

**DAVID BELLO, MD**Cardiology Section, San Francisco
Department of Veterans Affairs Medical Center**BARRY M. MASSIE, MD**Professor of Medicine, University of California,
San Francisco; Cardiology Section, San Francisco
Department of Veterans Affairs Medical Center

The current role of amiodarone in patients with congestive heart failure

■ ABSTRACT

Amiodarone in low to moderate doses is generally safe in controlling arrhythmias in patients with congestive heart failure (CHF). However, its role is uncertain, because it did not affect the overall mortality rate in three out of four large-scale studies. Whether some subgroups might benefit is a matter of speculation. In patients with sustained ventricular tachycardia, or in those who have survived an episode of sudden death, implantation of a cardioverter-defibrillator may be a better strategy.

■ KEY POINTS

Ventricular premature beats are common in patients with CHF, of whom 25% to 60% have runs of nonsustained ventricular tachycardia.

Amiodarone is perhaps the only antiarrhythmic agent that rarely worsens arrhythmias.

Two large trials specifically examined whether amiodarone would increase survival in patients with CHF, and these gave conflicting results. Possible explanations include differences in the etiology of heart failure, patient age and sex, and degree of sickness at baseline between the two study populations.

CONGESTIVE HEART FAILURE (CHF) imposes a high mortality rate, much of it in the form of sudden death, presumably due to arrhythmias. In theory, we should be able to reduce the mortality rate by giving drugs to control arrhythmias. Unfortunately, this theory has been difficult to prove.

Several recent large clinical trials showed that the antiarrhythmic drug amiodarone, in low to moderate doses, is generally safe and is, in fact, the antiarrhythmic agent of choice in CHF. In three of four of these trials, however, amiodarone did not affect the overall mortality rate at all. The trials suggested—but did not prove—that some subgroups of patients with CHF might benefit more from amiodarone: patients with severe CHF, primary (nonischemic) cardiomyopathy, or persistent sinus tachycardia. The data do not support giving amiodarone as a routine, empiric therapy in patients with asymptomatic ventricular arrhythmias. The data suggest also that patients with sustained ventricular tachycardia or who have survived an episode of sudden death may be better served with cardioverter-defibrillator implantation than with empiric amiodarone therapy.

This article reviews what recent clinical trials tell us—and do not tell us—about the role of amiodarone in CHF.

■ WHY USE ANTIARRHYTHMIC DRUGS IN CHF?

From 30% to 50% of deaths due to CHF are sudden and, presumably, due to arrhythmias in most cases. Over the past decade, a number of randomized, controlled trials showed that medical therapy, especially with angiotensin-

converting enzyme inhibitors, reduces the symptoms and increases the survival rate of CHF patients.^{1,2} However, these agents have a limited impact on the incidence of sudden death.

Asymptomatic ventricular arrhythmias do not predict sudden death

Nearly all patients with CHF have occasional ventricular premature beats,^{3,4} and 25% to 60% have runs of nonsustained ventricular tachycardia.⁵ Myocardial factors such as fibrosis, ischemia, and alterations in cellular physiology predispose patients to these rhythm disturbances. In addition, electrolyte disturbances, drug effects, and neurohormonal activation may also precipitate or exacerbate them.⁶⁻⁸

The relationship between ventricular ectopy and sudden death is not simple. Asymptomatic ventricular arrhythmias significantly and independently predicted all-cause mortality and sudden death in several studies,⁹⁻¹³ but not in others.^{14,15} However, even in studies where there was an association, these arrhythmias were no more predictive of sudden death than of death from all causes. In a series of patients with advanced CHF who died suddenly while being monitored electrocardiographically, Stevenson¹⁶ observed that ventricular tachycardia or ventricular fibrillation was the initial rhythm in only 52%. The remainder had bradyarrhythmias, conduction abnormalities, or electromechanical dissociation. No precipitating factors were identified in 47% of the arrests presenting as a ventricular tachyarrhythmia, nor in 67% of the arrests presenting as a bradyarrhythmia.

These numbers raise the possibility that undetected events such as myocardial infarctions, pulmonary embolisms, or abrupt hemodynamic deterioration caused many of the sudden deaths. They also imply that antiarrhythmic therapy may not prevent sudden death, particularly in patients with advanced heart failure or at high risk for acute coronary events.

CAST results challenge assumptions about arrhythmias and sudden death

Nevertheless, we often gave antiarrhythmic

drugs to such patients, owing to their high risk of sudden death and frequent ventricular arrhythmias, and to our assumption that suppressing these premonitory arrhythmias would prevent life-threatening ones.

This assumption was challenged by the unexpected findings of the Coronary Arrhythmia Suppression Trial (CAST),^{17,18} in which the class I antiarrhythmic agents encainide, flecainide, and moricizine suppressed ventricular ectopy but caused an increase in sudden deaths, attributed to their proarrhythmic effects.^{19,20} Subsequent experience and analyses indicated that CHF patients are much more vulnerable to drug-induced arrhythmias than are other patients.²¹⁻²³ Furthermore, most antiarrhythmic agents can further depress myocardial function in patients with CHF. Thus, the use of class I agents has been discouraged,²⁴ particularly to suppress asymptomatic arrhythmias.

Amiodarone shows encouraging results in small or retrospective studies

In the vacuum created by the CAST results, amiodarone emerged as perhaps the only antiarrhythmic agent that rarely worsens arrhythmias.^{25,26}

Several small studies suggested that patients with CHF benefit from amiodarone.²⁷⁻³⁰ Hamer et al,³⁰ in a placebo-controlled study in 34 patients with CHF, found that ventricular arrhythmias decreased significantly with amiodarone use, and that the ejection fraction and exercise tolerance increased. Cleland et al²⁷ noted, in a placebo-controlled study in 22 patients with stable chronic heart failure, that amiodarone reduced the frequency and complexity of ventricular arrhythmias without any deleterious effects on left ventricular function. Retrospective analyses suggested that amiodarone might improve survival in CHF.^{31,32} Finally, unlike the dismal experience with class I agents, several small studies suggested that amiodarone might improve prognosis in patients who survive myocardial infarction or cardiac arrest.³³⁻³⁵

These observations led to a series of prospective trials of amiodarone in patients with CHF and in survivors of myocardial infarction.

