,12,13,15-29}

Most adverse effects are reversible via dose reduction or discontinuation of amiodarone. Hyperthyroidism may exacerbate atrial fibrillation (AF) or precipitate ventricular tachyarrhythmias, and amiodarone should therefore be discontinued in patients with hyperthyroidism. Electrical storm or failure of pharmacosuppression may require thyroidectomy.^{18,19} Fatal complications

such as pulmonary fibrosis, cirrhosis, and bradycardia leading to cardiac arrest have been reported.^{12,20-22} Risk factors for pulmonary fibrosis include underlying lung disease, amiodarone dosages greater than 400 mg/d, cumulative dosage, and recent pulmonary

insults.²³ Follow-up is mandatory to detect, limit, and/or reverse adverse effects. Routine screening is often underused and may not be sensitive or specific for toxicity. It is vexing that early-stage pulmonary fibrosis may be missed. Although adverse effects are usually related to daily and cumulative doses, fulminant, acute pulmonary toxicity (generally reversible if the patient survives the initial insult) has been described.²¹ BOX 1 and TABLE 1 outline follow-up recommendations for physicians and practical advice for patients receiving amiodarone.

Drug Interactions

Amiodarone interacts with many other drugs.⁷ Perhaps the most important interaction is warfarin potentiation¹⁵; warfarin dosage must be reduced when initiating amiodarone, and international normalized ratios should be closely assessed for several months. Elevation of digoxin levels is also common; dose reduction (50%) and close monitoring of serum digoxin levels is recommended. Amiodarone can cause significant sinus or AV nodal depression, especially when combined with

β -blockers or calcium channel blockers. Additional drug-drug interactions are listed in BOX 2.

Atrial Fibrillation

Cardioversion of AF. Multiple small randomized controlled trials and 5 meta-analyses have compared amiodarone with placebo or other drugs for conversion of recent-onset AF.³²⁻⁴⁰ Two trials found no difference in conversion rates between amiodarone and placebo.^{32,33} Another found amiodarone and sotalol to be equally efficacious.³⁴ A study by Vardas et al³⁵ demonstrated the strongest evidence of superiority over placebo: in 200 study patients, 61% in the amiodarone group vs 40% in the placebo group converted to sinus rhythm at 24 hours.

Because of small patient numbers, differences in trial design, and conflicting results, 5 meta-analyses evaluated amiodarone's benefit in AF conversion.³⁷⁻⁴¹ One showed amiodarone to be more effective than placebo in converting AF to sinus rhythm; benefit was greater in patients who had experienced AF for longer than 48 hours.³⁷ Another demonstrated amiodarone to be more effective than pla-

Box 1. Amiodarone: Practical Advice for Clinicians and Patients¹²

Refer to cardiologist when amiodarone therapy is contemplated

Make every effort to use less toxic alternatives (other antiarrhythmic drugs or ablation)

Do not use in patients with symptomatic conduction system disease, significant liver disease, hyperthyroidism, or significant pulmonary disease

Patients should wear sunscreen and limit sun exposure

To avoid adverse drug-drug interactions, patients taking amiodarone should consult their pharmacist/cardiologist whenever a new drug is prescribed

Table 1. Amiodarone Monitoring and Recommendations

System	Monitoring		Possible Adverse Effect	Recommendation
	Baseline	Follow-up		
Cardiac	ECG (at baseline and during loading dose)	Yearly	QT prolongation; torsade de pointes	Reduce amiodarone dose or discontinue use
			Symptomatic sinoatrial or conduction system impairment	Reduce amiodarone dose or discontinue use
Dermatologic	Physical examination	As needed for signs/symptoms	Photosensitivity to UV light	Avoid sunlight; use sunscreen
			Blue-gray skin discoloration	Reduce amiodarone dose or discontinue use
Endocrine	Thyroid function tests	Every 6 mo	Hyperthyroidism	Discontinue amiodarone; refer to endocrinologist
			Hypothyroidism	Treat with levothyroxine
Hepatic	AST or ALT	Every 6 mo	AST or ALT elevation $\geq 2\times$ upper limit of reference range	Reduce amiodarone dose or discontinue use
Neurologic	Physical examination	As needed for signs/symptoms	See "Evidence Synthesis"	Reduce amiodarone dose or discontinue use
Ophthalmologic	Eye examination	As needed for signs/symptoms	Corneal microdeposits	Continue amiodarone treatment
			Optic neuropathy	Discontinue treatment
Pulmonary	Pulmonary function tests	As needed for signs/symptoms	Pulmonary toxicity (cough, fever, dyspnea)	Discontinue amiodarone immediately; consider corticosteroid treatment
	Chest radiograph	Yearly		

