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Amiodarone as a First-Line Therapy for the Conversion of Atrial Fibrillation or Long-term Maintenance of Sinus Rhythm Once Cardioversion Has Been Achieved

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Amiodarone as a First-Line Therapy for the Conversion of Atrial Fibrillation or Long-term Maintenance of Sinus Rhythm Once Cardioversion Has Been Achieved

Abstract

Background: Optimal, long-term drug strategies for cardioversion of atrial fibrillation (AF) and maintenance of sinus rhythm (SR) have been controversial. Amiodarone is an old drug that is an effective class III antiarrhythmic for both converting and maintaining sinus rhythm in patients with atrial fibrillation, however, there have been few recent, blinded, randomized controlled studies comparing amiodarone to other pharmacological agents to determine if it is an effective first-line therapy.

Hypothesis: Amiodarone when used as a first-line therapy is an effective pharmacological strategy for converting atrial fibrillation or maintaining sinus rhythm in patients with AF.

Study Design: A systematic review of randomized controlled studies.

Methods: A thorough electronic search of multiple databases including EBSCO, Medline, OVID, and PUBMED were conducted in the English language using “amiodarone,” “atrial fibrillation,” and “randomized controlled studies” as MeSH headings. Inclusion criteria were randomized controlled studies that included patients in all age groups with recent-onset, paroxysmal, persistent or chronic AF who were treated with either intravenous or oral amiodarone compared to placebo or another antiarrhythmic medication. Exclusion criteria were studies older than ten years that were not randomized controlled studies, amiodarone used in conjunction with other therapies, and post-surgical cardiac patients with recent-onset atrial fibrillation. Methodological quality of each study was evaluated using the JADAD score. Studies with a score of >3 were considered to be of high quality and were included in the review.

Results: Eight studies met the inclusion criteria for this review. All but one study demonstrated amiodarone's efficacy in converting or maintaining sinus rhythm. The study comparing dofetilide to amiodarone for the conversion of either recent-onset AF or atrial flutter (Af) at three hours, proved to be more effective than amiodarone, with 35% of dofetilide patients converting to SR compared to only 4% in the amiodarone group (p <0.001). In the study that evaluated conversion of either AF or Af to SR after 48 hours with ibutilide or amiodarone, findings were similar to that of dofetilide, but when AF was the only rhythm evaluated, there was no statistical difference between amiodarone and ibutilide at converting AF (69% vs. 77%, p = ns). However, when rapid cardioversion was desired in patients with AF or Af, ibutilide was faster at converting patients to SR compared to amiodarone (53.4 +/- 25.8 min vs. 492 +/- 186 min, p =0.000). Two studies evaluating the efficacy of amiodarone versus sotalol in maintaining SR at one year demonstrated amiodarone's superiority over sotalol (p=0.002; AFFRIM substudy) and (p <0.001; SAFE-T study) respectively, but when patients with ischemic heart disease were analyzed separately in the SAFE-T study, amiodarone was equally as effective as sotalol 4 in this patient subgroup (p=0.053) Two studies comparing amiodarone to class I antiarrhythmics including propafenone (AFFRIM substudy), or to propafenone and sotalol combined (CTAF study), found that amiodarone was superior in maintaining SR after one year (p <0.001) and (p <0.001) respectively, while in Kochaidakis et al comparing amiodarone to propafenone alone found no statistically significant difference between them for the suppression of recurrent symptomatic AF (p = 0.44). This finding was true only when adverse events were factored into the primary endpoint. Without adverse events amiodarone was slightly more effective than propafenone, and was just shy of statistical significance (p = 0.058). Three studies compared amiodarone to placebo for either maintaining SR or cardioverting AF. One
study found amiodarone was more effective than placebo in maintaining AF after one year (p <0.001; SAFE-T study), and Vardas et al found amiodarone was more effective than placebo in converting patients to sinus rhythm at the 30-day mark (OR 6.21%; 95% CI, 3.33 to 11.57; p < 0.0001). In contrast, the third study comparing dofetilide to amiodarone or placebo found that amiodarone was no more effective than placebo after 3 hours for cardioverting AF, where 4% of patients in the amiodarone group compared to 4% of patients in the placebo group had cardioverted at three hours. The final study evaluating the efficacy of digoxin verses amiodarone or sotalol in converting recent-onset AF to SR, found digoxin was inferior to amiodarone and sotalol combined (p <0.05; RR 5.4.; 95% CI 1.5 to 19.2), while sotalol versus amiodarone showed no statistical difference (p=0.23).

Conclusion: In all but one study, amiodarone proved to be an effective first-line medication for the conversion or maintenance of sinus rhythm in patients with atrial fibrillation. However, its use as a first-line agent in symptomatic recent-onset AF is less effective than either ibutilide or dofetilide when prompt time to conversion is required. Amiodarone also proved to be more effective than sotalol in maintaining SR after one year, and demonstrated superior effectiveness when compared to class I antiarrhythmics. When compared to propafenone, amiodarone demonstrated either equal or superior effectiveness for maintaining SR at one year. However, because propafenone is a class I-C antiarrhythmic, it is contraindicated in patients with underlying structural heart disease, whereby amiodarone is a reasonable first-line alternative.
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AMIODARONE AS A FIRST-LINE THERAPY FOR THE
CONVERSION OF ATRIAL FIBRILLATION OR LONG-TERM
MAINTENANCE OF SINUS RHYTHM ONCE CARDIOVERSION
HAS BEEN ACHIEVED

By:

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A Clinical Research Project Submitted to the Faculty of the
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Faculty Advisor: James Ferguson, PA-C
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Biography

Nicole Dwyer was raised near Denver, Colorado and earned her undergraduate degree in Biology from the University of Colorado at Denver in 2003. Prior to that, she served in the United States military as a Hospital Corpsman with a specialty in surgical technology. After leaving Denver, she went on to study massage therapy at the Brian Utting School of Massage Therapy in Seattle, Washington, earning her National Certification in Massage Therapy in 2007. Following graduation from Pacific University, she is planning to return to Seattle where she plans on working in an orthopedic surgical specialty.
Abstract

**Background:** Optimal, long-term drug strategies for cardioversion of atrial fibrillation (AF) and maintenance of sinus rhythm (SR) have been controversial. Amiodarone is an old drug that is an effective class III antiarrhythmic for both converting and maintaining sinus rhythm in patients with atrial fibrillation, however, there have been few recent, blinded, randomized controlled studies comparing amiodarone to other pharmacological agents to determine if it is an effective first-line therapy.