Almost all CHF patients have occasional ventricular premature beats



Pharmacology of amiodarone

AMIODARONE has unique properties that distinguish it from other antiarrhythmic agents.^{36,37} It prolongs the refractory period in all tissues and also depresses sinus and AV node function, resulting in a negative chronotropic effect. Although it prolongs the QT interval (and thus is considered a class III agent by the Vaughan-Williams scheme), it rarely causes torsades de pointes.²⁵

Amiodarone has characteristics of other antiarrhythmic classes as well:

- Like class I agents it blocks sodium channels (and also some potassium channels).
- Like class II agents it has antiadrenergic properties—of particular interest in light of the growing evidence of the benefit of beta-blockers in CHF.^{38–42} These effects are mediated through a decrease in the number of beta-adrenoreceptors, as well as through peripheral blockade.^{43–45}
- Like class IV agents, it blocks calcium channels.
- It also has antithyroid and anti-ischemic effects, which may contribute to its antiarrhythmic actions.⁴⁶

ONSET OF ACTION

The onset of action of amiodarone is dose-related; higher loading doses (800 to 1,600 mg

per day) achieve effect in 2 to 5 days, whereas lower loading doses (≤ 600 mg per day) may take 1 to 2 weeks to achieve full effect.⁴⁷ However, higher loading doses may cause substantial bradycardia and have adverse hemodynamic effects.

Intravenous amiodarone has a different pharmacologic and hemodynamic profile, resulting in a faster onset of antiarrhythmic effects, but with insignificant vasodilation. It has been used safely and effectively to treat refractory ventricular arrhythmias in patients with acute myocardial infarction, shock, and heart failure,⁴⁴ but this aspect of amiodarone therapy is beyond the scope of this article.

ABSORPTION AND ELIMINATION

Because amiodarone is extremely lipophilic and accumulates in many tissues (particularly in adipose tissue and the liver, lungs, and nervous system), its elimination half-life is very long. Therefore, the plasma concentration is not helpful for clinical monitoring.

Amiodarone is eliminated by hepatic metabolism and biliary excretion. Urinary excretion is minimal, and no dosage adjustment is needed in renal impairment. However, amiodarone is highly bound to protein, and dialysis does not effectively remove the drug.⁴⁸

GESICA AND CHF-STAT STUDIED SURVIVAL OF CHF PATIENTS

Two randomized trials^{49,50} specifically addressed whether amiodarone would increase survival in patients with heart failure. Unfortunately, they gave conflicting results (TABLE 1).

GESICA: Amiodarone increased survival

The GESICA trial (*Grupo de Estudio de la Sobrevida en la Insuficiencia Cardíaca en Argentina*)⁴⁹ included 516 patients with severe CHF (predominantly New York Heart Association [NYHA] class III or IV, with evidence of cardiac enlargement or an ejection fraction $\leq 35\%$).

Patients did not need to have ventricular arrhythmias to enter the trial, but they were stratified according to whether they had non-sustained ventricular tachycardia on 24-hour Holter monitoring. In all, 173 patients (33.5%) had nonsustained ventricular tachycardia, and 343 (66.5%) did not. The mean age was 65 years, and 78% of the patients were men. More than 60% of patients in the study had CHF of nonischemic origin. Chagas disease, which causes a high incidence of ventricular arrhythmias, was the etiology in approximately 10% of patients.

Patients received either amiodarone (600 mg/day for 14 days, followed by 300 mg/day for the duration of the study) or no treatment.

TABLE 1

Major clinical trials of amiodarone in CHF and after infarction

TRIAL	PATIENT CHARACTERISTICS	EFFECT OF AMIODARONE ON SURVIVAL
GESICA*	Severe CHF	Amiodarone better than no treatment (reduction in sudden deaths and CHF-related deaths)
CHF-STAT†	Moderate CHF	Amiodarone no better than placebo (suggestion of benefit in nonischemic cardiomyopathy)
EMIAT‡	Left ventricular dysfunction after recent myocardial infarction	Amiodarone no better than placebo (significant reduction in deaths due to arrhythmia)
CAMIAT§	Frequent ventricular arrhythmias after myocardial infarction	Amiodarone no better than placebo (significant reduction in deaths due to arrhythmia)

*GESICA = *Grupo de Estudio de la Sobrevida en la Insuficiencia Cardíaca en Argentina*, reference 49

†CHF-STAT = Veterans Affairs Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure, reference 50

‡EMIAT = European Myocardial Infarction Arrhythmia Trial, reference 51

§CAMIAT = Canadian Amiodarone Myocardial Infarction Arrhythmia Trial, reference 52

GESICA was halted due to a significant survival advantage in the amiodarone group

Results. The GESICA trial was discontinued after a mean follow-up of 13 months, owing to a significant survival advantage in the amiodarone group. Overall, the amiodarone group had 28% fewer deaths ($P = .024$), owing to similar reductions in both sudden deaths and deaths due to progressive heart failure. The amiodarone group also experienced improved NYHA functional class and had significantly fewer hospitalizations.

Nonsustained ventricular tachycardia independently predicted sudden death,¹¹ regardless of whether patients received amiodarone. The reason is probably that patients with nonsustained ventricular tachycardia had greater impairment of ventricular function and worsening overall clinical status. In this group, the reduction in mortality with amiodarone did not quite achieve statistical significance (a risk reduction of 34%, $P = .056$).