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECG, electrocardiogram.

cebo; however, propafenone and flecainide were even more effective.³⁸ A third study showed amiodarone to be more effective than placebo, with no difference compared with other antiarrhythmic drugs. Adverse events were significantly higher with amiodarone vs placebo but were comparable to those with other antiarrhythmic drugs.³⁹ In contrast, Miller et al⁴⁰ did not demonstrate amiodarone efficacy compared with placebo. They analyzed only 3 trials (108 patients), 2 with high spontaneous conversion rates, and demonstrated effective conversion with ibutilide, dofetilide, flecainide, and propafenone.

Conversion rates with amiodarone have never been superior, and conversion occurs faster with other antiarrhythmic drugs.⁴¹⁻⁴⁸ Therefore, amiodarone's role in chemical cardioversion of AF is limited. We recommend trying ibutilide or dofetilide before amiodarone in patients with left ventricular dysfunction when restoring sinus rhythm seems clinically important. ACC/AHA/ESC guidelines support amiodarone as an alternative when conversion to sinus rhythm is necessary (class IIa recommendation, evidence level A).⁶

Maintenance of Sinus Rhythm. A few randomized trials have found amiodarone to be more effective than other antiarrhythmic drugs.^{34,44,49,50} A substudy of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) found amiodarone to be significantly more effective at maintaining sinus rhythm than sotalol or class I agents. Adverse effects causing drug discontinuation were common in all 3 groups.⁴³ Another study demonstrated amiodarone to be more effective than sotalol or propafenone. Amiodarone caused more adverse effects, but this was not statistically significant.⁴⁹ A large meta-analysis also found amiodarone to be significantly better at reducing AF recurrence compared with sotalol or class I drugs.⁵⁰ Amiodarone was associated with less drug withdrawal and proarrhythmia than class I agents. Outcomes were measured at 1 year (amiodarone's adverse effects increase over time).

Box 2. Interactions of Amiodarone With Specific Other Drugs^{6,12,23,30,31}

- Azole antifungals (may prolong QTc)
- β-Blockers (may cause sinus bradycardia or AV block)
- Nondihydropyridine calcium channel blockers (may cause sinus bradycardia or AV block)
- Cimetidine (may increase amiodarone levels)
- Cholestyramine (may decrease amiodarone levels)
- Clonazepam (may increase effect of clonazepam)
- Cyclosporine (may increase levels of cyclosporine—monitor levels)
- Digoxin (increases digoxin levels—reduce digoxin dose by 50% and monitor levels)
- Fentanyl (may cause bradycardia, sinus arrest, and hypotension)
- Flecainide (increases flecainide levels—reduce flecainide dose by 25%)
- Fluoroquinolones (may prolong QTc—use of sparfloxacin contraindicated)
- Statins (lovastatin, simvastatin) (may increase the risk of rhabdomyolysis or myopathy)
- Lidocaine (may increase serum levels/toxicity of lidocaine)
- Macrolide antibiotics (may prolong QTc)
- Procainamide (increases procainamide levels—reduce procainamide dose by 33%)
- Protease inhibitors (may increase amiodarone levels and toxicity)
- Quinidine (increases quinidine levels—reduce quinidine dose by 33%; may prolong QTc)
- Rifampin (may decrease amiodarone levels)
- St John's wort (may decrease amiodarone levels)
- Theophylline (may increase theophylline levels)
- Warfarin (potentiates effect—reduce warfarin dose by 25%-33% and monitor international normalized ratio)

Because AFFIRM demonstrated no significant differences in stroke, quality of life, or mortality with rhythm vs rate control, physicians must consider the risk-benefit ratio of antiarrhythmic drugs to maintain sinus rhythm.⁵¹ Dofetilide is a less toxic alternative for patients with congestive heart failure (CHF). Due to adverse effects, we reserve maintenance of sinus rhythm with amiodarone for symptomatic patients having significant structural heart disease. Amiodarone is also reasonable in symptomatic elderly patients in whom concerns about long-term toxicity are limited. Amiodarone is useful for control of rhythm, rate, or both in patients with suspected tachycardia-mediated cardiomyopathy. Once left ventricular function normalizes, switching to less toxic antiarrhythmic drugs seems prudent. ACC/AHA/ESC guide-

lines recommend amiodarone for maintenance of sinus rhythm in patients with significant left ventricular hypertrophy and CHF.⁶

