Effectiveness of Amiodarone for Conversion of Atrial Fibrillation to Sinus Rhythm

A Meta-analysis

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Background: Although clinicians sometimes choose amiodarone to convert atrial fibrillation (AF) to sinus rhythm, no current and comprehensive systematic review has summarized its effectiveness.

Objective: To review the effectiveness of amiodarone in converting AF to sinus rhythm over a 4-week period.

Methods: Two reviewers conducted a systematic search for randomized trials in databases, complemented by hand searches and contact with experts. Selected trials compared amiodarone with placebo, digoxin, or calcium channel blockers for conversion of AF to sinus rhythm. Reviewers evaluated the methodology and extracted data from each primary study.

Results: Twenty-one studies met eligibility criteria. Duration of AF proved to be a source of heterogeneity, leading to 2 analyses. The relative risk (RR) for achieving sinus rhythm was 4.33 (95% confidence interval [CI], 2.76-6.77) for trials with mean AF duration of greater than 48 hours and 1.40 (95% CI, 1.25-1.57) for those with AF of 48 hours or less. The risk differences for these 2 groups were 27% and 26%, respectively, yielding a number needed to treat of 4 for both groups. The low control event rate among trials with a duration of 48 hours or less, explained the difference in the RR for conversion. We found that the size of the left atrium, presence of cardiovascular disease, and protocols of amiodarone administration did not influence the magnitude of effect. Serious adverse events were infrequent.

Conclusions: Amiodarone is effective for converting AF to sinus rhythm in a wide range of patients. Although use of amiodarone is apparently safe, safety data are too scarce for definitive conclusions.

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Atrial fibrillation (AF) is the most commonly encountered arrhythmia. The incidence increases with age and the presence of structural heart disease. For men and women aged 55 to 64 years, one study estimated the 2-year incidences as 0.6% and 0.4%, respectively, whereas for men and women aged 85 to 94 years, they increased to 7.6% and 6.3%, respectively, representing an odds ratio of approximately 2 for each advancing decade in both sexes. Atrial fibrillation may cause symptoms such as palpitation, dyspnea, angina, syncope, and more serious complications such as tachycardia-induced cardiomyopathy, hemodynamic instability, heart failure, and stroke. Furthermore, AF may represent an independent risk factor for death.

Authors advocate 2 strategies for managing AF. Clinicians may restore and maintain sinus rhythm or may choose to control ventricular rate without attempting to terminate AF. The Pharmacological Intervention in Atrial Fibrillation (PIAF) trial showed no difference between these 2 strategies in improvement of symptoms and quality of life. The recently presented Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study did not find a statistically significant difference between the 2 strategies in terms of total mortality and ischemic stroke among elderly patients with AF at high risk for stroke. Nevertheless, selected patients and those younger than 65 years may benefit from conversion to sinus rhythm.

Electrical cardioversion and/or antiarrhythmic drugs provide options for clinicians choosing conversion to sinus rhythm. Investigators have studied a number of classes I and III antiarrhythmic drugs for conversion of AF to sinus rhythm. Among these drugs, amiodarone, a class III antiarrhythmic drug, seems promising because of its low proarrhythmic profile and...
its safety in patients with structural heart disease, especially when used in low doses. Despite these properties, the role of amiodarone in conversion of AF to sinus rhythm remains unestablished.

In considering amiodarone for converting AF to sinus rhythm, clinicians should be aware of the magnitude of its effectiveness, ideally summarized in a systematic review of randomized trials. We found one such review that addressed the efficacy and safety of different antiarrhythmic drugs compared with placebo, digoxin, or calcium channel blockers (CCBs) in conversion of nonpostoperative AF to sinus rhythm. Since the conduct of this review, which included only 3 trials of amiodarone, there have been 12 new randomized trials. We therefore conducted a systematic review and meta-analysis of randomized clinical trials. We found one such review that addressed the efficacy and safety of different antiarrhythmic drugs compared with placebo, digoxin, or calcium channel blockers (CCBs) in conversion of nonpostoperative AF to sinus rhythm. Since the conduct of this review, which included only 3 trials of amiodarone, there have been 12 new randomized trials. We therefore conducted a systematic review and meta-analysis of randomized clinical trials on the effectiveness and safety of amiodarone in achieving sinus rhythm in patients with AF of any etiology.

METHODS

ELIGIBILITY CRITERIA

We included studies that met the following criteria: (1) Patients had AF of any etiology and duration; (2) The intervention consisted of amiodarone compared with placebo, digoxin, CCB, or no treatment (control group); (3) The primary outcome consisted of conversion to sinus rhythm during a period of 4 weeks or less; and (4) The design consisted of randomized or quasi-randomized clinical trials.