In patients with a baseline heart rate greater than 90 beats per minute, the mortality rate was 38% in the amiodarone group compared with 62% in the control group.⁵³ In contrast, amiodarone did not alter survival in patients with a baseline heart rate less than 90. This apparent benefit might be mediated partly by a reduction in heart rate that is in turn mediated by amiodarone's beta-blocking properties.

There was no statistically significant difference in mortality between patients whose CHF was thought to be due to coronary artery disease and those thought to have a nonischemic cause.

CHF-STAT: Amiodarone did not increase survival

The Veterans Affairs Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure (CHF-STAT)⁵⁰ included 674 patients with moderate to severe CHF (NYHA class II to IV), 55% of whom were in NYHA class II. All had ejection fractions below 40%, cardiac enlargement by chest radiography or echocardiography, and 10 or more premature ventricular contractions per hour. The mean age was 69 years. Nearly all (99%) of the patients in the study were men, and 72% had ischemic cardiomyopathy.

Patients received either amiodarone (800 mg/day for 14 days, then 400 mg/day for 50 weeks, then 300 mg/day until the end of the study) or placebo. The median follow-up was 45 months, and the primary endpoint was all-cause mortality.

Results. Unlike in the GESICA trial, patients receiving amiodarone did not have a lower overall mortality rate. Further, although amiodarone suppressed ventricular ectopy and episodes of ventricular tachycardia, it did not

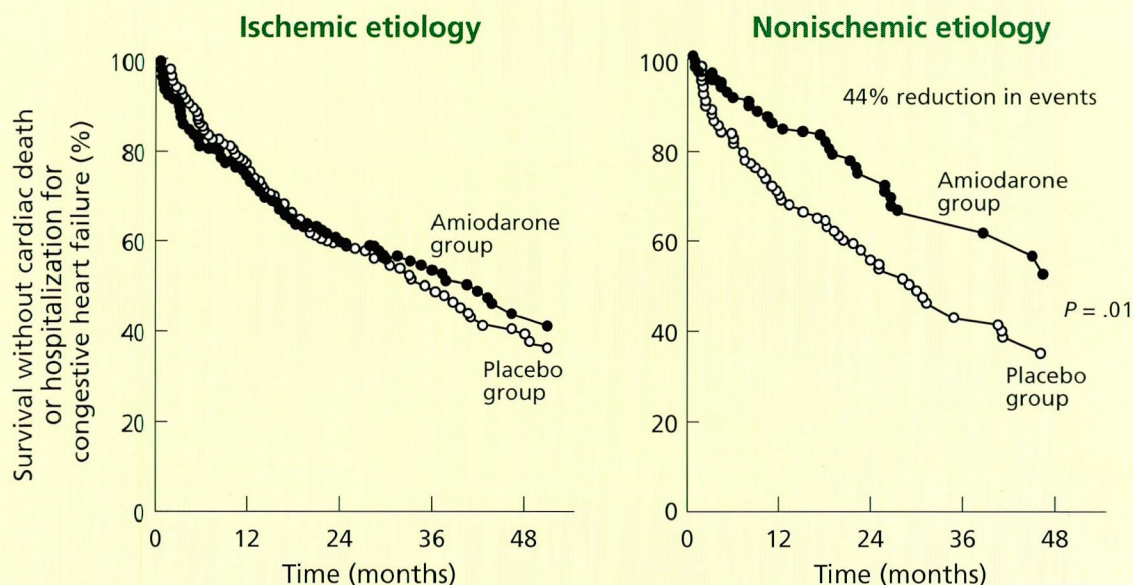


FIGURE 1. Survival without cardiac death or hospitalization in patients in the CHF-STAT trial with congestive heart failure of ischemic vs nonischemic etiology. A 44% reduction in events was seen in the nonischemic group, while no difference in event rates was seen in the ischemic group.

SOURCE: ADAPTED FROM MASSIE BM, FISHER SG, RADFORD M, ET AL, REFERENCE 54

reduce the incidence of sudden death.

In the subgroup of patients with nonischemic cardiomyopathy, those who received amiodarone had a slightly lower mortality rate than those who did not, but the trend was not statistically significant ($P = .07$). This group did have a significantly higher rate of survival free of the combined endpoint of cardiac death or hospitalization for CHF ($P = .01$) (FIGURE 1).⁵⁴ Since nonischemic patients constituted the majority in the GESICA trial, this result may explain some of the discordance in the results of the two trials and may identify a group of patients more likely to benefit from amiodarone.

The left ventricular ejection fraction increased substantially in patients who received amiodarone—from $24.9 \pm 8.3\%$ at baseline to $35.4 \pm 11.5\%$ at 2 years—but not in the placebo group ($25.7 \pm 8.2\%$ at baseline to $29.8 \pm 12.2\%$ at 2 years). However, symptoms did not improve, nor did hospitalizations decrease.⁵⁴

Different patient populations may explain differing results

Why did amiodarone appear to increase survival in the GESICA trial, but not in the

CHF-STAT trial? Possible explanations include differences in the patient populations and in study design.^{55,56}

Etiology of heart failure. The GESICA trial had a much higher proportion of patients with nonischemic cardiomyopathy than did the CHF-STAT. The GESICA patients may have benefited from the beta-blocker action of amiodarone, since some evidence indicates that beta-blockers are more effective in patients with primary cardiomyopathy than with ischemic cardiomyopathy.^{39,40}

Age. The CHF-STAT patients were older than the GESICA trial patients (mean age 69 years vs 65 years).

Gender. CHF-STAT included virtually no women. In the GESICA trial the reduction in overall mortality was greater in women, but not significantly so.

Acuity of illness. The GESICA patients were substantially sicker than the CHF-STAT patients: 78% of GESICA patients were in NYHA class III or IV, vs 42% in CHF-STAT. Mortality was higher in GESICA (30% at 1 year and 50% at 2 years) than in CHF-STAT (23% and 30%, respectively). Further, GESI-

Unlike in GESICA, CHF-STAT patients did not have a lower overall mortality

CA patients had a higher baseline heart rate (90 bpm vs 80 bpm)—and baseline tachycardia identified the group of patients who responded in GESICA.