Rate Control. Amiodarone slows ventricular rate in AF, even when sinus rhythm is not restored.^{32,33,38,42,52,53} Rate reduction occurs soon after intravenous administration. Intravenous amiodarone controls ventricular rate as effectively as diltiazem in critically ill patients, with less hypotension.⁵³ In contrast, class I agents may increase ventricular rate (vagolytic effects, organization to atrial flutter with 1:1 AV conduction). ACC/AHA/ESC guidelines assign intravenous amiodarone a class IIa recommendation for acute rate control in patients with AF when other measures are unsuccessful or contraindicated (evidence level C).⁶ Oral amiodarone is not appropriate first-

line therapy for chronic rate control. If β -blockers, calcium channel blockers, or digoxin (alone or combined) are ineffective, AV junction ablation and pacemaker implantation may be preferable to chronic use of amiodarone. Oral amiodarone in the nonacute setting is an ACC/AHA/ESC class IIb recommendation (evidence level C).⁶ Because cardioversion or embolization may occur, anticoagulation (3 weeks of therapeutic warfarin or intravenous heparin plus transesophageal echocardiography without thrombus) is pivotal prior to amiodarone initiation in AF present for longer than 48 hours. Warfarin should be continued for 4 weeks postconversion.

AF and CHF. Amiodarone does not exacerbate CHF and may improve ventricular function (vasodilation).⁵⁴ Equally important, it produces less proarrhythmia than other antiarrhythmic drugs. A subanalysis of the Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy (CHF-STAT) evaluated the effect of amiodarone on morbidity and mortality in patients with AF and CHF.⁵⁵ Patients (N=667) with dilated cardiomyopathy and frequent premature ventricular complexes were randomized to receive amiodarone (300 mg/d) or placebo. Analysis of 103 patients with AF at baseline demonstrated that the amiodarone group converted to sinus rhythm more often, and ventricular rate significantly decreased when AF persisted. In contrast to AFFIRM, survival improved in patients who converted to sinus rhythm while receiving amiodarone. In patients with baseline sinus rhythm, new-onset AF occurred less often with amiodarone.⁵⁵ The risk-benefit ratio of amiodarone in patients with CHF and asymptomatic AF seems prohibitive, and in such patients we prefer a conventional rate control strategy. In patients with CHF and symptomatic AF, we recommend dofetilide or amiodarone.

AF and Wolff-Parkinson-White Syndrome. Atrial fibrillation occurs in approximately one-third of patients with Wolff-Parkinson-White syndrome and is potentially life-threatening.

^{8,56} Repetitive ventricular conduction during AF can result in a rapid ventricular response, hemodynamic compromise, and degeneration to ventricular fibrillation (VF). Hemodynamic compromise requires direct-current cardioversion. Procainamide and ibutilide prevent rapid conduction through the accessory pathway and may be used when hemodynamic stability permits.^{56,57} Although small studies demonstrated efficacy with amiodarone, there are reports of ventricular rate acceleration leading to VF, especially after intravenous administration.⁵⁸⁻⁶⁰ Use of intravenous amiodarone is limited by its relatively slow onset of action. The long half-life of amiodarone may impede diagnostic and interventional electrophysiologic procedures.⁵⁶

Long-term therapy is aimed at alleviating symptoms and reducing risk from preexcited AF. The most effective therapy is catheter ablation. Even the low annual incidence of sudden death (0.15% to 0.39% over 3- to 10-year follow-up) supports liberal ablation indications.⁵⁶ Ablation eliminates atrial fibrillation in more than 90% of patients.^{56,61} Amiodarone is generally not warranted because of its adverse-effect profile. Exceptions might include patients with structural cardiac disease who are not ablation candidates or when other available options have been exhausted.⁵⁶ Amiodarone is an ACC/AHA/ESC class IIb recommendation in hemodynamically stable patients with AF involving accessory pathway conduction (evidence level B).⁶

AF and Hypertrophic Cardiomyopathy. Atrial fibrillation can be catastrophic in patients with hypertrophic cardiomyopathy (HCM).^{62,63} Amiodarone has been advocated for atrial arrhythmias in patients with HCM; however, this is based on limited, nonrandomized controlled trials.^{64,65} In a retrospective evaluation of patients with HCM and AF, amiodarone was associated with fewer electrical cardioversions and embolic events compared with class I drugs.⁶⁶ Due to a paucity of data, we do not recommend AF prophylaxis with

amiodarone in patients with HCM. Although HCM-specific data are limited, amiodarone is viewed as the most effective antiarrhythmic drug for preventing recurrences of AF.^{6,54} Amiodarone is an ACC/AHA/ESC class IIa recommendation (evidence level C) to prevent recurrent AF in patients with HCM.⁶