We included published and unpublished studies without language restriction. We excluded studies in which 30% or more of the participants had non-AF supraventricular arrhythmias such as atrial flutter and studies that concerned primary prevention of AF. Studies that presented insufficient data regarding our primary outcome, conversion to sinus rhythm, for which we could not get additional information from the authors, were also excluded.

Our secondary outcomes were mortality and adverse events (AEs), but we did not exclude from the primary analysis studies that failed to report these outcomes.

Search

We searched for relevant studies in the electronic databases MEDLINE (January 1966 to February 2001), EMBASE (January 1980 to September 2000), Cochrane Controlled Trial Register (Cochrane Library 2000, issue 3), and Best Evidence (January 1991 to September 2000), using the terms atrial fibrillation and amiodarone (Medical Subject Headings or text words). We restricted the search to articles indexed as randomized controlled trials (publication type) or drug therapy (subject heading) or those that included the words random, placebo, or trial in their titles or abstracts. We also hand searched abstracts that were presented in major meetings of cardiology societies between 1995 and 2000 and published in supplemental issues of Circulation, Journal of the American College of Cardiology, European Heart Journal, and Pacing and Clinical Electrophysiology. We reviewed the reference lists from major cardiology and internal medicine textbooks, UpToDate version 2000 (volume 8, No. 2), recently published reviews on AF, and all included articles.

Other attempts to identify unpublished studies included contact with experts in the field, authors of included articles, and 1 drug company.

SELECTION

Two of 3 authors (L.M.L., K.U., and J.E.) independently reviewed each title or abstract to identify relevant articles. Citations that 1 reviewer considered relevant were further assessed independently by 2 of us (L.M.L. and K.U.) for inclusion, using the full publication or the abstracts if they were never published in full. We contacted 18 authors of articles with ambiguity of their study design and asked them to clarify issues to decide their inclusion. Of these, 7 replied. For the other 11 studies, we based our decision on available information. We measured agreement and resolved disagreement by consensus.

The reviewers also identified duplicate or updated publications and contacted the authors to clarify uncertainty about originality of data. We included only the most complete data set in our review.

QUALITY ASSESSMENT

Two authors (L.M.L. and K.U.) independently assessed concealment of treatment allocation; masking of patients, caregivers, or outcome assessors; and completeness of follow-up for each trial. Reviewers classified concealment of treatment allocation as adequate if those enrolling patients called a central randomization facility or opened sealed opaque envelopes or if the central pharmacy prepared and distributed numbered drug kits. Reviewers classified any other methods, such as nonsealed envelopes or medical chart numbers (quasi-randomization) as inadequate. When the article failed to make concealment methods explicit and the author failed to provide adequate clarification, we assumed concealment was inadequate. We measured agreement and resolved disagreement by consensus when no more information could be obtained from authors.

DATA EXTRACTION

Two of 3 authors (L.M.L., K.U., and J.E.) independently extracted, in duplicate, data regarding patient characteristics, the amiodarone and comparison drug therapy regimens, rate of conversion to sinus rhythm, mortality, and AEs from each article. For articles reporting outcomes at more than 1 time point, the primary analysis focused on the measurement closest to but no later than 4 weeks from randomization. For a study that compared amiodarone with digoxin or diltiazem hydrochloride, our analysis pooled data from the 2 control arms; for a study that compared placebo with 2 different doses of amiodarone, we pooled data from the amiodarone arms.

We considered AEs described in the studies irrespective of their putative relation to the drugs and extracted the number of events rather than the number of patients. We included AEs that we considered to be serious, defined as follows: (1) severe ventricular arrhythmia, including ventricular fibrillation, torsades de pointes, and sustained ventricular tachycardia; (2) any other ventricular arrhythmia, including nonsustained ventricular tachycardia and isolated premature ventricular beats; (3) any supraventricular arrhythmia; (4) bradyarrhythmias if they were symptomatic or required treatment, termination, or reduction of the study drug therapy, or a ventricular rate of less than 40 beats/min; (5) hypotension if it was symptomatic or required treatment or systolic blood pressure of less than 90 mm Hg; (6) other major cardiovascular events, including stroke, transient ischemic attack, myocardial infarction, or heart failure; and (7) other AEs that required withdrawal or reduction of the drug dosage.

We contacted the authors of all included studies for additional essential information missing from the report or to clarify inconsistent or ambiguous data relevant to our analysis.