Study design. The lack of blinding in GESICA may have introduced bias in patient management.

■ EMIAT AND CAMIAT: MI SURVIVORS

Two other major trials examined the use of amiodarone in survivors of myocardial infarction, not CHF per se.^{51,52} Nevertheless, they are relevant, since patients in these studies had reduced ejection fractions, and many had CHF. Indeed, ejection fraction is the most powerful predictor of survival after myocardial infarction.^{57,58} In both studies, amiodarone did not affect the survival rate at all.

EMIAT and all-cause mortality

EMIAT (European Myocardial Infarction Arrhythmia Trial)⁵² was designed to assess the effect of amiodarone on mortality in patients with left ventricular dysfunction after a recent myocardial infarction, with or without ventricular arrhythmias. The 1,486 study patients all had left ventricular ejection fractions of 40% or lower; 50% were in NYHA class I, and 50% were in NYHA classes II or III.

The patients received either amiodarone (800 mg for 14 days, 400 mg for 14 weeks, and then 200 mg until the end of the study) or placebo. The mean duration of follow-up was 21 months.

Results. The all-cause mortality rate was the same in both groups (14.5% vs 14.69%), but deaths due to arrhythmia were 35% lower in the treated group ($P = .05$). The mortality rate was higher in those with frequent or complex arrhythmias than in those without (20% vs 10%), but this group represented only 40% of the sample. Notably, a strong tendency toward a favorable interaction between the use of beta-blockers and amiodarone treatment was found. Patients receiving a beta-blocker at baseline had a 50% lower rate of cardiac mortality on amiodarone than on placebo, while patients not receiving a beta-blocker had no reduction ($P = .06$ for interaction).

CAMIAT: Risk reduced

The CAMIAT (Canadian Amiodarone Myocardial Infarction Arrhythmia Trial)⁵¹ was designed to assess the effect of amiodarone on the risk of resuscitated ventricular fibrillation or death due to arrhythmia, among survivors of myocardial infarction with baseline ectopy. Similar to the EMIAT patients, the 1,202 CAMIAT patients had all survived a myocardial infarction. However, instead of a decreased ejection fraction, the entry criterion for the CAMIAT patients was frequent or repetitive ventricular premature beats (> 10 per hour or more than one run of ventricular tachycardia).

Patients received amiodarone (10 mg/kg daily for 2 weeks, 300 to 400 mg daily for 3.5 months, 200 to 300 mg daily for 4 months, and then 200 mg for 5 to 7 days per week for 16 months) or placebo. The mean follow-up was 1.79 years.

Results. As in EMIAT, amiodarone did not reduce the total mortality rate significantly (5.2% vs 6.4% per year, $P = .129$). However, a 38% (2.3% vs 3.7% per year) reduction in the combination of resuscitated ventricular fibrillation plus arrhythmic death was observed ($P = .029$).

Amiodarone also suppressed ventricular premature beats: by the fourth month of the trial, the rate of arrhythmia had decreased in 84% of amiodarone-treated patients and in 35% of placebo patients, and similar findings were present at the eighth month. However, the number of outcome events was insufficient to enable the investigators to assess whether the reduction in ventricular premature beats was related to the amiodarone treatment.

Role of amiodarone after MI is unclear

The role of amiodarone in postinfarction patients remains unsettled. In post hoc analyses of both trials, patients with CHF or an infarction before the index event had more evidence of benefit. Both studies also found that patients taking amiodarone and beta-blockers had fewer cardiac deaths and a greater improvement in left ventricular function.

■ DRAWING CONCLUSIONS FROM THE TRIAL DATA

Taken together, these four trials show that

Amiodarone's role in post-MI patients remains unsettled

amiodarone can be used safely in patients with CHF, making it the drug of choice for treating arrhythmias in CHF.

However, with respect to efficacy, the trials do not resolve the question of whether amiodarone has a role in the treatment of *asymptomatic* ventricular arrhythmias or of CHF per se, since patients with CHF are at increased risk for sudden death. Without a more conclusively positive trial, the use of amiodarone cannot be recommended for the CHF population as a whole.

Which patients are more likely to benefit from amiodarone therapy?

Looking at the four trials together, if one were to try to identify a group of patients in whom amiodarone might be more likely to be beneficial, one might select patients with more severe CHF due to nonischemic cardiomyopathy who present with persistent tachycardia. The latter point raises the possibility that some (perhaps even most) of the apparent benefit of amiodarone in some patient subgroups is due to its beta-blocking actions.

AMIODARONE FOR ATRIAL FIBRILLATION IN PATIENTS WITH CHF

Although this article focuses on ventricular arrhythmias, amiodarone has also emerged as an important agent in managing supraventricular arrhythmias.

Atrial fibrillation is common in CHF. Indeed, 27% of patients in the GESICA trial and 15% of those in CHF-STAT were in atrial fibrillation at baseline. In CHF-STAT, the amiodarone group experienced a significantly lower rate of new-onset atrial fibrillation.⁵⁰ Perhaps more as a marker than as a mechanism, atrial fibrillation appears to be associated with an increased risk of death in patients with CHF.⁵⁹

Amiodarone is effective in reestablishing and maintaining sinus rhythm in CHF patients with atrial fibrillation^{60,61} and, as noted above, is the only agent whose safety is established in this setting. Stevenson et al⁶² found that patients with advanced heart failure and atrial fibrillation treated with amiodarone had a markedly better 2-year rate of surviving and not experiencing sudden death

than did those treated with class IA antiarrhythmic agents. Whether the beneficial effect of amiodarone is through restoration of sinus rhythm or rate control is unknown, but amiodarone should be considered the drug of choice in CHF patients for both applications.

