Efficacy and Safety of Quinidine Therapy for Maintenance of Sinus Rhythm After Cardioversion
A Meta-Analysis of Randomized Control Trials

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Because individual studies evaluating the role of quinidine in the maintenance of sinus rhythm after cardioversion from chronic atrial fibrillation have involved relatively few patients, a meta-analysis of randomized control trials was performed. Six trials published between 1970 and 1984 were selected by two blinded reviewers based on study design and statistical analysis. Data from these six trials involving 808 patients were pooled after testing for homogeneity of treatment effects across trials. Life table estimates of the percent of patients still in sinus rhythm at 3, 6, and 12 months after cardioversion were constructed for quinidine and control groups. The proportion of patients remaining in sinus rhythm in the quinidine group was 69%, 58%, and 50% at 3, 6, and 12 months postcardioversion respectively. The proportion of patients remaining in sinus rhythm in the control group was 45%, 33%, and 25% at the same time intervals. The pooled rate difference, or difference in proportion of patients in sinus rhythm between quinidine and control groups, was 24%, 23%, and 24% at 3, 6, and 12 months of follow-up (p<0.001 at all time intervals). The unadjusted total mortality rate in the quinidine-treated patients was 2.9% and in the control group was 0.8%. The odds of dying in the quinidine-treated group were approximately three times that of the control group ("typical" odds ratio=2.98, p<0.05). Thus, quinidine treatment is more effective than no antiarrhythmic therapy in suppressing recurrences of atrial fibrillation but appears to be associated with increased total mortality. (Circulation 1990;82:1106–1116)

Atrial fibrillation (AF), a common cardiac rhythm disorder that may affect 0.4% of the adult population, is often associated with embolic events and dyspnea, chest discomfort, fatigue, or syncope.1 To prevent the development of these symptoms as well as to reduce the likelihood of embolic events, it is common clinical practice in many patients to try to restore and maintain sinus rhythm. When direct-current cardioversion is used, sinus rhythm can be restored at least temporarily in 80–90% of patients with AF.2 Quinidine, a class IA antiarrhythmic agent, is the drug most frequently prescribed to suppress recurrences of AF. However, nonrandomized and open-label trials evaluating the efficacy of quinidine in preventing recurrences of AF have reported widely ranging estimates of the percent of patients still in sinus rhythm 1 year after cardioversion varying from 8% to 54%.3–5 In some studies administration of quinidine was stopped because of an unacceptably high incidence of toxicity that included ventricular fibrillation, syncope, and death.5,6 Nevertheless, a precise estimate of mortality secondary to quinidine is lacking in the literature. This is particularly relevant in light of recent observations regarding the proarrhythmic potential of antiarrhythmic agents and the recently published report of the Cardiac Arrhythmia Suppression Trial,7 which demonstrated increased mortality in patients randomized to encainide and flecainide treatment for suppression of ventricular arrhythmias after myocardial infarction.
Several randomized trials have been published assessing the efficacy of quinine in maintaining sinus rhythm after cardioversion. Because these randomized trials individually enrolled small numbers of patients, the present meta-analysis was undertaken to pool the results from several trials using contemporary biostatistical methods to obtain a more precise estimate of quinine’s effectiveness. In addition, this meta-analysis was performed to provide a more accurate estimate of quinine-related mortality when the drug is used for the treatment of AF.

Methods

Acquisition of Data

To identify all randomized control trials (RCTs) of quinine in maintaining sinus rhythm after cardioversion, the English and non-English language literature was searched from 1966 to July 1989, using the MEDLINE data bases of the National Library of Medicine. The MEDLINE strategy used the terms “quinidine,” the chemical registry number for quinine, and then was intersected with the terms “atrial fibrillation” or “atrial flutter.” The result then was intersected with a broad strategy for retrieval of clinical trials. Initial selection of studies was made by two investigators (T.C.C. and P.H.) from the MEDLINE record and the entire article before the studies were blinded. Additional sources included references from papers identified in the above searches.