Atrial Flutter. Atrial flutter and fibrillation often coexist. Typical (type I or isthmus-dependent) flutter is a macroreentrant arrhythmia with atrial rates of 250 to 350 per minute, and 2:1 AV conduction is common. Atrial fibrillation is more rapid (400-600 per minute in the atria). Concealed AV nodal conduction (and subsequent refractoriness) results in slower ventricular rates. Atrial flutter is difficult to rate control, often requiring higher medication doses, multiple AV nodal-blocking drugs, or both. Several studies have demonstrated amiodarone effective at maintaining sinus rhythm in patients with AF or flutter; however, this is based on limited numbers of patients with flutter.^{67,68} Ablation is more effective first-line treatment for typical atrial flutter than amiodarone or other antiarrhythmic drugs.^{69,70}

Other Supraventricular Tachyarrhythmias. Amiodarone has terminated multifocal atrial tachycardia in small series of adult patients.⁷¹ It has been used successfully for automatic AV junctional tachycardia in adults and children.^{72,73} Although amiodarone is effective for AV nodal-dependent supraventricular tachycardias, catheter ablation or less toxic drugs are treatments of choice.⁷⁴

Ventricular Arrhythmias. In the 1980s, the respective roles of amiodarone and implantable cardioverter-defibrillators (ICDs) were defined nearly simultaneously, at times, during direct competition. Amiodarone remained popular despite the manifest efficacy of ICDs. Skeptics speculated that ICDs simply changed the mode of death (arrhythmic to pump failure).

Following Myocardial Infarction. Patients with complex ventricular ectopy following myocardial infarction (MI) are at risk of sudden cardiac death

Table 2. Use of Amiodarone Following Myocardial Infarction

Source	No. of Participants	Population	Randomization	Main Outcomes
BASIS, ⁷⁶ 1990	312	Prior MI; asymptomatic frequent multiform or repetitive ventricular arrhythmias (Lown class 3 or 4b)	Individualized antiarrhythmic drug therapy vs amiodarone vs placebo	Reduction in total mortality with amiodarone compared with placebo Reduction in arrhythmic events with amiodarone No significant mortality reduction with individualized antiarrhythmic drug therapy
CAMIAT, ⁷⁷ 1997	1202	Prior MI; ≥ 10 PVCs/h or NSVT	Amiodarone vs placebo	Reduction in resuscitated VF or arrhythmic death
EMIAT, ⁷⁸ 1997	1486	Prior MI; LVEF $\leq 40\%$	Amiodarone vs placebo	No reduction in total mortality Significant (35%) risk reduction in arrhythmic deaths

Abbreviations: BASIS, Basel Antiarrhythmic Study of Infarct Survival; CAMIAT, Canadian Amiodarone Myocardial Infarction Arrhythmia Trial; EMIAT, European Myocardial Infarction Amiodarone Trial; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSVT, nonsustained ventricular tachycardia; PVC, premature ventricular contraction; VF, ventricular fibrillation.

(SCD). Despite ectopy suppression, the Cardiac Arrhythmia Suppression Trial (CAST) demonstrated increased mortality with class Ic drugs.⁷⁵ Amiodarone (not used in CAST) remained a theoretical option for prevention of sudden death. The Basel Antiarrhythmic Study of Infarct Survival (BASIS) demonstrated reduced total mortality and SCD with prophylactic amiodarone. Patients underwent follow-up for only 1 year, and β -blocker use was limited.⁷⁶ The Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT) and the European Myocardial Infarction Amiodarone Trial (EMIAT) both demonstrated reduction of arrhythmic death with amiodarone. Neither revealed a decrease in overall mortality.^{77,78} β -Blockers reduce the risk of sudden and overall post-MI mortality.⁷⁹ They cost less, have no long-term adverse effects, and are preventive drugs of choice post MI.⁸⁰ The role of amiodarone in patients with normal left ventricular function following MI is very limited. (TABLE 2).