SIDE EFFECTS

Concerns about the side effects of amiodarone have limited its use. However, the large randomized trials reviewed above suggest that amiodarone rarely causes serious cardiac adverse effects such as ventricular arrhythmias. Bradyarrhythmias are perhaps more common, but rarely life-threatening. Noncardiac toxicity and side effects remain the primary limitation of long-term amiodarone therapy.

In contrast to earlier reports when higher amiodarone doses were common, severe amiodarone toxicity is relatively infrequent today.

Pulmonary toxicity

The most feared problem, pulmonary toxicity, illustrates this point. CHF-STAT investigators evaluated the pulmonary effects of amiodarone in patients with CHF, in those with chronic pulmonary obstructive disease, and in those undergoing a surgical procedure.⁶³ Chest radiography and pulmonary function tests, including the diffusing capacity of carbon monoxide (DLCO), were performed at the time of entry into the trial, and annually thereafter. No significant differences in DLCO were seen at any time in either the amiodarone or the placebo group. Only at 1 year was a slight but significant difference in DLCO noted between all survivors and those with chronic obstructive pulmonary disease. No difference between the two groups was noted in terms of noncardiac mortality for all patients or those with chronic obstructive pulmonary disease.

In patients undergoing surgery, the rate of noncardiac perioperative death was similar for the amiodarone and placebo groups. Pulmonary fibrosis as shown on chest radiography was seen in three patients (0.8%) receiving placebo and in four patients (1.1%) treated with amiodarone. Other pulmonary complications, such as effusions and consoli-

Severe amiodarone toxicity is less frequent today with lower dosing

TABLE 2

Adverse effects of amiodarone

ADVERSE EFFECT	EVENTS IN THE AMIODARONE GROUP (N=738)	EVENTS IN THE PLACEBO GROUP (N=727)
Hepatic	9 (1.2%)	6 (0.8%)
Gastrointestinal	31 (4.2%)	24 (3.3%)
Pulmonary	14 (1.9%)	5 (0.7%)
Thyroid	27 (3.7%)	3 (0.4%)
Neurologic	34 (4.6%)	14 (1.9%)
Skin	17 (2.3%)	5 (0.7%)
Eye	11 (1.5%)	1 (0.4%)
Bradycardia	24 (3.3%)	10 (1.4%)
Drug discontinued	169 (22.9%)	112 (15.4%)

Adapted from Vorperian et al, reference 64

dation, occurred in one patient (0.3%) on placebo and in six patients (1.8%) in the amiodarone-treated group. The overall incidence of pulmonary complications in patients with and without COPD was similar (2.4% vs 2.8%). This study demonstrated that amiodarone can be safely used, with an acceptable level of pulmonary toxicity.

Reduce digoxin doses before starting amiodarone

Other side effects

Other frequent side effects continue to limit the use of amiodarone. In a recent meta-analysis, Vorperian et al⁶⁴ calculated that amiodarone in low doses produced no higher rates of hepatic and gastrointestinal side effects than did placebo, but did produce significantly higher rates of thyroid, neurologic, skin, and ocular side effects and bradycardia. They also observed a trend toward increased pulmonary adverse effects, although this did not reach statistical significance (TABLE 2).

Although amiodarone can cause significant thyroid abnormalities (especially hypothyroidism), this usually becomes apparent on thyroid function tests performed in the first year of treatment and can be managed with thyroid hormone replacement therapy or, uncommonly, thyroid suppression.

PATIENT COMPLIANCE

Major complaints of adverse effects in patients taking amiodarone are few. However, because

of the high rate of minor side effects, patients may feel less well taking amiodarone, so compliance is a significant problem. In the meta-analysis,⁶⁴ patients were significantly more likely to discontinue low-dose amiodarone than to discontinue placebo. A high rate of discontinuation was also noted in the clinical trials (TABLE 3). All trials but GESICA, which was not blinded, showed a high rate of discontinuation of the drug. The much lower withdrawal rate in the GESICA trial probably reflects a greater effort to continue therapy in patients known to be receiving the active drug.

Drug interactions

Drug interactions with amiodarone require careful attention in heart failure patients. For example, amiodarone reduces digoxin clearance by approximately 30%.⁶⁵ Therefore, digoxin doses should be reduced by 30% to 50% (depending on pretreatment digoxin levels) when starting amiodarone. Similarly, amiodarone potentiates the effects of warfarin by approximately 50%.⁶⁶ Accordingly, warfarin therapy should be started at low doses if the patient is already taking amiodarone, and warfarin doses should be monitored closely or reduced by about 30% when amiodarone is started.

REMAINING CHALLENGES

Implantable devices and amiodarone

The incidence of sudden death remains high in CHF patients, particularly in those with symptomatic or sustained ventricular arrhythmias. Our experience has generated considerable interest in device therapy for these patients.

Three recent trials have evaluated the role of implantable cardiac defibrillators in patients who have experienced hemodynamically unstable ventricular arrhythmias or have survived ventricular arrhythmias. The Antiarrhythmics vs Implantable Defibrillators (AVID) trial compared antiarrhythmic therapy (amiodarone, in the majority of patients) with implantable cardiac defibrillators in 1,016 patients with an ejection fraction of 40% or less, 55% of whom had CHF, and found a 37% lower 2-year mortality (12% vs 20%) with the device.

**TABLE 3****Rates of discontinuation in amiodarone trials**

TRIAL	DISCONTINUATION FOR ANY REASON		DISCONTINUATION FOR SIDE EFFECTS	
	AMIODARONE	PLACEBO	AMIODARONE	PLACEBO
GESICA*	6%	Not given	5%	Not given
CHF-STAT†	40%	33%	27%	23%
CAMIAT‡	26%	26%	26%	14%
EMIAT§	39%	21%	31%	12%

*GESICA = *Grupo de Estudio de la Sobrevida en la Insuficiencia Cardíaca en Argentina*, reference 49

†CHF-STAT = Veterans Affairs Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure, reference 50

‡EMIAT = European Myocardial Infarction Arrhythmia Trial, reference 51

§CAMIAT = Canadian Amiodarone Myocardial Infarction Arrhythmia Trial, reference 52

In the Cardiac Arrest Study Hamburg (CASH), survivors of cardiac arrest fared better with implantable devices than with either amiodarone or metoprolol. The same trends were observed in the Canadian Implantable Defibrillator Study (CIDS), in which there was a 19.5% reduction in mortality with the implantable device vs amiodarone ($P = .07$).