As reported in previous meta-analyses, studies that were considered potentially acceptable had the sources and results sections masked so that the decision to include or reject the paper could be made in a blinded fashion. Two investigators (S.E.C. and E.M.A.) then independently evaluated the methods and results of all trials using a previously published standardized analysis form. Specific features of RCTs screened included trial entry criteria, demographics, methods, statistical analysis, major end points of the trial, and handling of withdrawals and side effects. Trials were included in this meta-analysis if both investigators agreed that the RCT met the following inclusion criteria: 1) patients with chronic AF (dysrhythmia lasting longer than 72 hours) undergoing cardioversion were randomized to quinine or control treatment groups; 2) the trial followed patients longitudinally to assess the efficacy of quinine in maintaining sinus rhythm, and these data were available in a form that permitted calculation of the percentage of patients remaining in sinus rhythm at one or more predetermined times after cardioversion (3, 6, or 12 months); 3) the minimum follow-up time was 3 months postcardioversion; and 4) digoxin was the only other antiarrhythmic agent administered simultaneously. Exclusion criteria included absence of randomization and unclear descriptions of the treatment regimens for the quinine and control groups. Studies evaluating the effect of quinine in the early postoperative period also were excluded. A reject log was maintained of studies that did not meet the above criteria.

Statistics

Kaplan-Meier life-table techniques were used to estimate the probability of maintaining sinus rhythm for the quinine and control group at 3, 6, or 12 months postcardioversion. Patients followed longitudinally in each study are referred to herein as the long-term treatment group, and the data were analyzed by the intention-to-treat method. Patients who withdrew from the study or died were treated as recurrences of AF unless their rhythm was known to be sinus rhythm at the time of their death, in which case their data were treated as censored events in the Kaplan-Meier analysis.

Pooled estimates of the percentage of patients remaining in sinus rhythm across trials at 3, 6, and 12 months postcardioversion were calculated in the following manner, which provided a correction factor for interstudy variability:

\[ P_t = \frac{\Sigma (S_t \cdot W_t)}{\Sigma W_t} \]

where \( P_t \) is the pooled estimate of the percent of patients remaining in sinus rhythm at time \( t \), \( S_t \) is the percentage of patients remaining in sinus rhythm at time \( t \) for each study, and \( W_t \) is \( 1/(\text{variance of } S_t) \). Details of this calculation are shown in the “Appendix.”

The rate difference (RD) is the difference between the percent of patients in sinus rhythm in the quinine and control groups. For each study, RD was calculated from the Kaplan-Meier estimates of the percent of patients remaining in sinus rhythm and the variance of the above estimates. Because some inter- and intrastudy variability exists, the methods described by Cochran and DerSimonian and Laird were used to calculate a weighted average RD. Each study’s contribution to the weighted average RD is dependent on the variance of RD for the individual study. The mean RD is calculated as follows:

\[ \text{Mean RD} = \frac{\Sigma (RD_t \cdot W_{RD})}{\Sigma W_{RD}} \]

where RD, is the rate difference for a study at time \( t \), and \( W_{RD} \) is \( 1/(\text{variance of } RD) \). If the studies are relatively homogeneous, then the treatment effect in each study should be similar, the variance of RD among studies should be close to zero, and no further adjustment for between-study variability need occur. If heterogeneity exists, an estimate of the degree of variability is determined (\( \tau \) factor), and the weighted average RD is recalculated accordingly. This method is described fully in the “Appendix.” The statistical significance of the pooled RD is determined by calculation of a z value, where
and is compared with values from a table of the standard normal distribution. For example, a z value greater than 1.96 suggests a two-sided p value less than 0.05.

Data regarding deaths and side effects were collected. Crude pooled mortality rates were calculated. Because the authors of the RCTs did not provide sufficient data, these calculations could not be adjusted for age, sex, underlying disease, duration of follow-up, or study variability. The method of calculating odds ratios (OR) described by Yusuf et al\textsuperscript{14} was used to compare mortality in the quinidine and control groups. This method was used because the data involve a single point observation (mortality) rather than a series of rate measurements (e.g., percent of patients in sinus rhythm at 3, 6, and 12 months postcardioversion) and are more readily interpretable from a clinical standpoint. Comparison of deaths in a given treatment group was made exclusively with the control group in the same trial. No comparison was made between trials and no assumption was made that any differences in mortality rates were of the same magnitude across trials. For each trial, the number of deaths observed (O) in the quinidine-treated group was compared with the number of deaths that would have been expected (E) if deaths were equally distributed among the quinidine and control groups. The value O−E (observed minus expected deaths) was calculated and would be expected to differ only randomly from zero if quinidine treatment did not consistently affect mortality. Individual study estimates then were pooled with a total variance equal to the sum of the individual study variances. The statistical significance of this pooled value was determined by calculating z, where