STATISTICAL ANALYSIS

We used weighted $\kappa$ statistics to measure chance-corrected agreement between independent reviewers in selection, inclusion, and quality assessment.

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We calculated the relative risk (RR) for conversion to sinus rhythm and its 95% confidence interval (CI) for each study using as the denominator the number of patients for whom the outcome of interest was known, whether still receiving the study drug or not (intention-to-treat principle). We combined the RR from each study by means of a meta-analytic technique using a random-effects model as described by DerSimonian and Laird.14

We used the $\chi^2$ test to assess heterogeneity among results of the studies with a $P$ value of less than .05 as the level of statistical significance. We explored possible explanations for heterogeneity according to a priori hypotheses, which included differences in prognostic baseline patient characteristics, type of control treatment, time of outcome measurement, and methodological quality. Specifically, we compared the results of studies grouped by the following factors: (1) mean duration of the current AF episode (≤48 vs >48 hours); (2) mean left atrial size (<45 mm vs ≥45 mm); (3) proportion of patients with underlying cardiovascular disease, including hypertension, ischemic or valvular heart disease, cardiomyopathy, heart failure, and heart surgery (<50% vs ≥50%); (4) type of control treatment (placebo or no treatment vs digoxin vs CCB); (5) amiodarone regimen (single vs continuous oral or intravenous dosage); and (6) time to outcome measurement (<12 vs ≥12 hours from initiation of treatment). Recognizing that any cut point is to some extent arbitrary, we chose cut points before analyzing the data using 2 criteria. First, thresholds had to be biologically sensible; and second, they had to divide the trials into 2 subgroups with a more or less similar number of trials.

For methodological issues, we considered concealment of treatment allocation (adequate vs inadequate) and masking of caregivers and outcome assessors (masked vs not masked). We considered caregivers and outcome assessors together because all included trials had the same masking status for these participants. Furthermore, we looked for difference in results between studies reported as abstracts in cardiology meetings and full reports published in medical journals.

The logarithm transformation of the RR and the $z$ test provided the statistical approach for comparing the magnitude of treatment effect between the 2 groups. Any hypothesis for which the difference between subgroups reached a predefined $P$ value of less than .05 for statistical significance was considered a source of heterogeneity and therefore led to a separate meta-analysis.

**RESULTS**

We identified 382 citations, including an unpublished study undertaken by a drug company. We contacted the company but were unable to obtain the data at the time of this writing. Figure 1 illustrates the flow of the selection process, $\kappa$ agreement among reviewers, and reasons for exclusion. Table 1 describes the characteristics of the 21 included studies.3,11,12,16-13 Of the 21 authors we contacted, 13 (62%) responded to our request for additional information on their trials.* Seven studies12,22,24-26,29,33 were reported as abstracts presented in cardiology meetings, of which two22,26 have been published while we prepared this article. We received a reply from 5 of these 7 authors. The other 14 studies were full articles published in medical journals. The control treatment consisted of placebo in 10 studies, no treatment in 1, digoxin in 5, CCB (diltiazem or verapamil hydrochloride) in 4, and digoxin and diltiazem in 1.

**METHODOLOGICAL QUALITY**

Weighted $\kappa$ between the 2 reviewers ranged from 0.41 to 0.81 for the 5 methodological aspects considered. Table 1 summarizes the quality of the studies. Follow-up was 100% in 17 studies and ranged from 81% to 96% in 4.

**PATIENT CHARACTERISTICS**

Investigators randomized a total of 2000 patients. The outcome status was available in 1930 patients included in this analysis; 1002 were randomized to amiodarone and 928 to control treatment. The mean age of patients ranged from 58 to 71 years, and men constituted 43% to 86% of the study population. Most studies included patients with and without underlying cardiovascular diseases, except 1 that included only patients with AF associated with cardiac surgery16, and 2 that included only patients with AF complicating acute myocardial infarction.16,24 Two other studies20,23 included patients with AF after cardiac surgery. Two studies21,28 included patients with severe heart failure; twelve3,11,16-20,23,30-32 excluded patients with New York Heart Association class III or IV or a left ventricular ejection fraction of less than 30%; and seven12,22,24-26,29,33 were not explicit. The mean left atrial size ranged from 31 to 50 mm. One study11 limited patients to those with a left atrial size of less than 55 mm, whereas the other 20 did not specify left atrial size in their eligibility criteria. Mean AF duration was 48 hours or less in 16 studies. Most studies excluded patients with clinical thyroid disorder, conduction abnormalities, bradycardia, or hemodynamic instability.