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**Conclusion:** In all but one study, amiodarone proved to be an effective first-line medication for the conversion or maintenance of sinus rhythm in patients with atrial fibrillation. However, its use as a first-line agent in symptomatic recent-onset AF is less effective than either ibutilide or dofetilide when prompt time to conversion is required. Amiodarone also proved to be more effective than sotalol in maintaining SR after one year, and demonstrated superior effectiveness when compared to class I antiarrhythmics. When compared to propafenone, amiodarone demonstrated either equal or superior effectiveness for maintaining SR at one year. However, because propafenone is a class I-C antiarrhythmic, it is contraindicated in patients with underlying structural heart disease, whereby amiodarone is a reasonable first-line alternative.

**Keywords:** Atrial fibrillation, cardioversion, first-line therapy, antiarrhythmics
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List of Abbreviations

AE ............................................................... Adverse events
AF ............................................................... Atrial fibrillation
Af ................................................................. Atrial flutter
ACC .......................................................... American College of Cardiology
AFFIRM ......... Atrial Fibrillation Follow-up Investigation of Rhythm Management
CTAF ......................................................... Canadian Trial of Atrial Fibrillation
COPD ......................................................... Chronic Obstructive Pulmonary Disease
LVEF ........................................................ Left Ventricular Ejection Fraction
LV ............................................................... Left Ventricular
SAFE-T ...................... Sotalol Amiodarone Atrial Fibrillation Efficacy Trial
SR ............................................................. Sinus Rhythm
Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice today, accounting for approximately five million physician office visits and 350,000 hospitalizations each year. It is estimated that 2.2 million people experience paroxysmal or persistent atrial fibrillation in the U.S. with direct expenditures for AF estimated at about U.S. $7 billion annually. Atrial fibrillation can occur alone, but is often associated with other co-morbidities such as, left ventricular dysfunction, structural cardiomyopathies, hypertension, coronary artery disease, heart failure, chronic obstructive pulmonary disease (COPD), and sleep apnea, and it can temporarily exacerbate or permanently worsen any of these conditions. It is well known that the incidence of AF increases with age with 50% of cases occurring in patients older than 75 years. The impact will increase in significance as the U.S. population continues to age and as the healthcare burden and related costs attributable to the treatment of atrial fibrillation increases. Establishing effective prevention and treatment of atrial fibrillation remains an urgent issue. However, the best treatment options have yet to be determined as advances in electrical and pharmacologic interventions are incorporated into recommendations.

Pharmacological Cardioversion

One of several treatment strategies is the restoration and maintenance of normal sinus rhythm using a pharmacological approach with antiarrhythmics indicated for AF. Arguments for this approach focus on prevention of electrical and structural remodeling of the myocardium that leads to sustained AF and subsequent left ventricular dysfunction,
hemodynamic instability, ischemic heart changes, and heart failure \(^3,^4\). Additionally, AF increases the risk of ischemic stroke to approximately 5% per year, with death or severe neurologic deficit occurring in 50% to 70% of cases \(^5\). The risk of stroke attributable to AF annually is 1.5% in patients 50 to 59 years old and rises sharply to 23.5% in those aged 80 to 89 years \(^3\). To mitigate this risk, anticoagulation is the standard of care, however, this also increases the risk of major bleeding, especially in the elderly population in which AF is more likely to occur \(^3,^5,^6\). Consequently, morbidity and mortality related to AF is significantly increased independent of underlying cardiac disease. The rationale, therefore, is prompt treatment of AF with either electrical or pharmacological cardioversion to sinus rhythm to prevent electrical and structural remodeling, to avoid the need for oral anticoagulation in patients for whom it would otherwise be appropriate, to prevent hospitalizations or lengthy hospital stays related to AF, and to improve overall patient compliance \(^6\).

Optimal, long-term drug strategies for cardioversion of AF and maintenance of sinus rhythm have been controversial. Each antiarrhythmic drug carries its own risk, and adverse effects must be weighed against the benefits. Furthermore, variables that depend on patient presentation and co-morbidities often determine the choice of drug. For example, class I-C antiarrhythmic agents such as propafenone are contraindicated due to their proarrhythmic effects in patients with structural heart disease \(^3\). In contrast, amiodarone is an old drug that is an effective class III antiarrhythmic for both converting and maintaining sinus rhythm in patients with atrial fibrillation, and is not contraindicated in patients with underlying heart failure \(^3\). Unfortunately, amiodarone has a side effect profile that involves many different organ systems. As many as 80% of patients
experience side effects ranging from minimal gastrointestinal symptoms such as nausea, vomiting, and diarrhea to the more severe thyroid abnormalities, and pulmonary and ocular toxicity ⁷. However, only 10% to 15% of patients require withdrawal of the drug due to serious toxicity ⁷. Regardless, these numbers make its use as a first-line therapy undesirable for many practitioners. Consequently, there have been few blinded, randomized controlled studies to determine if amiodarone is an effective initial monotherapy. The purpose of this systematic review is to evaluate the efficacy of amiodarone as a first-line therapy in the conversion or maintenance of normal sinus rhythm in patients with atrial fibrillation.