\[
z = \frac{\text{Pooled O-E}}{\text{Pooled SD}}
\]

and comparing this value to a table of the standard normal distribution. This technique and measures of its significance also are discussed in the “Appendix.”

Using the combined data from all trials, an estimate of the “typical” OR, or likelihood of dying on quinidine as compared with control, was calculated using the exponential function exp(\(z/SD\)) with 95% confidence limits given by exp(\(z/SD\)±(1.96/SD)).\textsuperscript{14} An OR of 0.75 would be roughly equivalent to a 25% reduction in deaths on quinidine. Heterogeneity between treatment effects in different trials was assessed by subtracting the \(\chi^2\) statistic for the overall result from the sum of \(\chi^2\) statistics for each separate trial (see “Appendix”). In addition, for assessment of the internal consistency of the observations on mortality and because of the possibility of potential bias in the one-step (Peto) method for pooling study results,\textsuperscript{15} a “summary” OR was calculated using techniques described by Mantel and Haenszel\textsuperscript{16} for combining the information from a series of 2×2 tables.

Mortality data were collected on patients who were randomized and received study medication even if the patient did not achieve sinus rhythm after cardioversion or had no long-term follow-up. This group will be called the full-exposure group; analysis of mortality data in this group includes the number of patients who were randomized to and received quinidine in the precardioversion period and therefore were at risk for mortality during this interval. Mortality data in the long-term treatment group also were tabulated in this meta-analysis and similar calculations performed. The long-term treatment group is smaller than the full-exposure group, because it excludes patients who failed to achieve sinus rhythm after cardioversion and patients who experienced adverse effects shortly after starting quinidine.

For each of the various cardiac diagnoses noted in the trials, we tested whether the proportion of patients in the quinidine group with a given diagnosis was equal to 0.5 using a normal approximation to the binomial distribution.

Results

Characteristics of Trials Analyzed

The literature search and review of references identified 52 papers addressing quinidine’s effectiveness in maintaining sinus rhythm after cardioversion. Six of these studies met criteria for inclusion in the meta-analysis.\textsuperscript{17−22} The remaining 46 reports were not included in this meta-analysis for the following reasons: the study did not allocate patients randomly to treatment versus control groups (\(n=24\)); the study did not include a concurrent control group, or the study design compared quinidine versus another antiarrhythmic agent rather than control therapy (\(n=12\)); the study group consisted of patients with acute AF rather than chronic AF (\(n=2\)); or results were presented in anecdotal or case report format (\(n=8\)). The six selected trials were published between 1970 and 1984 and involved 808 randomized patients. Characteristics of the six RCTs are shown in Table 1. Patient ages were reported in four studies and ranged from 15 to 79 years (mean, 53). The duration of AF in patients enrolled in the six RCTs ranged from less than 1 month to up to 10 years; few patients had been in AF for longer than 3 years before cardioversion. In three papers, details of the duration of AF in the two treatment groups were provided, and there were no significant differences in the duration of AF between the quinidine and control groups in any of those trials.\textsuperscript{19,20,22}