Based on these results, an implantable cardiac defibrillator is recommended for patients with symptomatic ventricular tachycardia or who have survived ventricular fibrillation, unless the patient's prognosis is poor due to end-stage CHF or other medical problems.⁶⁷⁻⁶⁹ If frequent shocks result, amiodarone becomes a useful adjunctive therapy.⁷⁰

Managing asymptomatic ventricular arrhythmias

The management of patients with asymptomatic ventricular arrhythmias remains much more problematic, and there is no consensus on the best approach. As noted in this article, empiric amiodarone has been disappointing as a general approach but may be useful in selected individuals.


The recently published Multicenter Automatic Defibrillator Implantation Trial (MADIT)⁷¹ has been interpreted as indicating that patients with prior myocardial infarction, left ventricular dysfunction, and asymptomatic ventricular arrhythmias may have a better prognosis with an implantable cardioverter-defibrillator, provided they have inducible but not suppressible sustained ven-

tricular tachycardia on electrophysiologic testing. Notably, the MADIT trial was not directed at a population with CHF and was not a randomized trial of antiarrhythmic vs device therapy. Furthermore, there was little use of beta-blockers in the medical therapy limb. Additional studies will be required before devices can be recommended for CHF patients with asymptomatic ventricular arrhythmias.

Several trials are in progress or have been recently completed comparing implantable cardiac defibrillators with conventional therapy for ventricular arrhythmias.⁷²⁻⁷⁵ Most relevant to the heart failure population is the ongoing Sudden Cardiac Death Heart Failure Trial (SCD-HeFT),⁷⁵ which is randomizing patients in NYHA class II or III CHF and with ejection fractions below 35% to placebo, amiodarone, or implantation of a cardiac defibrillator. This trial will demonstrate which therapy is the best.

The MADIT-II trial is also evaluating the role of implantable cardiac defibrillators as therapy in patients with CHF who have not experienced symptomatic arrhythmias.

Use of beta-blockers in CHF

As the use of beta-blocker therapy in CHF increases, this may prove to be equally or more effective than amiodarone in many patients, with amiodarone reserved for those whose CHF is unstable or severe enough to contraindicate beta-blockers. This important question will also be assessed in SCD-HeFT. 