**Methods**

A thorough search of the literature was conducted from 1999 to 2009 using multiple electronic databases including EBSCO, Medline, OVID, and PUBMED. “Amiodarone,” “atrial fibrillation,” and “randomized controlled studies” were used as MeSH headings. Inclusion criteria were published, randomized controlled studies in the English language, which included patients in all age groups who had either recent-onset, paroxysmal, persistent or chronic AF, and who were treated with either intravenous or oral amiodarone compared to placebo or another antiarrhythmic medication. Exclusion criteria were studies older than ten years that were not randomized controlled studies, trials in which amiodarone was not used as a monotherapy, but in conjunction with other therapies, or if amiodarone was used in post-cardiac surgery patients with new onset atrial fibrillation. Methodological quality of each study was evaluated using the JADAD score (See table 1). Studies with a score of >3 were considered to be of high quality and were included in the review. Furthermore, references from all primary studies, meta-
analysis, and systematic reviews from the initial search were scrutinized to identify additional studies meeting the inclusion criteria that may have been missed in the first search.

Results

A search of over 200 articles yielded eight studies that met the inclusion and exclusion criteria for this systematic review (see table 2). All of the relevant studies located were prospective, randomized controlled studies ranging in publication dates from 2000-2006. Methods of randomization varied between studies with three studies using a computer-generated random number algorithm, three studies using a permuted-block randomization method, and two studies not specifying randomization methods. The AFFIRM substudy did a second randomization of patients in the rhythm arm of the initial study to either amiodarone, sotalol, class I-A or I-B antiarrhythmic agents that included quinidine, procainamide, diospyramide, moricizine, or the class I-C agents, propafenone or flecanide. Only one study, the SAFE-T, was a double blinded study with the exception of Bianconi et al, which was double blinded when comparing dofetilide to placebo, but single blinded when comparing amiodarone to dofetilide or placebo. Five studies were single blinded, and the Canadian Trial of Atrial Fibrillation was an open label study. All studies had JADAD scores of greater than three, with two studies scoring a five, while the remaining six scored values of three. This was due largely to the fact that the remaining six studies were not double blinded, which inevitably introduces a modicum of bias.
**Patient Characteristics**

Patient characteristics varied between studies depending on the endpoint of interest (see table 2). Patients in all eight studies were either currently in AF, or had a recent history of being in AF. Atrial fibrillation was defined as ‘paroxysmal’ when it terminates spontaneously, usually within 24 hours, ‘persistent’ when pharmacological or electrical cardioversion is effective in terminating AF, and ‘permanent’ when cardioversion fails or is not attempted. Three studies, Joseph et al, Kafkas et al, and Bianconi et al evaluated patients with recent-onset AF lasting <24, <48, and between two hours and six months respectively. One study, the SAFE-T, evaluated patients with AF lasting ≥72 hours and specifically excluded patients in paroxysmal AF or atrial flutter (Af). The remaining studies evaluated symptomatic patients with either recent-onset, paroxysmal, or persistent AF. In all but two studies, which evaluated recent-onset AF <24 hours, patients were treated with anticoagulants prior to cardioversion as recommended by the American College of Cardiology (ACC) guidelines to reduce the risk of thromboembolism, which is greatest when AF has been present for more than 48 hours. Concerning evaluation of left ventricular function and heart failure, three studies excluded patients with New York Heart Association Class III or IV heart failure, three studies used left ventricular ejection fraction (LVEF) parameters of < 0.30-0.40 as exclusion criteria, one study used LV dysfunction, but did not quantify this characteristic, and the final study excluded patients with clinically unstable heart failure as a result of AF or atrial flutter (Af). Only one study allowed for patients with varying stages of heart failure, but failed to include this data when evaluating the results. A lack of uniform
comparisons between patient characteristics for overall ventricular function and stage of heart failure in this review likely introduces some variability in results between studies.  

**Endpoints and Outcomes**

Four studies measured conversion to sinus rhythm as the primary endpoint, with three of these studies measuring time to conversion as the secondary endpoint (see table 3). Two studies specifically evaluated patients with recent-onset AF or Af <24 to 48 h, one study evaluated patients with symptomatic AF admitted to the emergency department (ED) or treated in an outpatient setting, and one study included AF or Af of varying duration from 2 hours to 6 months (see table 2). Joseph et al compared the efficacy of sotalol, amiodarone, and digoxin in terms of reversion or ventricular rate after discontinuation of the study drug, time of reversion, and numbers of adverse events in 120 patients admitted to the ED with new-onset, rapid AF or atrial flutter (Af) lasting < 24 hours. Evidence showed that patients treated with amiodarone or sotalol were significantly more likely to have reverted to sinus rhythm compared to the digoxin group at 48 hours (p < 0.05). It also found a significant reduction in time to reversion of sinus rhythm with sotalol (13.0 +/- 2.5 hours, p < 0.01) and amiodarone (18.1 +/- 2.9 hours, p < 0.05) compared with digoxin (26.9 +/- 3.4 hours). Finally, the sotalol-treated patients demonstrated a markedly lower ventricular rate compared with digoxin and amiodarone at 24 and 48 hours (p<0.05). A follow-up time of 48 hours was monitored following administration of treatment. No patients were lost to follow-up and five patients had protocol violations and were excluded from further analysis.
In the second study, Kafkas et al evaluated 152 patients with AF or Af lasting between three and 48 hours in duration and compared intravenous amiodarone with intravenous ibutilide for termination of these atrial arrhythmias. Follow-up was 24 hours. In total, the conversion rate for the ibutilide group (n=56/AF, n=23/Af) was significantly higher than the amiodarone group (n=52/AF, n=23/Af) with 80% of patients in the ibutilide group successfully reverting to sinus rhythm compared to 57% in the amiodarone group (p = 0.0054). However, conversion rates for the two groups did not differ significantly when the arrhythmia analyzed was AF where 77% in the ibutilide group compared to 69% in the amiodarone group converted to sinus rhythm (p >0.05). Furthermore, conversion rates of amiodarone were significantly more effective when the arrhythmia was AF verses Af (69% vs. 29%, p = 0.000). Finally, termination time was significantly shorter with ibutilide than with amiodarone for AF (53.4 +/- 25.8 vs. 492 +/- 186 min, p = 0.000). Each drug markedly lengthened the QTc interval, however, the average lengthening of the QTc interval was not significantly different between the two groups (p = ns).