The various cardiac diagnoses and possible etiologies of AF in each study are shown in Table 2. Valvular heart disease, primarily rheumatic, existed in 52% of the randomized population, with individual studies having from 31% to 69% of patients with this underlying process. Ischemia and “lone” AF were
TABLE 1. Characteristics of Studies Included in Analysis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year of publication</th>
<th>Study Dates of study</th>
<th>Patients* (n)</th>
<th>AF duration (mo)</th>
<th>Age (yr) Mean Range</th>
<th>Sex (M-F)</th>
<th>Quinidine preparation</th>
<th>Quinidine dose (g)</th>
<th>Time quinidine started</th>
<th>Cardioversion success rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17. Boissel et al</td>
<td>1981</td>
<td>1 NA 212</td>
<td>NA NA NA NA</td>
<td>1-120</td>
<td>54 30-70</td>
<td>49:43</td>
<td>Bisulfate</td>
<td>0.55 b.i.d.</td>
<td>After CV</td>
<td>...†</td>
</tr>
<tr>
<td>19. Hartel et al</td>
<td>1970</td>
<td>3 5/67-6/68 175</td>
<td>NA NA NA NA</td>
<td>1-120</td>
<td>54 22-77</td>
<td>46:54</td>
<td>Sulfate</td>
<td>0.2-0.6 b.i.d.</td>
<td>Before CV</td>
<td>85</td>
</tr>
<tr>
<td>20. Hillestad et al</td>
<td>1971</td>
<td>4 1968-71 100</td>
<td>NA NA NA NA</td>
<td>1-120</td>
<td>54 22-77</td>
<td>46:54</td>
<td>Sulfate</td>
<td>0.8-1.2 daily</td>
<td>Before CV</td>
<td>82</td>
</tr>
<tr>
<td>21. Lloyd et al</td>
<td>1984</td>
<td>5 NA 53</td>
<td>1-36</td>
<td>46 15-79</td>
<td>NA</td>
<td>Gluconate</td>
<td>Bisulfate</td>
<td>0.48 t.i.d.</td>
<td>After CV</td>
<td>...†</td>
</tr>
<tr>
<td>22. Sodermark et al</td>
<td>1975</td>
<td>6 1969-70 176</td>
<td>1-36</td>
<td>58 24-78</td>
<td>125:51</td>
<td>Gluconate</td>
<td>Bisulfate</td>
<td>0.6-0.8 b.i.d.</td>
<td>Before CV</td>
<td>85</td>
</tr>
</tbody>
</table>

NA, not available; b.i.d., twice daily; CV, cardioversion; t.i.d., three times daily.

*Number of patients who underwent randomization to quinidine and control in each study.

†Randomization to quinidine and control groups occurred postcardioversion.

representative cardiac diagnoses of 16% and 12% of patients, respectively. Slightly more patients with ischemic heart disease or thyroid dysfunction were randomized to quinidine as opposed to control, but these differences were not statistically significant. This suggests that randomization was successful in distributing patients with various underlying diagnoses approximately equally to quinidine and control groups. Only limited data on the relative degree of illness in the two treatment groups was provided in the six RCTs. Two papers estimated heart volume from the chest radiograph and found similar values for the quinidine and control groups. One paper reported New York Heart Association functional classification, and there were no significant differences between the quinidine and control groups.

Randomization to quinidine and control groups occurred before cardioversion in four trials and after cardioversion in two trials. Placebo tablets were used in the trials of Lloyd et al. and Boissel et al., and the other trials used no therapy for the group assigned to control treatment. The choice of quinidine preparation and exact dosage varied for each trial. Quinidine levels were determined by fluorometric methods in four trials to help assess patient compliance, assess adequacy of therapy, or adjust dosages. Desired quinidine levels varied from 1–3 mg/l in the paper by Hartel et al. to 4–6 mg/l in the paper by Hillestad et al. Only the paper by Byrne-Quinn and Wing reported the actual quinidine levels measured (mean of 2.2 mg/l, which was in the middle of the therapeutic range for the assay used) and did not find a statistically significant difference in quinidine levels in those patients relapsing to AF and those patients remaining in sinus rhythm.

Concurrent digoxin therapy was optional in all trials and generally was withheld for at least 2 days before cardioversion. None of the trials reported measurements of serum glycoside concentrations. Anticoagulation was optional in all but one trial. Sinus rhythm was achieved in 82–86% of cases by direct current cardioversion. In all six RCTs, recurrences of AF were documented by standard electrocardiographic (ECG) recordings; telephone ECG transmissions and ambulatory ECG recordings were not used.

Maintenance of Sinus Rhythm After Cardioversion

Of the randomized patients (n=808), eight were lost to follow-up, leaving 800 patients who constitute the full-exposure group. Seventy-three patients were excluded from longitudinal follow-up for various reasons, including inadequate compliance or failure to reach target quinidine dosages.