Primary Prevention of SCD and Ischemic Cardiomyopathy. Sudden cardiac death in ischemic cardiomyopathy (left ventricular ejection fraction $<35\%$ - 40%) remains a substantial problem despite improved medical treatment. Multiple studies have compared ICDs with antiarrhythmic drugs for primary prevention of SCD. The Multicenter Automatic Defibrillator Trial I (MADIT I), the first randomized trial comparing ICDs with con-

ventional medical therapy in patients with prior MI at high risk of ventricular arrhythmias, demonstrated a significant decrease (54%) in overall mortality with ICD therapy.⁸¹ Amiodarone was the most frequently used antiarrhythmic (conventional) therapy; some patients received class I drugs, sotalol, or no antiarrhythmic drug. ICD benefit was reconfirmed in the larger Multicenter Unsustained Tachycardia Trial (MUSTT).⁸² In both studies, use of β -blockers was limited, and proarrhythmia from class I antiarrhythmic drugs could not be excluded. MADIT II evaluated ICDs without comparison to antiarrhythmic drugs.⁸³ Significant total mortality reduction with ICD therapy confirmed benefit in ischemic cardiomyopathy. Overestimating ICD benefit (due to class I drug-induced proarrhythmic mortality) was not an issue.⁸⁴ In the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), 1310 patients with ischemic cardiomyopathy and New York Heart Association (NYHA) class II or III CHF were randomized to receive ICD, placebo, or amiodarone.⁸⁵ ICD recipients had significantly lower mortality, whereas amiodarone did not impact survival; thus, ICDs are the treatment of choice to prevent SCD in patients with ischemia-related ventricular dysfunction (TABLE 3).

Amiodarone, Ventricular Arrhythmias, and CHF. The GESICA (Grupo de Estudio de la Sobrenda en la Insuficiencia Cardiaca en Argentina) trial was

a large randomized trial of prophylactic amiodarone (300 mg/d) in patients with CHF (NYHA class II to IV).⁸⁹ There was significant reduction in SCD, death due to progressive CHF, and overall mortality. In addition, there was a decrease in hospital admission for CHF. The standard regimen for CHF (at the time) did not include β -blockers. In contrast, CHF-STAT demonstrated no difference in overall mortality between amiodarone and placebo.⁵⁴ Approximately two-thirds of GESICA patients were nonischemic, vs only one-third of CHF-STAT patients. There was a trend toward reduced mortality in amiodarone-treated patients with nonischemic cardiomyopathy in CHF-STAT. The possibility that amiodarone might reduce mortality in nonischemic cardiomyopathy remained open.

Primary Prevention of Sudden Death in Nonischemic Cardiomyopathy. Several trials have been conducted to delineate the role of antiarrhythmic drugs and ICDs in patients with nonischemic cardiomyopathy.⁸⁵⁻⁸⁸ Neither the Cardiomyopathy Trial (CAT)⁸⁶ nor the Amiodarone Versus Implantable Defibrillator in Patients With Nonischemic Cardiomyopathy and Asymptomatic Nonsustained Ventricular Tachycardia (AMIOVIRT)⁸⁷ trial demonstrated significant total mortality reduction with ICDs. AMIOVIRT demonstrated a trend toward improved arrhythmia-free survival with amiodarone. Asymptomatic tachycardias may not have been recognized in patients receiving amio-

darone. SCD-HeFT, which included 1211 patients with nonischemic cardiomyopathy and NYHA class II or III CHF and left ventricular ejection fraction of 35% or less, demonstrated significant total mortality reduction with ICDs.⁸⁵ Amiodarone had a neutral effect.

ICDs are first-line therapy for primary prevention in patients with CHF and nonischemic cardiomyopathy. Data for asymptomatic patients with nonischemic cardiomyopathy are less definitive. ICD therapy should be considered on an individual basis.^{83,85,87,88,90,91} Prophylactic amiodarone is not indicated for primary prevention in patients with nonischemic cardiomyopathy (Table 3).

Secondary Prevention of SCD. A retrospective study of patients who declined ICD implantation found amioda-

rone to be as effective as ICDs (no significant mortality difference) in secondary prevention of SCD.⁹² In contrast, a similar nonrandomized study demonstrated significant mortality benefit from ICDs in patients with reduced ejection fraction and inducible ventricular tachycardia (VT) while receiving amiodarone.⁹³ The Cardiac Arrest in Seattle: Conventional versus Amiodarone Drug Evaluation (CASCADE) compared empirical amiodarone with conventional antiarrhythmic drugs guided by electrophysiological testing, holter monitoring, or both.⁹⁴ Amiodarone reduced recurrences of ventricular arrhythmia and improved long-term survival in survivors of out-of-hospital VF arrest. Amiodarone-related adverse effects were common, especially as duration of therapy increased.