In the third study, Bianconi et al randomized 150 patients to either dofetilide (n=48), amiodarone (n=50), or placebo (n=52) and found that 17 of 48 (35%) patients given dofetilide had converted to SR within the three hour study period compared to two out of 50 patients (4%) in the amiodarone group (p <0.001), and two out of 52 patients (4%) in the placebo group. The mean time to conversion was measured in the secondary endpoint where patients taking dofetilide had a mean conversion time of 55 +/- 15 minutes after the infusion began, and 65% of dofetilide patients converted to SR within 30 minutes. A greater percentage of patients responded to dofetilide if their arrhythmia
lasted <7 days (9 of 21; 43%) than those whose arrhythmia lasted >7 days (8 of 27; 30%), however, this did not show statistical significance (p=0.59).

In the fourth study, Vardas et al randomized 208 patients with symptomatic AF to either amiodarone or placebo with conversion to AF as the primary endpoint. Patients were followed for a total of 30 days. All patients in this study were treated with digoxin for ventricular rate control. Intravenous loading doses were administered initially with oral dosing for maintenance thereafter. Findings suggested that amiodarone was more effective than placebo in converting patients to sinus rhythm at the 30-day mark where 87 patients (80.5%) in the amiodarone group, and 40 patients (40%) in the placebo group had converted (OR 6.21%; 95% CI, 3.33 to 11.57; p <0.0001). Thirty-eight percent of amiodarone patients and 25% of placebo patients converted to SR within the first hour (OR 1.84; 95% CI, 1.1 to 3.33; p <0.05). Another 25 patients in the amiodarone group and 15 in the placebo group converted to SR between one and 24 hours. Multivariate predictors of conversion, using a logistic regression analysis, found that treatment, left atrial size, and atrial fibrillation duration, were significant independent predictors for conversion to SR. Patients with new-onset AF and left atrial size <40 mm were more likely to revert to SR regardless of treatment, however, when treated with amiodarone the number of patients successfully converted to SR was 99.7% compared to 88.7% in the placebo group (p <0.0001). Conversely, in patients with persistent AF and left atrial size <40 mm, those treated with amiodarone had conversion rates of 99.1% compared to 69.2% in the placebo group (p <0.0001), and in patients with chronic AF and left atrial size <40 mm, these values changed to 89.3% and 14.4% respectively (p <0.0001; see table 4).
The remaining four studies compared amiodarone to placebo, sotalol, propafenone, or class I antiarrhythmics and measured the time to recurrence of AF as the primary outcome. In all but one study amiodarone proved statistically superior to these medications in maintaining SR. P-values ranged from $p < 0.001$ to $< 0.05$. The Canadian Trial of Atrial Fibrillation (CTAF) found that the median length of time to recurrence with propafenone or sotalol was 98 days compared to 468 days in the amiodarone group ($p < 0.001$), and the probability of remaining in SR at one year without recurrence of AF was higher in the amiodarone group (69%) verses the propafenone or sotalol groups (39%, $p < 0.001$). For the patients in the amiodarone group, the hazard ratio for a recurrence of AF was 0.43 (95% CI, 0.32 to 0.63), which equates to a 57% reduction in the risk of recurrence$^8$.

In the AFFIRM substudy, 410 patients were treated with amiodarone compared to sotalol or class I antiarrhythmics. The primary endpoint measured maintenance of sinus rhythm with no additional cardioversion while still taking the assigned drug at one year, and the number of antiarrhythmic-related deaths, making this the only study that included mortality as an end point. At one year, 62% of patients in the amiodarone group compared to 23% of patients in the class I group were still in normal sinus rhythm ($p < 0.001$)$^1$. Moreover, at one year, 60% of patients in the amiodarone group were still in SR compared to only 38% of patients in the sotalol group ($p = 0.002$). Amiodarone was also more effective than class I agents and sotalol at maintaining sinus rhythm at the end of the follow-up period of 3.84 +/- 1.3 years ($p = 0.0114$) and ($p = 0.0003$) respectively. Concerning antiarrhythmic deaths, more deaths occurred in patients randomized to the class I agents (26 patients) than to amiodarone (10 patients). In both cases the deaths
were more likely to occur after the assigned drug had been discontinued. No significant difference was noted in death rates between amiodarone and sotalol, or between sotalol and class I agents.

In the SAFE-T study, 665 male patients with AF ≥72 hours were treated with amiodarone, sotalol, or placebo with the primary endpoint being the time to the first recurrence of AF after successful restoration of SR. Patients were followed for 12 to 54 months. Amiodarone and sotalol proved to be statistically more effective than placebo in increasing the time to recurrence of AF after sinus rhythm had been restored (p < 0.001). The median time to recurrence of AF in the amiodarone group was 487 days compared to 74 days in the sotalol group and 6 days in the placebo group. The SAFE-T study also found that amiodarone was six times as effective as sotalol in the intention to treat analysis and four times as effective in the analysis of the treatment actually received in maintaining SR. However, when ischemic heart disease was reviewed, the results for amiodarone were not statistically significant compared to those for sotalol in maintaining SR in the subset where the time to recurrence was 569 days in the amiodarone group and 428 days in the sotalol group (p = 0.53).