**INTERVENTION**

Table 1 illustrates that the protocols of amiodarone administration varied considerably. Sixteen studies used intravenous infusion for 24 hours or less and then stopped therapy or continued administration of oral amiodarone. Four studies3,11,29,33 used only an oral regimen, and 1 study included intravenous and oral arms.12 Four studies used a single-dose intravenous17,20,26 or oral29 regimen.

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*References 11, 12, 17, 19, 20, 22-24, 28, 29, 31-33.
<table>
<thead>
<tr>
<th>Reference (Country) Year</th>
<th>No. of Patients A/C</th>
<th>Mean Age, y/% Male</th>
<th>% With CVD/Mean LA, mm</th>
<th>Mean AF Duration</th>
<th>Amiodarone Therapy Protocol</th>
<th>Comparison Treatment</th>
<th>Time to Outcome Measure</th>
<th>Concealed/% Follow-up</th>
<th>Masked Patients/Caregiver/Assessor</th>
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<tr>
<td>Cowan et al,16 (England) 1986</td>
<td>18/16</td>
<td>68/NA</td>
<td>≥76/NA</td>
<td>NA</td>
<td>IV, 7 mg/kg in 30 min + 1000 mg in 23 h</td>
<td>IV digoxin, 0.5 mg in 30 min twice, 30 min apart</td>
<td>24 h</td>
<td>Yes/100</td>
<td>No/no/no</td>
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<td>Noc et al,17 (Slovenia) 1990</td>
<td>13/11</td>
<td>71/83</td>
<td>NA/NA</td>
<td>20 min to 48 h</td>
<td>IV, 5 mg/kg in 3 min</td>
<td>IV verapamil hydrochloride, 0.075 mg/kg in 1 min, repeated after 10 min</td>
<td>3 h</td>
<td>No/100</td>
<td>Yes/no/no</td>
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<td>Capucci et al,18 (Italy) 1992</td>
<td>19/21</td>
<td>58/56</td>
<td>31/46</td>
<td>28 h</td>
<td>IV, 5 mg/kg in 5 min + 1.8 g in 24 h</td>
<td>IV digoxin, 0.5 mg in 30 min + 0.25 mg at 2 h + 0.125 mg at 5 h + 0.125 mg at 9 h</td>
<td>24 h</td>
<td>No/100</td>
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<td>Cochrane et al,19 (Australia) 1994</td>
<td>15/15</td>
<td>63/70</td>
<td>100†/NA</td>
<td>1 h</td>
<td>IV, 5 mg/kg in 30 min + 25-40 mg/h in 24 h</td>
<td>Placebo</td>
<td>3 and 8 h</td>
<td>NA/100</td>
<td>Yes/no/no</td>
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<td>Donovan et al,20 (Australia) 1995</td>
<td>32/32</td>
<td>58/NA</td>
<td>65†/NA</td>
<td>10 h</td>
<td>IV, 7 mg/kg in 30 min</td>
<td>Placebo</td>
<td>2 and 8 h</td>
<td>Yes/100</td>
<td>Yes/yes/yes</td>
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<td>Hou et al,21 (Taiwan) 1995</td>
<td>20/19</td>
<td>70/86</td>
<td>62/48</td>
<td>9 h‡</td>
<td>IV, 5 mg/min for 1 h + 3 mg/min for 3 h + 1 mg/min for 6 h + 0.5 mg/min for 14 h</td>
<td>IV digoxin, 0.004 mg/kg in 30 min every 2 h for 3 dosages</td>
<td>24 h</td>
<td>NA/100</td>
<td>No/no/no</td>
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<td>Kondili et al,22 (Albania) 1995</td>
<td>21/21</td>
<td>NA/NA</td>
<td>72/31</td>
<td>30 h</td>
<td>IV, 300 mg + 900 mg in 24 h</td>
<td>IV verapamil, 2 bolus of 5 mg each in 30 min</td>
<td>3, 6, and 12 h</td>
<td>No/100</td>
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<td>Galve et al,23 (Spain) 1996</td>
<td>50/50</td>
<td>61/55</td>
<td>52†/42</td>
<td>21 h</td>
<td>IV, 5 mg/kg in 30 min + 1.2 g in 24 h</td>
<td>Placebo</td>
<td>2, 6, and 12 h</td>
<td>Yes/100</td>
<td>NA/yes/no</td>
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<td>Kontoyannis et al,24 (Greece) 2001</td>
<td>16/26</td>
<td>NA/NA</td>
<td>100/43</td>
<td>30 min</td>
<td>IV, 300 mg in 2 h + 44 mg/h in 22 h</td>
<td>IV digoxin, 0.5 mg bolus + 0.25 mg 1 h later + PRN</td>
<td>2, 8, and 96 h</td>