REFERENCES

- Massie BM. Heart failure 1997: A time to take stock. *Curr Opin Cardiol* 1997; 12:209-217.
- The Consensus Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987; 316:1429-1435.
- Francis GS. Development of arrhythmias in the patient with congestive heart failure: pathophysiology, prevalence and prognosis. *Am J Cardiol* 1986; 57:3B-7B.
- Chakko CS, Gheorghiade M. Ventricular arrhythmias in severe heart failure: Incidence, significance, and effectiveness of antiarrhythmic therapy. *Am Heart J* 1985; 109:497-504.
- Massie BM, Conway M. Survival of patients with congestive heart failure: past, present, and future prospects. *Circulation* 1987; 75(Suppl IV):IV-11-IV-19.
- Podrid PJ, Fogel RI, Tordjman-Fuchs T. Arrhythmia in patients with a cardiomyopathy and congestive heart failure: Part III. Congestive Heart Failure May/June 1997:35-54.
- Packer M. New concepts in the pathophysiology of heart failure: beneficial and deleterious interactions of endogenous hemodynamic and neurohormonal mechanisms. *J Intern Med* 1996; 4:327-333.
- Cleland JG, Dargie HJ, Robertson JL, Henderson E, East WB. Heart failure, renin, potassium and arrhythmias (abstract). *Circulation* 1985; 72(Suppl III):III-283.
- Cleland JG, Dargie HJ, Ford I. Mortality in heart failure: clinical variables of prognostic value. *Br Heart J* 1987; 58:572-582.
- Bigger JT. Why patients with congestive heart failure die: arrhythmias and sudden cardiac death. *Circulation* 1987; 75(Suppl IV):IV-28-35.
- Doval HC, Nul DR, Grancelli HO, et al. Nonsustained ventricular tachycardia in severe heart failure Independent marker of increase mortality due to sudden death. *Circulation* 1996; 94:3198-3203.
- Gradman A, Deedwania P, Cody R, et al. Predictors of total mortality and sudden death in mild to moderate failure. *J Am Coll Cardiol* 1989; 14:564-590.
- Holmes J, Kubo SH, Cody RJ, Kligfield P. Arrhythmias in ischemic and nonischemic dilated cardiomyopathy: Prediction of mortality by ambulatory electrocardiography. *Am J Cardiol* 1985; 55:146-151.
- Olshausen KV, Schafer A, Mehmel HC, Schwarz F, Seneges J, Kubler W. Ventricular arrhythmias in idiopathic dilated cardiomyopathy. *Br Heart J* 1984; 51:195-201.
- Wilson JR, Schwartz JS, St John Sutton M, et al. Prognosis in severe heart failure: Relation to hemodynamic measurements and ventricular ectopic activity. *J Am Coll Cardiol* 1983; 2:403-410.
- Stevenson WG, Stevenson LW, Middlekauff HR, Saxon LA. Sudden death prevention in patients with advanced ventricular dysfunction. *Circulation* 1993; 88:2953-2691.
- Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med* 1989; 321:406-410.
- The Cardiac Arrhythmia Suppression Trial II Investigators. Effects of the antiarrhythmic agent moricizine on survival after myocardial infarction. *N Engl J Med* 1992; 327:227-233.
- Anderson JL, Platia EV, Hallstrom A, et al. Interaction of baseline characteristics with the hazard of encainide, flecainide and moricizine therapy in patients with myocardial infarction. *Circulation* 1994; 90:2843-2852.
- Restivo M. Reentrant arrhythmias in the subacute infarction period. *Circulation* 1995 91:1236-1246.
- Chakko CS, Gheorghiade M. Ventricular arrhythmias in severe heart failure: Incidence, significance and effectiveness of antiarrhythmic therapy. *Am Heart J* 1985; 109:497-504.
- Stanton MS, Prystowsky EN, Fineberg NS, Miles W, Zipes DP, Heger JJ. Arrhythmogenic effects of antiarrhythmic drugs: a study of 506 patients treated for ventricular tachycardia or fibrillation. *J Am Coll Cardiol* 1989; 14:209-215.
- Pratt CM, Eaton CM, Francis CM, et al. The inverse relationship between baseline left ventricular ejection fraction and outcome of antiarrhythmic therapy: a dangerous imbalance in the risk-benefit ratio. *Am Heart J* 1989; 118:433-440.
- Epstein AE, Hallstrom AP, Rogers WJ, et al. Mortality following ventricular arrhythmia suppression by encainide, flecainide, and moricizine after myocardial infarction. *JAMA* 1993; 270:2451-2455.
- Hohnloser SH, Klingenhoben T, Singh BN. Amiodarone associated proarrhythmic effects: a review with special references to torsades de pointes tachycardia. *Ann Intern Med* 1994; 121:529-535.
- Singh BN, Fletcher RD, Fisher S, et al. Veterans Affairs congestive heart failure antiarrhythmic trial. *Am J Cardiol* 1993; 72:99F-102F.
- Cleland JG, Dargie HJ, Findlay IN, Wilson JT. Clinical, hemodynamic, and antiarrhythmic effects of long term treatment with amiodarone of patients with heart failure. *Br Heart J* 1987; 57:436-45.
- Nicklas JM, Mickelson JK, Das SK, et al. Prospective, double blind, placebo-controlled trial of low dose amiodarone in patients with severe heart failure and asymptomatic frequent ventricular ectopy. *Am Heart J* 1991; 122:1016-1021.
- Kerin NZ, Rubenfire M, Blevins RD, et al. Long-term efficacy, safety and survival of patients with potentially lethal ventricular arrhythmias treated with low dose amiodarone. *Clin Cardiol* 1988; 11:II-31-II-40.
- Hamer AF, Arkes B, Johns J. Beneficial effects of low dose amiodarone in patients with congestive heart failure: a placebo controlled trial. *J Am Coll Cardiol* 1989; 14:1768-1774.
- Cleland MD, Dargie HJ. Arrhythmias in heart failure: The role of amiodarone. *Clin Cardiol* 1988; 11:II-26-II-30.
- Chatterjee K. Amiodarone in chronic heart failure (editorial). *J Am Coll Cardiol* 1989; 14:1775-1776.
- Burkart F, Pfisterer M, Kiowski W, Follath F, Burkhardt D. Effect of antiarrhythmic therapy on mortality in survivors of myocardial infarction (BASIS). *J Am Coll Cardiol* 1990; 16:1711-1718.
- Ceremuzinski L, Kleczar E, Kreminska-Pakula M, et al. Effect of amiodarone on mortality after myocardial infarction: a double blind, placebo-controlled, pilot study. *J Am Coll Cardiol* 1992; 20:1056-1062.
- The CASCADE Investigators. Randomized antiarrhythmic therapy in survivors of cardiac arrest (CASCADE study). *Am J Cardiol* 1993; 72:280-287.
- Podrid PG. Amiodarone: re-evaluation of an old drug. *Ann Intern Med* 1995; 122:689-700.
- Singh BN. Amiodarone: historical development and pharmacologic profile. *Am Heart J* 1983; 106:788-797.
- Eichhorn EJ. The paradox of β -adrenergic blockade for the management of congestive heart failure. *Am J Med* 1992; 92:527-538.
- Waagstein F, Bristow MR, Swedberg K, et al. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. Metoprolol dilated cardiomyopathy (MDC) Trial Study Group. *Lancet* 1993; 342:1441-1446.