In the study by Kochiadakis et al comparing low dose oral amiodarone to propafenone in 146 patients with recurrent, symptomatic AF in which successful electrical or chemical cardioversion had been achieved, the primary analysis included adverse effects in the end point and found that amiodarone had no significant advantage over propafenone in maintaining sinus rhythm (p = 0.44). However, in the secondary analysis when adverse events were not figured in the data, the difference between the two drugs was just short of statistical significance (p = 0.058) with amiodarone appearing to
be better than propafenone in women (p = 0.03) and in patients < 65 years old (p = 0.01). Additionally, in the amiodarone group, the average length of time to recurrence was significantly longer at 9.8 months compared to 3.8 months in the propafenone group, while the number of patients experiencing side effects and consequently discontinuing medication was higher in the amiodarone group (n = 12) versus the propafenone group (n = 2).

**Follow-up and Adverse Events**

Follow-up between studies varied markedly with the longest duration of 12 to 54 months in the SAFE-T study and 3.84 +/- 1.3 years in the AFFIRM study, and the shortest follow-up times at 3 hours, 24 hours and 48 hours in Bianconi et al, Joseph et al, and Kafkas et al respectively. The most common adverse events (AE) experienced in patients taking either oral or intravenous amiodarone were minor bleeding, hypotension, localized infusion reactions, GI disturbances, thyroid dysfunction, and pulmonary toxicity. In the SAFE-T study, there were no significant differences in the rates of adverse events among study groups except rates of minor bleeding, which were significantly higher in the amiodarone group compared to sotalol and placebo combined (p < 0.04). Mortality between all three groups also did not differ significantly, with a death rate of 4.36 per 100 person-years’ follow-up in the amiodarone and sotalol groups combined compared to 2.84 per 100 person-years’ of follow-up in the placebo group (P = 0.13). In Vardas et al no patients were lost to follow-up after 30 days and no adverse events requiring discontinuation of the study medication occurred. Minor events included a significant drop in systolic blood pressure (SBP) within the first hour of amiodarone infusion in 12 patients, and phlebitis occurring at the infusion site in 17
amiodarone patients. In the AFFIRM substudy, there was no difference in adverse events requiring discontinuation of the study drug between the amiodarone patients (12.3%) and the sotalol patients (11.1%), however, this percentage was comparatively higher in patients taking class I antiarrhythmics (28.1%). Death due to arrhythmias was more likely to occur in patients taking class I agents compared to both amiodarone and sotalol combined. In the study by Kochiadakis et al, patients taking amiodarone had more adverse effects than those taking propafenone where 14 out of 17 patients experienced thyroid problems in the amiodarone group. While the authors noted those taking propafenone had fewer incidences of side effects, statistical analysis was not enumerated for comparison. No deaths occurred in this study. In the CTAF study, a total of 36 patients in the amiodarone group (18%), compared to 23 patients in the combined sotalol and propafenone groups (11%) discontinued the study drug due to adverse events (p = 0.06). The incidence of cardiac events requiring permanent discontinuation of the study drug was similar in the two groups where patients experiencing ventricular tachycardia, QTc prolongation, heart failure, and bradyarrhythmias were similar. The incidence of mortality was essentially the same between groups in which nine patients in the amiodarone group died compared to a combined eight patients in the sotalol or propafenone groups.

The final three studies by Bianconi et al, Joseph et al, and Kafkas et al, had follow-up durations of 3h, 24h, and 48 hours respectively, where side effects directly related to amiodarone are less likely to occur because of the relatively slow pharmacokinetic properties of this drug. Joseph et al found that patients taking digoxin versus sotalol or amiodarone were more likely to experience left ventricular heart
failure (six patients treated with digoxin compared to two treated with amiodarone, p <0.05), and hypothesized that this was probably due to poor rate control with digoxin over the other two agents. No episodes of hypotension were reported, and only one patient in the amiodarone group experienced thrombophlebitis. In the study conducted by Kafkas et al, ibutilide was more likely to cause ventricular arrhythmias such as torsades des points (n=3), premature ventricular beats (9% compared to 3% in the amiodarone group, p = ns), and non-sustained ventricular tachycardia (10 patients compared to 2 in the amiodarone group, p = 0.033). Two patients in the amiodarone group had hypotension, and five patients had localized infusion reactions. Bianconi et al had similar findings of torsades des pointes in 8% of patients treated with dofetilide, and an additional four dofetilide-treated patients experienced either isolated non-sustained ventricular tachycardia (n=2), premature ventricular beats with frequent couplets (n=1), or prolongation of the QT interval from 439 ms to 577 ms. Only one patient experienced an episode of mild hypotension that lasted for 13 minutes after the start of the infusion.

**Discussion**

In all but one study, the results of this systematic review found that amiodarone was an effective first-line therapy in both converting atrial fibrillation to sinus rhythm or maintaining patients in sinus rhythm after they have been cardioverted regardless of the type of AF they presented with. However, not all atrial fibrillation responds the same way to amiodarone, where its overall success is influenced by a number of factors such as the duration of AF, underlying structural heart disease, age, and gender ³.⁴.
In recent-onset AF, the more selective class III antiarrhythmics, ibutilide and dofetilide, proved to be superior alternatives to amiodarone for rapid conversion of AF. This is likely due to amidarone’s complex pharmacokinetics involving multiple compartments of distribution, hepatic breakdown of the parent drug into its active metabolite, and a long half-life, all of which slow its effects. Kafkas et al found that although amiodarone was as effective as ibutilide at converting AF to SR, ibutilide proved to be faster with a mean conversion time of 2.2 days compared to a mean of 20.5 days with amiodarone ($p = 0.000$). In contrast, Bianconi et al found dofetilide to be superior to amiodarone or placebo at converting either AF or AF to SR where 35% of patients taking dofetilide converted to SR within the first three hours compared to only 4% in the amiodarone group ($p < 0.001$) and 4% in the placebo group. The mean time to conversion for dofetilide was 55 +/-15 minutes after the infusion began with 65% of patients converting to SR within 30 minutes. Although amiodarone showed no benefit over placebo for conversion to SR in this study, the follow-up time was only three hours, which was probably insufficient to capture the overall efficacy of amiodarone. Regardless, when prompt pharmacological cardioversion is required, the selective class III antiarrhythmics appear to be more effective than amiodarone in converting recent-onset AF.