<td>Yes/100</td>
<td>NA/yes/no</td>
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<td>Bellandi et al,25 (Italy) 1999</td>
<td>60/60</td>
<td>NA/NA</td>
<td>NA/NA</td>
<td>≤48 h</td>
<td>IV, 120 mg/h for 24 h</td>
<td>Placebo</td>
<td>24 h</td>
<td>NA/100</td>
<td>NA/NA/NA</td>
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<tr>
<td>Cotter et al,26 (Israel) 1999</td>
<td>50/50</td>
<td>66/43</td>
<td>≥67&lt;45§</td>
<td>10 h</td>
<td>IV, 125 mg/h for 24 h</td>
<td>Placebo</td>
<td>24 h</td>
<td>NA/100</td>
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<td>Kochiadakis et al,27 (Greece) 1999</td>
<td>135/69</td>
<td>65/47</td>
<td>60/42</td>
<td>13 h</td>
<td>IV, 300 mg in 1 h + 20 mg/kg in 1 d + 15 mg/kg in 1 d or oral 500 mg 4 times for 1 d + 200 mg 4 times for 1 d</td>
<td>Placebo</td>
<td>48 h</td>
<td>Yes/100</td>
<td>Yes/no/no</td>
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<td>Peuhkurinen et al,28 (Finland) 2000</td>
<td>31/31</td>
<td>59/73</td>
<td>74/39</td>
<td>3 to 48 h</td>
<td>Oral, 30 mg/kg single dose</td>
<td>Placebo</td>
<td>24 h</td>
<td>Yes/86</td>
<td>Yes/yes/yes</td>
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<td>Vardas et al,29 (Greece) 2000</td>
<td>108/100</td>
<td>65/49</td>
<td>43/43</td>
<td>26 h</td>
<td>IV, 300 mg in 1 h + 20 mg/kg in 24 h + oral 600 mg/d for 1 wk + 400 mg/d for 3 wk</td>
<td>Placebo</td>
<td>1 and 24 h, 28 d</td>
<td>Yes/100</td>
<td>Yes/no/no</td>
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<td>Joseph and Ward,30 (Australia) 2000</td>
<td>39/36</td>
<td>63/56</td>
<td>46/39</td>
<td>&lt;24 h</td>
<td>IV, 5 mg/kg in 30 min + oral, 400 mg 3 times per day for 2 d</td>
<td>IV digoxin, 0.5 mg in 30 min + oral 0.25 mg every 6 h for 24 h + 0.25 mg/d</td>
<td>4, 24, and 48 h</td>
<td>No/96</td>
<td>No/no/no</td>
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<td>Cybulski et al,31 (Poland) 2001</td>
<td>106/54</td>
<td>NA/NA</td>
<td>92/41</td>
<td>18 h</td>
<td>IV, 5 mg/kg in 30 min + 10 mg/kg in 20 h</td>
<td>Control group</td>
<td>20 h</td>
<td>Yes/100</td>
<td>Yes/no/no</td>
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<td>Natale et al,32 (United States) 1998</td>
<td>42/43</td>
<td>NA/NA</td>
<td>NA/NA</td>
<td>≥48 h</td>
<td>IV, 600 mg in 20 min + 66 mg/h</td>
<td>IV diltiazem hydrochloride</td>
<td>12 h</td>
<td>NA/100</td>
<td>NA/NA/NA</td>
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<td>Bianconi et al,33 (Italy) 2000</td>
<td>41/42</td>
<td>64/56</td>
<td>73/44</td>
<td>≥7 d§</td>
<td>IV 5 mg/kg in 15 min</td>
<td>Placebo</td>
<td>3 h</td>
<td>Yes/94</td>
<td>Yes/no/no</td>
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<td>Galperin et al,34 (Argentina) 2000</td>
<td>47/48</td>
<td>63/73</td>
<td>94/48</td>
<td>35 mo</td>
<td>Oral, 600 mg/d for 4 wk</td>
<td>Placebo</td>
<td>28 d</td>
<td>Yes/100</td>
<td>Yes/yes/yes</td>
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<td>Hohlsower et al,35 (Germany) 2000</td>
<td>95/108</td>
<td>61/73</td>
<td>85/46</td>
<td>16 wk</td>
<td>Oral, 600 mg/d for 3 wk</td>
<td>Oral diltiazem hydrochloride 180-270 mg/d for 3 wk</td>
<td>3 wk</td>
<td>NA/81</td>
<td>No/no/no</td>
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<td>Villani et al,36 (Italy) 2000</td>
<td>44/30/46j</td>
<td>58/67</td>
<td>47/50</td>
<td>17 wk</td>
<td>Oral, 400 mg/d for 1 mo</td>
<td>Oral digoxin, 0.25 mg/d or oral diltiazem hydrochloride 180-360 mg/d for 1 mo</td>
<td>1 mo</td>
<td>No/100</td>
<td>Yes/no/no</td>
</tr>
</tbody>
</table>