Three randomized prospective trials compared ICDs with amiodarone or other antiarrhythmic drugs in secondary prevention of SCD.⁹⁵⁻⁹⁷ The Canadian Implantable Defibrillator Study (CIDS) and the Cardiac Arrest Study Hamburg (CASH) both demonstrated reduced all-cause mortality with ICDs compared with amiodarone, but neither result reached statistical significance.^{95,96} The effect of amiodarone was comparable with that of metoprolol in CASH. The largest of the 3 trials, the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial, demonstrated significant overall mortality reduction with ICDs compared with antiarrhythmic drugs in patients resuscitated from near-fatal ventricular arrhythmias.⁹⁷ Amiodarone was used in most patients receiving drug therapy, whereas

Table 3. Primary Prevention of Sudden Cardiac Death in Ischemic and Nonischemic Cardiomyopathy

Source	No. of Participants	Population	Randomization	Main Outcomes
Ischemic Cardiomyopathy				
MADIT, ⁸¹ 1996	196	Prior MI; LVEF \leq 35%; asymptomatic NSVT; NYHA class I-III; inducible VT refractory to intravenous procainamide on electrophysiological study	Antiarrhythmic therapy (74% amiodarone) vs ICD	Reduction in total mortality with ICD therapy
MUSTT, ⁸² 1999	704	CAD; LVEF \leq 40%; NSVT; inducible VT on electrophysiological study	Electrophysiologically guided therapy [antiarrhythmic or ICD] vs conventional therapy	Reduction in total mortality with electrophysiologically guided therapy solely due to ICD therapy. Amiodarone used in 10% of patients in antiarrhythmic group
MADIT II, ⁸³ 2002	1232	Prior MI; LVEF \leq 30%	Conventional therapy vs ICD (no antiarrhythmic drug group)	Reduction in total mortality with ICD therapy
SCD-HeFT, ⁸⁵ 2005	2521	NYHA class II/III CHF (ischemic and nonischemic); LVEF \leq 35%	Conventional therapy vs amiodarone vs ICD	Reduction in mortality with ICD therapy in patients with ischemic cardiomyopathy. Amiodarone had neutral mortality effect
Nonischemic Cardiomyopathy				
CAT, ⁸⁶ 2002	104	NYHA class II/III; nonischemic dilated cardiomyopathy; LVEF \leq 30%; asymptomatic NSVT	Conventional therapy vs ICD (no antiarrhythmic drug group)	No reduction in total mortality with ICD therapy
AMIOVIRT, ⁸⁷ 2003	103	NYHA class I-III; nonischemic dilated cardiomyopathy; LVEF \leq 35%, asymptomatic NSVT	Amiodarone vs ICD	No reduction in total mortality with ICD therapy. Trend toward improved arrhythmia-free survival with amiodarone
DEFINITE, ⁸⁸ 2004	458	NYHA class I-III; nonischemic dilated cardiomyopathy; LVEF \leq 36%; \geq 10 PVCs/h or NSVT	Conventional therapy vs ICD (no antiarrhythmic drug group)	Nonsignificant reduction in total mortality with ICD therapy. Significant reduction in death from arrhythmia with ICD therapy
SCD-HeFT, ⁸⁵ 2005	2521	NYHA class II/III CHF (ischemic and nonischemic); LVEF \leq 35%	Conventional therapy vs amiodarone vs ICD	Reduction in mortality with ICD therapy in patients with nonischemic cardiomyopathy. Amiodarone had neutral mortality effect

Abbreviations: AMIOVIRT, Amiodarone Versus Implantable Cardioverter-Defibrillator in Patients with Nonischemic Cardiomyopathy and Asymptomatic Nonsustained Ventricular Tachycardia; CAD, coronary artery disease; CAT, Cardiomyopathy Trial; CHF, congestive heart failure; DEFINITE, Prophylactic Defibrillator Implantation in Patients With Nonischemic Dilated Cardiomyopathy; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MADIT, Multicenter Automatic Defibrillator Trial; MI, myocardial infarction; MUSTT, Multicenter Unsustained Tachycardia Trial; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; PVC, premature ventricular contraction; SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial; VT, ventricular tachycardia.

a limited number received sotalol. A meta-analysis of these 3 trials demonstrated significant relative reduction in total (27%) and arrhythmic (53%) mortality with ICDs.⁹⁸ ICDs are the therapy of choice for secondary prevention of SCD (TABLE 4).