While these findings are promising for symptomatic patients who require immediate cardioversion, care must be taken to monitor for the proarrhythmic effects of these drugs. Kafkas et al found a higher incidence of arrhythmias in patients treated with ibutilide compared to amiodarone in which torsades des pointes occurred in 3.8% of patients in the ibutilide group with none in the amiodarone group, and another ten
patients experienced monomorphic non-sustained ventricular tachycardia in the ibutilide group compared to only two in the amiodarone group (p =0.033). Similarly, Bianconi et al also found a higher incidence of torsades des pointes in patients treated with dofetilide where 8% of patients experienced this arrhythmia. Neither of these studies had arrhythmia-related deaths, and the arrhythmias were successfully terminated in all patients. This clearly highlights some of the precautions needed when administering these drugs. In addition, dofetilide is primarily cleared through the kidneys and can be nephrotoxic in patients with kidney disease. The FDA requires providers to be certified in the dosing and administration of dofetilide, and patients must be hospitalized for a minimum of three days to monitor kidney and heart function. While the benefit of their rapid action demonstrates their superiority over amiodarone in the acute and symptomatic presentation of AF, risk of dangerous ventricular arrhythmias, and the added cost of administering the drugs must be weighed against their benefits.

The duration of AF, and the presence of underlying structural heart disease are powerful predictors of successful cardioversion to SR in patients with AF. This is likely due to electrical remodeling that promotes AF in patients with cardiomyopathies and heart failure. These patients are less likely to convert to SR on their own and may require pharmacological intervention. This was illustrated in the study by Vardas et al where amiodarone was compared to placebo in patients with symptomatic AF, regardless of the type of AF, and followed for 30 days to evaluate efficacy of converting AF and maintaining SR at the 30-day mark. In the first 24 hours, patients with an initial intravenous loading dose of amiodarone and subsequent oral dosing experienced higher conversion rates and longer periods of maintained SR than the placebo group. Overall,
after a total of 30 days, conversion rates with amiodarone were 80.5% compared to 40%
in the placebo group (p <0.0001), but in patients with a very large left atrium >46 mm
and chronic AF, these rates fell to 61% and 34.6% respectively. In the placebo group,
these percentages dropped sharply to 9.7% in patients with left atrium size >46 mm, and
no patients in chronic AF converted to sinus rhythm. These findings illustrate the benefit
of amiodarone over placebo in patients with longer-duration AF and underlying structural
heart disease. Furthermore, amiodarone becomes a reasonable alternative to class I-C
agents such as propafenone in which their use is contraindicated in patients with
structural heart disease due to their proarrhythmic effects ³, ⁶, ¹⁴.

In the SAFE-T, CTAF, AFFIRM substudy and the study by Kochiadakis et al,
where the primary endpoint measured was the time to recurrence of AF after SR had been
restored, all studies demonstrated amiodarone’s superiority over placebo, sotalol,
propafenone, and class I-C antiarrhythmic agents in maintaining SR at one year.
However, there were several exceptions to this finding. First, the study by Kochiadakis et
al comparing low dose propafenone to amiodarone in maintaining SR, found amiodarone
to be superior to propafenone with an average time to recurrence of 9.8 months in 25
patients treated with amiodarone compared to only 3.8 months in 33 patients treated with
propafenone. However, when adverse events were analyzed in the primary endpoint,
equal efficacy was demonstrated between medications. They concluded that the
advantage of amiodarone over propafenone in maintaining AF was offset by its side
effect profile ¹³. Furthermore, they found amiodarone to be superior to propafenone in
female patients and patients ≤ 65 years of age with AF, indicating that both female
gender and a younger age may predict a more favorable outcome for conversion to SR
when amiodarone is chosen over propafenone. Second, in the SAFE-T study, investigators were surprised to find that in subgroups of patients with ischemic heart disease, amiodarone and sotalol were equally as effective at maintaining SR after one year ($p = 0.53$). Further studies to measure the efficacy of antiarrhythmic medications in patients with ischemic heart disease and are needed to evaluate these findings.

Concerning adverse events, findings in this systematic review were difficult to compare between studies given the differences in AF type, variation in patient characteristics such as left atrial size and the presence or absence of underlying structural heart disease, and lengths of follow-up time. The SAFE-T and AFFIRM substudy had follow-up times of a minimum of one year and a maximum of 54 months and $3.84 \pm 1.3$ years respectively, and each study had similar patient characteristics. Both studies demonstrated no statistical difference in adverse events between amiodarone and sotalol, however, in the AFFIRM substudy, amiodarone and sotalol were significantly less likely to cause adverse events or death compared to class I agents. In contrast, the CTAF study found that 18% of patients in the amiodarone group compared to 11% in the combined sotalol and propafenone groups, discontinued the study drug due to adverse events ($p = 0.06$), however, serious events with amiodarone were uncommon and no proarrhythmic events occurred. In Joseph et al comparing amiodarone to digoxin or sotalol for cardioversion of recent–onset AF with rapid ventricular response, patients treated with digoxin were more likely to experience left ventricular (LV) heart failure (six treated with digoxin and two treated with amiodarone) compared to amiodarone and sotalol combined. When these patients were evaluated for LV dysfunction with echocardiogram, two patients in the digoxin group and two patients in the amiodarone group already had
pre-existing LV dysfunction. The authors concluded that the remaining four patients in the digoxin group who experienced heart failure likely had poor rate control. This finding is interesting given the fact that digoxin is primarily indicated for rate control in rapid AF.