Abbreviations: A/C, amiodarone/control arms; AF, atrial fibrillation; CVD, cardiovascular disease; IV, intravenous; LA, left atrial size; NA, not available; PRN, as needed.
*Assumed to be less than 48 hours for the analysis because patients had AF related to acute myocardial infarction.
†Includes patients with cardiac surgery.
‡Expressed as the mean duration of the 2 groups.
§Indicates median duration.
||Includes 2 comparison arms.
OUTCOMES

Conversion to Sinus Rhythm

Our primary outcome was the RR for conversion to sinus rhythm during a period of 4 weeks or less. Fourteen studies assessed conversion to sinus rhythm at 24 hours or less; 3, from 48 to 96 hours; and 4, from 3 to 4 weeks.

We found statistically significant variation among the study results (test of heterogeneity, \( P < .001 \)), leaving us reluctant to pool the results across all studies. We therefore explored the possible sources of heterogeneity according to our a priori hypotheses. Among them, the mean duration of AF \( (P < .001) \) and the use of a CCB as the control drug \( (P = .03 \) and \( P = .008 \) compared with placebo and digoxin, respectively) were statistically significant. The \( P \) value associated with mean duration of AF, a biologically sensible explanatory variable, was far smaller than that associated with CCB. Furthermore, the analysis showed that studies using a CCB as the comparison drug were also the ones that enrolled patients with a longer AF duration. We therefore concluded that the duration of AF was the main source of heterogeneity and proceeded to perform 2 separate meta-analyses, one for studies with a mean AF duration of greater than 48 hours (long duration), and the other for those studies with a mean AF duration of 48 hours or less (short duration). For a study that enrolled patients with AF complicating acute myocardial infarction and did not report the mean duration of AF, \( \text{AF duration} \leq 48 \text{ h} \) we assumed the duration to be less than 48 hours.

**Figure 2** depicts the RRs and 95% CIs for conversion to sinus rhythm with amiodarone compared with control treatments for each of the 21 studies and 2 pooled RRs, 1 for each of the 2 subgroups according to the mean AF duration.

Among the 5 studies including patients with a mean AF duration of greater than 48 hours, \( \text{AF duration} > 48 \text{ h} \), the test of heterogeneity was no longer statistically significant \( (P = .49) \). The pooled RR for conversion to sinus rhythm was 4.33 (95% CI, 2.76-6.77). The funnel plot is not informative owing to the small number of trials.

Among the 16 studies enrolling patients with a mean AF duration of 48 hours or less, the variation among the results was still significant (test of heterogeneity, \( P = .009 \)). None of our a priori hypotheses explained this residual variation (**Table 2**). The type of comparison drug was no longer significant in this subgroup analysis, thus supporting our hypothesis that the significance of CCB was related to the duration of AF. The pooled analysis demonstrated an RR for conversion to sinus rhythm of 1.40 (95% CI, 1.25-1.57). The lower boundary of the CI at 1.25 reflects that amiodarone would be at least 25% more effective than placebo or control drugs to convert AF to sinus rhythm. The funnel plot did not show evidence of publication bias (**Figure 3**).

Differences in control event rates explain the large difference in RRs in the studies with a mean AF duration of 48 hours or less compared with those with a mean duration of greater than 48 hours. The proportion of control patients who converted to sinus rhythm varied from 35% to 84% in all but one \( ^{17} \) of the former set of studies and from 0% to 16% in the latter.

In an analysis using RD as the measure of effect, the difference between the 2 groups was no longer evident. The RDs were 0.27 (95% CI, 0.08-0.47) for the group with a long AF duration and 0.26 (95% CI, 0.18-0.34) for the short-duration group (difference between RDs, \( P = .93 \)). The numbers needed to treat were 4 (95% CI, 3-14) and 4 (95% CI, 3-6) for the 2 groups, respectively.