40. CIBIS Investigators and Committees. A randomized trial of β -blockade in heart failure. The Cardiac Insufficiency Bisoprolol study (CIBIS). *Circulation* 1994; 90:1765-1773.
41. Packer M, Bristow MR, Colucci WS, Cohn JN, Gilbert EM, Shusterman NH. Effects of carvedilol on morbidity and mortality in chronic heart failure. *N Engl J Med* 1996; 334:1349-1355.
42. Heidenreich PA, Lee T, Massie BM. Effect of beta-blockade on mortality in patients with heart failure: A meta-analysis of randomized clinical trials. *J Am Coll Cardiol* 1997; 30:27-34.
43. Kadish AH, Chen RF, Schmaltz S, Morady F. Magnitude and time course of beta-adrenergic antagonism during oral amiodarone therapy. *J Am Coll Cardiol* 1990; 16:1240-1245.
44. Desai AD, Sung C, Sung RJ. The role of intravenous amiodarone in the management of cardiac arrhythmias. *Ann Intern Med* 1997; 127:294-303.
45. Sager PT, Follmer C, Uppal P, Pruitt C, Gofrey R. The effects of β -adrenergic stimulation on the frequency-dependent electrophysiologic actions of amiodarone and sotalolol in humans. *Circulation* 1994; 90:1811-1819.
46. Singh BN, Nademanee K. Amiodarone and thyroid function: clinical implications during antiarrhythmic therapy. *Am Heart J* 1983; 106:857-69.
47. Gottlieb SS, Riggio DW, Lauria S, et al. High dose oral amiodarone loadings exerts important hemodynamic actions in patients with congestive heart failure. *J Am Coll Cardiol* 1994; 23:560-564.
48. Roden DM. Pharmacokinetics of amiodarone: implications for drug therapy. *Am J Cardiol* 1993; 72:45F-50F.
49. Doval HC, Nul DR, Grancelli HO, Perrone SV, Bortman GR, Curiel R. Randomized trial of low-dose amiodarone in severe congestive heart failure. *Grupo de Estudio de la Sobrevida en la Insuficiencia Cardíaca en Argentina (GESICA)*. *Lancet* 1994; 344:493-498.
50. Singh SN, Fletcher RD, Fisher SG, et al. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure. *N Engl J Med* 1995; 333:77-82.
51. Julian DG, Camm AJ, Frangin G, et al. Randomised trial of effect of amiodarone on mortality in patients with left-ventricular dysfunction after recent myocardial infarction (EMIAT). *Lancet* 1997; 349:667-74.
52. Cairns JA, Connolly SJ, Roberts R, Gent M. Randomised trial of outcome after myocardial infarction in patients with frequent or repetitive ventricular premature depolarizations (CAMIAT). *Lancet* 1997; 349:675-682.
53. Nul DR, Doval HC, Grancelli HO, et al. Heart rate is a marker of amiodarone mortality reduction in severe heart failure. *J Am Coll Cardiol* 1997; 29:1199-1205.
54. Massie BM, Fisher SG, Radford M, et al. Effect of amiodarone on clinical status and left ventricular function in patients with congestive heart failure. *Circulation* 1996; 93:2128-2134.
55. Hammill SC, Packer DL. Amiodarone in congestive heart failure: unravelling the GESICA and CHF-STAT differences. *Heart* 1996; 75:6-7.
56. Breithardt G. Amiodarone in patients with heart failure (editorial). *N Engl J Med* 1995; 333:121-122.
57. Bigler JT, Flaiss JL, Kleiger J, et al. The relationship among ventricular arrhythmias, left ventricular dysfunction, and mortality in two years after myocardial infarction. *Circulation* 1984; 69:250-258.
58. Pitt B. Sudden cardiac death: role of left ventricular dysfunction. *Ann NY Acad Sci* 1982; 382:218-228.
59. Stevenson WG, Stevenson LW, Middlekauff HR. Prognostic significance of atrial fibrillation in advanced heart failure. *Circulation* 1991; 84:40-48.
60. Graboys TB, Podrid PJ, Lown B. Efficacy of amiodarone for refractory supraventricular tachyarrhythmias. *Am Heart J* 1983; 106:870-876.
61. Chun SH, Sager PT, Stevenson WG, Nademanee K, Middlekauff HHR, Singh BN. Long term efficacy of amiodarone for maintenance of normal sinus rhythm after cardioversion of atrial fibrillation and flutter. *Am J Cardiol* 1995; 76:47-50.
62. Stevenson WG, Stevenson LW, Middlekauff HR, et al. Improving survival for patients with atrial fibrillation and advanced heart failure. *J Am Coll Cardiol* 1996; 28:1458-1463.
63. Singh SN, Fisher SG, Deedwania PC, Rohatgi P, Singh B, Fletcher RD. Pulmonary effects of amiodarone in patients with heart failure. *Am Coll Cardiol* 1997; 30:514-517.
64. Vorperian VR, Havighurst TC, Miller S, January CT. Adverse effects of low dose amiodarone: A meta analysis. *J Am Coll Cardiol* 1997; 30:791-798.
65. Nademanee K, Kannan R, Hendrickson J, Oskhtens M, Kay I, Singh BN. Amiodarone digoxin interaction: clinical significance, time course of development, potential pharmacokinetic mechanisms and therapeutic implications. *J Am Coll Cardiol* 1984; 4:111-116.
66. Heirmark LD, Wienkers LL, Kunze K, et al. The mechanism of the interaction between amiodarone and warfarin in humans. *Clin Pharmacol Ther* 1992; 53:398-407.
67. Weber EFD, Hauer RNW, Van Capelle FJL, et al. Randomized study of implantable defibrillators as first-choice therapy versus conventional strategy in postinfarction sudden death survivors. *Circulation* 1995; 91:2195-2203.
68. Powell AC, Fuchs TF, Finkelstein DM, et al. Influence of implantable cardioverter defibrillators on the long term prognosis of survivors of out of hospital cardiac arrest. *Circulation* 1993; 88:1083-1092.
69. Stevenson WG, Friedman PL. Unsustained ventricular tachycardia: To treat or not to treat (editorial). *N Engl J Med* 1996; 335:1984-1985.
70. Stevenson WG, Sweeney MO. Pharmacologic and non pharmacologic treatment of ventricular arrhythmias in heart failure. *Curr Opin Cardiol* 1997; 12:242-250.
71. Moss AJ, Hall J, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia for the Multicenter Automatic Defibrillator Implantation Trial Investigators. *N Engl J Med* 1996; 335:1933-40.
72. Klein H, Trappe HJ, Fieguth HG, Nisam S. Prospective studies evaluating prophylactic ICD therapy for high risk patients for prophylactic automatic implantable defibrillator therapy: status of prospective studies. *Pacing Clin Electrophysiol* 1993; 16:564-70.
73. Connolly SJ, Gent M, Roberts RS, et al. Canadian Implantable Defibrillator Study (CIDS). Study design and organization. *Am J Cardiol* 1993; 72:103F-108F.
74. AVID Investigators. Antiarrhythmics Versus Implantable Defibrillators (AVID): Rationale, design and methods. *Am J Cardiol* 1995; 75:470-475.
75. Epstein AE. MADIT does not provide the basis for developing therapeutic strategy for patients with severely depressed ventricular ejection fraction with nonsustained ventricular tachycardia. *J Cardiovasc Pharmacol Therapeut* 1997; 2:229-238.

ADDRESS: Barry M. Massie, MD, Veterans Affairs Medical Center (111C), 4150 Clement Street, San Francisco, CA, 94121.