The safety profile of amiodarone has created a great deal of apprehension in the medical community concerning its use. However, in this systematic review, when compared to other pharmacological agents, amiodarone demonstrated less proarrhythmic effects than the alternative class III agents, lower adverse events and mortality rates compared to class I agents, and was less likely to result in heart failure compared to digoxin. The most commonly experienced events specific to amiodarone were pulmonary toxicity occurring in four patients in the CTAF and AFFIRM substudy respectively, and in two patients in the SAFE-T study. None resulted in death. In Kochaidakis et al, thyroid dysfunction occurred in 14 patients resulting in discontinuation of the study drug, while GI disturbances were fairly common and easily mitigated by dose reduction or splitting of the dosage. Finally, in patients treated with intravenous amiodarone, hypotension was common and occurred in 12 patients in Vardas et al, five patients in Kafkas et al, and one case of mild hypotension in Bianconi et al. It is speculated that the mechanism for this is partially due to the effects of polysorbate 80, the solvent present in conventional amiodarone intravenous preparations, which is known to cause hypotension.

Differences concerning the incidence of adverse events in this review leave unanswered questions regarding the overall safety of amiodarone as a first-line agent in the treatment of AF. However, its demonstrated efficacy over placebo in this review is undisputed, and
its potential efficacy over sotalol, propafenone, and other class I agents warrant the consideration of its use as a first-line therapy in the management of AF.

**Conclusion**

In all but one study of this systematic review, the data showed that amiodarone was effective as a first-line therapy in either the conversion of AF or the maintenance of SR. However, the duration of AF, presence of structural heart disease, age, and gender were influential in its overall success. In recent-onset AF, amiodarone was less effective than the class III antiarrhythmics ibutilide and dofetilide when rapid cardioversion was desired. Both medications proved superior to amiodarone in the time to conversion of AF, but each had a higher occurrence of proarrhythmias, which required continuous electrical monitoring and limited their use to the hospital setting. Furthermore, dofetilide can be nephrotoxic requiring several days of inpatient monitoring, thereby adding to the initial cost of treatment. When treating AF of longer duration where underlying structural heart disease is present, amiodarone is a relatively safe and effective alternative to class I-C antiarrhythmics such as propafenone, and may be considered as a first-line therapy for conversion of AF to SR in this patient demographic. Amiodarone proved to be superior to sotalol at increasing the time to recurrence of AF, except in patients with ischemic heart disease where equal efficacy was demonstrated in this patient subgroup. Further studies are needed to evaluate this finding. Adverse events related to amiodarone were few, but serious events such as pulmonary toxicity and thyroid abnormalities do occur, and may be prevented through regular screening. Regardless, the incidence of serious adverse events with amiodarone are minimized by its beneficial effects, and in the right patient, amiodarone is an appropriate first-line therapy for the management of AF.
References


Table 1. JADAD Score Calculation*

<table>
<thead>
<tr>
<th>Item</th>
<th>Score</th>
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<tbody>
<tr>
<td>Was the study described as randomized?</td>
<td>0/1</td>
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<tr>
<td>Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer-generated, etc)?</td>
<td>0/1</td>
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<tr>
<td>Was the study described as double blind?</td>
<td>0/1</td>
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<tr>
<td>Was the method of double blinding described and appropriate (identical placebo, active placebo, dummy, etc)?</td>
<td>0/1</td>
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<tr>
<td>Was there a description of withdrawals and dropouts?</td>
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<tr>
<td>Deduct one point if the method used to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc.)?</td>
<td>0/-1</td>
</tr>
<tr>
<td>Deduct one point if the study was described as double blind but the method of blinding was inappropriate (e.g., comparison of tablet, vs. injection with no double dummy).</td>
<td>0/-1</td>
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</table>