**Mortality**

Eighteen studies \( ^{12,10-28,30-33} \) reported specific data on mortality during an observation period ranging from 3 hours to 30 days. In 12 studies, the observation period ranged from 1 to
3 days. Five of 816 patients died in the amiodarone groups compared with 5 of 696 in the comparison groups. The small numbers of deaths precluded further analysis. Three studies\textsuperscript{16,21,24} accounted for all of the reported deaths, and 1 of these\textsuperscript{16} for 4 deaths in each group, none of which appeared to be related to the study drugs.

### Adverse Events

Seventeen studies\textsuperscript{12,16-25,27,28,30-33} reported data on AEs during the same observation period as for mortality. The other 4 studies reported data on AEs beyond our 4-week period or in such a way that we could not match them with our definition set of AEs. Table 3 shows the range of percentages, among studies, of patients with major AEs, as previously defined, for each treatment group. Since most studies did not define AEs, Table 3 also presents the number of trials without AEs. The most common adverse effect was hypotension. The paucity of events precluded further analysis. However, we found no evidence of increased occurrence of any of the AEs in the amiodarone group when compared with any of the control groups.

### COMMENT

Our results show that amiodarone is effective for conversion of AF to sinus rhythm in a wide range of patients. The RRs were 4.33 for patients with an AF of greater than 48 hours’ duration and 1.40 for those with AF of 48 hours or less. The large and statistically significant difference ($P<.001$) between these 2 estimates of RR for conversion suggests a differing magnitude of effect related to the duration of AF.

However, when analyzed in absolute terms, we found no difference in the magnitude of effect in these 2 subgroups (RD, 27.1% vs 26.1%, respectively). This disparity in the RR and absolute risk reductions results from the differing spontaneous conversion rate among patients with a differing duration of AF. The rate of spontaneous conversion in the control group (0%-16%) in the 5 studies that enrolled patients with a longer AF duration was far lower than the event rate (35%-84%) in the control group of 15 studies that enrolled patients with short AF duration. The difference between RR and absolute risk reductions is a function of the statistical properties of both measures. The higher the control event rate (baseline risk) of the
When patients and interventions vary across studies (ie, meta-analysis), the effect size may be more or less the same. In this review, patients differ widely in their clinical context and duration of AF and in the dosage and route of drug administration. Nevertheless, we began with a hypothesis that, across these different types of patients and ways of administering amiodarone, the effect size may be more or less the same. When patients and interventions vary widely, thorough exploration of heterogeneity becomes mandatory. Those uncomfortable with pooling will justifiably argue that the effect of treatment may differ across patient groups and ways of administering the intervention. Exploration of heterogeneity allows investigators to test this hypothesis. If effects are similar across varying groups of patients, the original assumption of a more or less constant underlying effect is markedly strengthened.

In the present study, we explored a wide variety of possible explanations of heterogeneity, including duration of AF, size of the left atrium, presence of cardiovascular disease, regimen of amiodarone, type of control treatment, and time to outcome measurement. We found considerable consistency of treatment effects, and the only variable that explained the heterogeneity that did exist was duration of AF (only in an analysis examining relative, rather than absolute, likelihood of conversion to sinus rhythm).

Pooling is justified when the underlying biology is such that, across the range of patients, interventions, and outcomes, one anticipates that the effect size will be more or less the same. In this review, patients differed widely in their clinical context and duration of AF and in the dosage and route of drug administration. Nevertheless, we began with a hypothesis that, across these different types of patients and ways of administering amiodarone, the effect size may be more or less the same. When patients and interventions vary widely, thorough exploration of heterogeneity becomes mandatory. Those uncomfortable with pooling will justifiably argue that the effect of treatment may differ across patient groups and ways of administering the intervention. Exploration of heterogeneity allows investigators to test this hypothesis. If effects are similar across varying groups of patients, the original assumption of a more or less constant underlying effect is markedly strengthened.

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For clinicians who remain uncomfortable with pooling, given the variability in patients and ways of administering amiodarone, our results remain informative. The results of individual studies are consistent with large positive effects of amiodarone in converting AF to sinus rhythm in a wide variety of patient groups, and with a variety of methods of administration (Table 1 and Figure 2).

We considered digoxin and CCB control treatments similar to placebo in this review because the evidence has suggested that they are not effective in converting AF to sinus rhythm when compared with placebo. They are, as a result, recommended primarily for controlling ventricular rate. Support for this decision comes from our analysis demonstrating that, after considering the duration of AF, the RR for conversion to sinus rhythm with amiodarone was similar among studies using these different control interventions.