Adjunct to ICD Therapy. ICD recipients may have frequent arrhythmias that result in shocks. Since ICDs are usually implanted in patients with significant heart disease, class I antiarrhythmic drugs are relatively contraindicated. Amiodarone and sotalol are preferable for arrhythmia suppression. Catheter ablation eliminates inappropriate shocks from supraventricular tachyarrhythmias and is an attractive option for patients with hemodynamically stable ventricular tachycardias.

Amiodarone plus β -blockers proved more effective than sotalol or β -blockers alone in prevention of shocks, although there was an increase in drug-related adverse effects.⁹⁹ We recommend adjunctive amiodarone therapy for patients receiving β -blockers to reduce frequent ICD discharges. Amiodarone may slow rates of ventricular tachycardia, making it amenable to antitachycardia pacing. However, amiodarone may increase defibrillation thresholds. Whether this warrants routine repeat ICD testing is controversial.^{12,100-102} We repeat noninvasive programmed stimulation and testing of defibrillation thresholds after amiodarone loading. Sotalol, which may reduce defibrillation thresholds, may be a better choice for patients with high defibrillation energy requirements.

HCM and Ventricular Arrhythmias. Patients with HCM and ventricular arrhythmias have an increased risk of SCD.¹⁰³ Patients with 1 or more major risk factors should be considered for ICD prophylaxis.^{104,105} ICDs are indicated for secondary prevention in patients with HCM. Prior to ICD use, several small nonrandomized trials suggested that prophylactic amiodarone reduced SCD^{64,106}; however, routine amiodarone prophylaxis is not recommended.¹⁰³ Amiodarone is an acceptable alternative in patients with HCM who refuse ICD therapy.

Table 4. Secondary Prevention of Sudden Cardiac Death

Study	No. of Participants	Population	Randomization	Main Outcomes
CASCADE, ⁹⁴ 1993	228	Survived out-of-hospital VF arrest; ≥ 10 PVCs/h or inducible VT/VF inducible on electrophysiological study	Empirical amiodarone vs electro-physiologically guided/Holter guided conventional antiarrhythmic drugs	Amiodarone more effective than conventional antiarrhythmic drugs in preventing cardiac death and arrhythmic events Amiodarone had significant adverse effects
AVID, ⁹⁷ 1997	1016	Survived VT/VF/cardiac arrest; VT with syncope; VT with LVEF $\leq 40\%$	Antiarrhythmic drugs (97% amiodarone, 3% sotalol) vs ICD	Reduction in total mortality with ICD therapy
CASH, ⁹⁶ 2000	288	Survived VT/VF/cardiac arrest	Antiarrhythmic drugs: metoprolol or amiodarone vs ICD	Nonsignificant reduction in total mortality with ICD therapy Amiodarone was similar in efficacy to metoprolol
CIDS, ⁹⁵ 2000	659	Survived VT/VF/cardiac arrest; VT with syncope; symptomatic VT (≥ 150 /min) with LVEF $\leq 35\%$	Amiodarone vs ICD	Nonsignificant reduction in total mortality with ICD therapy Nonsignificant reduction arrhythmic death with ICD therapy

Abbreviations: AVID, Antiarrhythmics Versus Implantable Defibrillators; CASCADE, The Cardiac Arrest in Seattle: Conventional Vs Amiodarone Drug Evaluation; CASH, Cardiac Arrest Study Hamburg; CIDS, Canadian Implantable Defibrillator Study; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; PVC, premature ventricular contraction; VF, ventricular fibrillation, VT, ventricular tachycardia.

Hemodynamically Stable VT. Intravenous amiodarone is useful in acute management of hemodynamically stable VT.¹⁰⁷ The risk-benefit ratio favors short-term use to reduce adverse effects.

Stable VT is not a benign presentation in patients with structural heart disease. The AVID registry (4595 patients) demonstrated a trend toward increased mortality in stable compared with unstable VT.¹⁰⁸ Given the subsequent risks, clinicians should consider catheter ablation, ICD therapy, or both once the acute arrhythmia is stabilized. Because arrhythmic substrates evolve, we prefer global protection from ICDs over ablation alone.