* Adapted from (*Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Controlled Clinical Trials 1996;17[1]:1-12*)
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<tbody>
<tr>
<td>Study Design</td>
<td>Double blind, placebo controlled, permuted block randomization</td>
<td>Single blind, RCT</td>
<td>Prospective, non-blinded, RCT</td>
<td>Single blind, RCT</td>
<td>Single blind, RCT</td>
<td>Single blind, RCT</td>
<td>Double blind for dofetilide/placebo and single blind for amiodarone, RCT</td>
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<tr>
<td>JDAD Score</td>
<td>5</td>
<td>3</td>
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<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>5</td>
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<tr>
<td>Patient Population and Eligibility</td>
<td>N=665 male patients with AF≥72h seen in outpatient clinics (excludes paroxysmal AF)</td>
<td>N=410 with recent-onset, paroxysmal, or persistent AF</td>
<td>N=403 with at least one episode of symptomatic AF within last 6 months that lasted for &gt;10 minutes</td>
<td>N=146 with recurrent paroxysmal or persistent symptomatic AF in which successful chemical or pharmacological cardioversion had been achieved</td>
<td>N=208 with symptomatic AF seen in ED or outpatient clinic</td>
<td>N=120 with recent-onset AF or Af &lt;24h admitted to the ED</td>
<td>N=152 (103 male, 49 female) with symptomatic AF or Af of 3 to 48h admitted to the ED</td>
<td>N=150 with AF or Af of 2h to 6 months duration</td>
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<tr>
<td>Exclusion Criteria</td>
<td>Atrial flutter, paroxysmal AF, NYHA class III/IV. Hx of long QT-syndrome</td>
<td>Amiodarone/Sotalol: NYHA class ≥ II or HF with LVEF ≤0.30, or ≤0.25 alone. Disopyramide: LVEF &lt;0.30</td>
<td>AF &gt; 6 months, NYHA ≥II/IV. Hx of long QT syndrome or 2nd or 3rd HB. ECG confirmed LVEF &lt;0.40 and structural heart disease. Severe HF LVEF ≤0.30. Hx of 2nd or 3rd degree HB or sick sinus syndrome</td>
<td>AF &gt;24 days &amp; present within last 7 days. LV dysfunction. QTc &gt;450 ms.</td>
<td>Clinically unstable HF. Known sick sinus syndrome, or 2nd or 3rd degree HB.</td>
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Abbr: AF (atrial fibrillation), Af (atrial flutter), CHF (congestive heart failure), ED (emergency department), HB (heart block), HF (heart failure), LVEF (left ventricular ejection fraction), NYHA (New York Heart Association).
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<tr>
<td><strong>Drugs Compared</strong></td>
<td>1. Amiodarone vs. placebo</td>
<td>Amiodarone vs. sotalol or propafenone</td>
<td>Amiodarone vs. placebo</td>
<td>Amiodarone vs. placebo or sotalol</td>
<td>Digoxin vs. amiodarone or sotalol</td>
<td>Ibutilide vs. amiodarone</td>
<td>Dofetilide vs. amiodarone or placebo</td>
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<td>2. Amiodarone vs. sotalol</td>
<td>1. Amiodarone vs. sotalol</td>
<td>Amiodarone vs. sotalol</td>
<td>Amiodarone vs. sotalol</td>
<td>Amiodarone vs. sotalol</td>
<td>Amiodarone vs. placebo</td>
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<td>3. Sotalol vs. class I-C</td>
<td>2. Amiodarone vs. Class I-C</td>
<td>Amiodarone vs. propafenone</td>
<td>Amiodarone vs. placebo</td>
<td>Dofetilide vs. amiodarone</td>
<td>Amiodarone vs. placebo</td>
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<td>4. Amiodarone vs. class I-C</td>
<td>Amiodarone vs. propafenone</td>
<td>Amiodarone vs. placebo</td>
<td>Amiodarone vs. placebo</td>
<td>Amiodarone vs. placebo</td>
<td>Dofetilide vs. amiodarone</td>
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<td></td>
<td>vs. sotalol</td>
<td>Amiodarone vs. propafenone</td>
<td>Amiodarone vs. placebo</td>
<td>Amiodarone vs. placebo</td>
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<tr>
<td><strong>Endpoints</strong></td>
<td>First recurrence of AF after SR restored.</td>
<td>Composite: Patients alive, on drug, in SR, and no cardioversions at 4 months and 1 year, Also number of arrhythmic-related deaths</td>
<td>Length of time to recurrence of AF.</td>
<td>Lowest effective dose that could maintain SR at one year without producing AE.</td>
<td>Conversion to SR after 30 days.</td>
<td>Conversion to SR within 48h, and if not in SR, then ventricular rate.</td>
<td>Secondary endpoint: Time to conversion and AE</td>
<td>Conversion to SR and up to 4h following conversion, but &lt;24 hours.</td>
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<td>Secondary: Changes in quality of life scores.</td>
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<td></td>
<td>Secondary: Time to conversion</td>
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<tr>
<td><strong>P-values</strong>*</td>
<td>Amiodarone &amp; sotalol vs. placebo (p &lt;0.001)</td>
<td>Amiodarone vs. sotalol (p = 0.002)</td>
<td>Amiodarone vs. sotalol or propafenone (p &lt;0.001).</td>
<td>Amiodarone vs. placebo</td>
<td>Amiodarone or sotalol vs. digoxin (p &lt;0.05).</td>
<td>Amiodarone vs. amiodarone when AF or Af (p = 0.0054). When AF only, ibutilide vs. amiodarone (p &gt; 0.05).</td>
<td>Dofetilide vs. amiodarone (p &lt;0.001)</td>
<td>Amiodarone vs. placebo (P = ns).</td>
</tr>
<tr>
<td></td>
<td>Amiodarone vs. sotalol (p &lt;0.001)</td>
<td>Amiodarone vs. Class I-C (p &lt;0.001)</td>
<td>Amiodarone vs. propafenone (p &lt;0.001).</td>
<td>Without AE analyzed in the endpoint (p = 0.058).</td>
<td>Time to conversion with sotalol or amiodarone (13.0 +/- 2.5h; p&lt;0.01) and (18.1 +/- 2.9h; p &lt;0.05) respectively vs. digoxin (26.9 +/- 3.4h).</td>
<td>Conversion rates of amiodarone for AF vs. Af (69% vs. 29%, p = 0.000)</td>
<td>Time to conversion ibutilide vs. amiodarone (53.4 +/- 25.8 vs. 492 +/- 186 minutes, p = 0.000).</td>
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<td>Amiodarone vs. sotalol in pts with ischemic heart disease (p = 0.53)</td>
<td>Deaths: class I agents (n=26) and amiodarone (n=10)</td>
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Abbr: AE (adverse events), AF (atrial fibrillation), Af (atrial flutter), SR (sinus rhythm). *If the drug is listed first the corresponding p-value indicates that drugs efficacy over the comparison drug.
<table>
<thead>
<tr>
<th>Type of AF</th>
<th>Left Atrium &lt;40mm</th>
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<th>Left Atrium 40-46mm</th>
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<th>Left atrium &gt;46mm</th>
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<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Amiodarone</td>
<td>Placebo</td>
<td>Amiodarone</td>
<td>Placebo</td>
<td>Amiodarone</td>
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<tr>
<td>Recent-onset AF</td>
<td>88.7%</td>
<td>99.7% (p &lt; 0.0001)</td>
<td>36.3%</td>
<td>96.6%</td>
<td>27.9%</td>
<td>95.1%</td>
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<tr>
<td>Persistent AF</td>
<td>69.2%</td>
<td>99.1% (p &lt;0.0001)</td>
<td>14.1%</td>
<td>88.9%</td>
<td>9.9%</td>
<td>84.5%</td>
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<tr>
<td>Chronic AF</td>
<td>14.4%</td>
<td>89.3% (p &lt; 0.0001)</td>
<td>1.2%</td>
<td>37.7%</td>
<td>0.8%</td>
<td>29.1%</td>
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</table>

*Table adapted from Kochaidakis et al. Abbr: AF (Atrial fibrillation)*