We included studies that used quasi-randomization because we believe that any bias introduced by this type of treatment allocation is due to inadequate concealment of treatment allocation. Hence, their quality would be similar to those of randomized trials in which concealment was inadequate. A subgroup analysis showed no difference in magnitude of treatment effect between studies with adequate and inadequate concealment of treatment allocation (RR, 1.57 and 1.31, respectively; P = .15 [Table 2]). The trend in the data suggesting a smaller magnitude of treatment effect in studies with inadequate concealment of treatment allocation contrasts with the general findings that studies with weaker designs produce larger treatment effects than do those with more rigorous methodology. Thus, our inclusion of quasi-randomized studies, if it creates a bias at all, would bias the results against the effectiveness of amiodarone. Again, in contrast to the general situation, we also observed a trend toward a smaller magnitude of effect for studies that failed to mask caregivers and outcome assessors.

Including in a systematic review studies that have not been published in full in peer-reviewed...
journals remains controversial. In the present study, we included a number of abstracts. The primary argument against including these studies is that they may be methodologically inferior to published material, and thus are more likely to provide biased results. On the other hand, their inclusion minimizes the likelihood of publication bias and provides more power to the analysis. Including abstracts becomes increasingly defensible if the investigators contact the authors to obtain missing methodological details and test whether abstracts yield a different effect size than published studies. We used both safeguards in our study. Five of the 7 authors of abstracts contacted responded to our requests, which allowed us to assess these abstracts using the same standards as for peer-reviewed publications. Furthermore, as shown in Table 2, the point estimates of the RR for conversion for abstracts and full articles (1.48 vs 1.35; P=.37) were similar, and differences are attributable to chance. Finally, when considering the advantages and disadvantages of including unpublished studies such as abstracts, most clinical trials and methodologists believe the advantages outweigh the disadvantages.

We are limited in making any definitive conclusion regarding AEs related to amiodarone because they were not consistently reported in every trial, and because the small number of events precludes conducting a meta-analysis. However, none of the AEs considered proved more frequent in the amiodarone group than the control group. Although it appears likely that amiodarone is safe when used in the short-term setting for the conversion of AF to sinus rhythm, one would require studies with more detailed exploration of AEs to provide a definitive conclusion.

Our review has some limitations. Our a priori hypotheses could not explain the remaining heterogeneity among the 16 studies with a short mean duration of AF. One possible explanation is the arbitrariness of our cut points that may not be the best for finding differences between groups. On the other hand, experimenting with a wide variety of thresholds runs the substantial risk for capitalizing on the play of chance and identifying apparent subgroup differences that do not really exist. Other possible explanations for the unexplained heterogeneity include differences in the amiodarone regimen that were not captured in the subgroup analysis or differences in the definitions used for conversion in different studies that we were not able to explore. A limitation of using the random-effects model is that this estimate gives proportionately greater weight to smaller studies than do fixed-effects summaries. We were unable to obtain data from 1 unpublished study that we were aware of, raising the possibility of publication bias despite the result of our funnel plot (Figure 3) that provided no definitive suggestion of publication bias. Finally, for the study selection process, the reviewers were not masked to the journal, authors, institutions, or results. However, we tried to minimize bias through the use of explicit inclusion criteria and 2 independent reviewers. Masking the reviewers is a time-consuming process that may not affect the results of a systematic review.

Our review has a number of strengths, including a comprehensive literature search, explicit eligibility criteria, independent adjudication of eligibility by 2 reviewers with high agreement, and systematic and independent assessment of methodological quality.

Despite our finding of a large and widely generalizable treatment effect, experts do not typically recommend amiodarone as a first-choice drug for conversion of AF to sinus rhythm. A recent guideline on indications for amiodarone does not mention it for this purpose, and the US Food and Drug Administration has not approved the drug for this indication. Nevertheless, clinicians frequently use the drug to convert AF. Amiodarone is considered a slow-acting drug, which may explain its not being considered a first-line option for conversion of AF to sinus rhythm. However, most studies included in our meta-analysis show that amiodarone achieves conversion within 24 hours of administration (Table 1). This is a relatively short time to wait for patients without hemodynamic instability. Furthermore, and although maintenance of sinus rhythm after conversion of AF is beyond the scope of this systematic review, other studies have shown that amiodarone is superior to other antiarrhythmic agents for maintenance of sinus rhythm in patients with prior AF.

Some clinicians may find using the same drug for conversion and later maintenance of sinus rhythm for patients with AF appealing.

CONCLUSIONS

Amiodarone is effective and relatively rapid acting in converting AF to sinus rhythm in a wide range of patients. These features recommend its use as a first-line drug for stable patients without clinical thyroid disease or conduction abnormalities, particularly those who will require long-term antiarrhythmic treatment for preventing recurrence of AF.

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