Cardiac Arrest and Electrical Storm. Electrical storm is defined as VT or VF occurring 2 or more times in 24 hours, usually requiring electrical cardioversion or defibrillation.¹⁰⁹ Small nonrandomized trials demonstrated amiodarone to be safe and effective therapy for recurrent drug-refractory sustained ventricular arrhythmias.^{109,110} Intravenous

amiodarone is more effective than lidocaine for out-of-hospital VF resistant to shocks and epinephrine. More amiodarone-treated patients survive to hospital admission.¹¹¹ Fogel et al¹¹² demonstrated 80% 1-year survival in patients with recurrent hemodynamically destabilizing ventricular arrhythmias who were treated initially with intravenous amiodarone and were receiving oral amiodarone at discharge.¹¹² Following MI, patients with electrical storm treated with sympathetic blockade followed by oral amiodarone had significantly better short-term mortality compared with conventional antiarrhythmic drugs. Patients who received a combination of oral amiodarone and a β -blocker had the best outcomes.¹¹³ Although limited data exist, β -blockade in conjunction with amiodarone appears to be the most effective therapy for electrical storm.

Perioperative. A meta-analysis of perioperative prophylactic amiodarone demonstrated decreased AF/flutter, ventricular tachyarrhythmias, stroke, and re-

duced length of stay after cardiac surgery.¹¹⁴ Not all included studies used β -blockade, and the course of therapy was inconsistent among trials. The Prophylactic Oral Amiodarone for the Prevention of Arrhythmias That Begin Early After Revascularization, Valve Replacement, or Repair (PAPABEAR) study, a large randomized controlled trial, compared perioperative amiodarone (10 mg/kg daily beginning 6 days before and continuing for 6 days after surgery) with placebo and showed significant reduction in postoperative atrial tachyarrhythmias.¹¹⁵ Toxicity was limited because amiodarone was used for a short duration. Neither study demonstrated mortality benefit. The data for perioperative amiodarone in cardiac surgery is compelling; however, incremental benefit beyond β -blockade alone remains unclear. Sotalol and corticosteroids (less extensively investigated) also have been reported to prevent postoperative AF.^{116,117} It may remain reasonable to reserve amiodarone for postoperative AF in patients receiving β -blockers. Amiodarone should be discontinued 6 to 12 weeks postoperatively to limit adverse effects.

COMMENT

Amiodarone can be used to safely treat supraventricular and ventricular arrhythmias. It usually does not exacerbate CHF and is rarely proarrhythmic. The unique pharmacokinetics and pharmacodynamics of amiodarone make it difficult to predict individual patient responses. Substantial cardiac and non-cardiac adverse effects may (rarely) be fatal. Important drug-drug interactions frequently complicate management.

Does use of amiodarone expose patients to excessive risk for nonlethal arrhythmias? Amiodarone is not associated with increased mortality; nevertheless, its adverse effects and drug-drug interactions should elicit caution when prescribing this drug for nonlethal arrhythmias. Because of its efficacy and despite these limitations, amiodarone is one of the most frequently prescribed antiarrhythmic drugs in the United States.

But is amiodarone prescribed too often? Based on available evidence, we endorse amiodarone therapy for the following specific, limited indications: (1) Prophylactic amiodarone is appropriate only in the perioperative period of cardiac surgery. (2) Amiodarone can be used safely in patients with left ventricular dysfunction and CHF. (3) Amiodarone is useful acutely in both cardiac arrest and hemodynamically stable VT. (4) Amiodarone is a safe, effective adjunct to ICDs. (5) Amiodarone in conjunction with β -blockers is effective for electrical storm. (6) Amiodarone is appropriate first-line AF therapy only in symptomatic patients with left ventricular dysfunction and CHF. The risks and benefits of amiodarone should be compared with alternative strategies for treating refractory AF (rate control with anticoagulation, AF ablation) in each patient. (7) Typical atrial flutter and paroxysmal supraventricular tachycardia are best managed by catheter ablation. Amiodarone therapy has little or no role.

CONCLUSION

Amiodarone should be used judiciously (with close follow-up) in patients likely to derive the most benefit, namely those with AF and left ventricular dysfunction, those with acute sustained ventricular arrhythmias, those about to undergo cardiac surgery, and those with ICDs and symptomatic shocks.

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Study concept and design: Vassallo, Trohman.

Acquisition of data: Vassallo, Trohman.

Analysis and interpretation of data: Vassallo, Trohman.

Drafting of the manuscript: Vassallo, Trohman.

Critical revision of the manuscript for important intellectual content: Trohman.

Administrative, technical, or material support: Vassallo, Trohman.

Study supervision: Trohman.

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