TABLE 2. Cardiac Diagnoses in Patients Enrolled in Randomized Control Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (n) Valvular (Quin/Cont) Hypertension (Quin/Cont)</th>
<th>Ischemic heart disease (Quin/Cont)</th>
<th>Thyroid dysfunction (Quin/Cont)</th>
<th>Congenital heart disease (Quin/Cont)</th>
<th>Lone fibrillator (Quin/Cont)</th>
<th>Other (Quin/Cont)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>212</td>
<td>71/70</td>
<td>4/3</td>
<td>1/2</td>
<td>4/3</td>
<td>1/4</td>
</tr>
<tr>
<td>2</td>
<td>92</td>
<td>27/24</td>
<td>...</td>
<td>6*,9*</td>
<td>2/1</td>
<td>1/0</td>
</tr>
<tr>
<td>3</td>
<td>175</td>
<td>37/30</td>
<td>2/2</td>
<td>20/22</td>
<td>6/6</td>
<td>4/4</td>
</tr>
<tr>
<td>4</td>
<td>100</td>
<td>35/34</td>
<td>...</td>
<td>5/5</td>
<td>2/2</td>
<td>1/2</td>
</tr>
<tr>
<td>5</td>
<td>53</td>
<td>18/18</td>
<td>1/3</td>
<td>4/2</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>6</td>
<td>176</td>
<td>24/30</td>
<td>9/6</td>
<td>36/21</td>
<td>8/2</td>
<td>...</td>
</tr>
<tr>
<td>Sum Quin/Cont</td>
<td>212/206</td>
<td>16/14</td>
<td>72/61</td>
<td>22/14</td>
<td>7/10</td>
<td>46/47</td>
</tr>
</tbody>
</table>

Pooled (%) 808 418 (52%) 30 (4%) 133 (16%) 36 (5%) 17 (2%) 93 (12%) 81 (10%)

The number of patients with a given cardiac diagnosis in the quinidine (Quin) and control (Cont) groups is shown.

*Includes some patients with hypertension.
TABLE 3. Percent of Patients Remaining in Sinus Rhythm at 3, 6, and 12 Months After Cardioversion

<table>
<thead>
<tr>
<th>Study characteristics</th>
<th>3 Months</th>
<th>6 Months</th>
<th>12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Quinidine* (no. of patients)</td>
<td>Control* (no. of patients)</td>
<td>Rate difference %*</td>
</tr>
<tr>
<td>1</td>
<td>103</td>
<td>104</td>
<td>74.8 (4.3)</td>
</tr>
<tr>
<td>2</td>
<td>28</td>
<td>37</td>
<td>67.8 (8.8)</td>
</tr>
<tr>
<td>3</td>
<td>75</td>
<td>73</td>
<td>69.3 (5.3)</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>42</td>
<td>60.7 (7.7)</td>
</tr>
<tr>
<td>5</td>
<td>26</td>
<td>23</td>
<td>50.0 (9.8)</td>
</tr>
<tr>
<td>6</td>
<td>101</td>
<td>75</td>
<td>71.3 (4.5)</td>
</tr>
<tr>
<td>Pooled</td>
<td>373</td>
<td>354</td>
<td>69.4 (2.4)</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td></td>
<td>16.7–30.6</td>
</tr>
<tr>
<td>Z</td>
<td></td>
<td></td>
<td>6.7</td>
</tr>
<tr>
<td>p</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CI, confidence interval.

*Values shown are percentages; the standard error is shown in parentheses.
†Pooled rate difference reflects a correction for inter- and intrastudy variiances. Thus, pooled values for the quinidine group minus pooled values for the control group may not be exactly equal to pooled rate difference. See text for further explanation.

reasons, and these remaining 727 patients (90% of the original group) comprise the long-term treatment group. Reasons for exclusion included failure to achieve sinus rhythm (58 patients), intractable side effects (six patients), death after randomization and no longitudinal data available (three patients), and improper randomization (one patient). In addition, the trial of Byrne-Quinn and Wing18 excluded five patients who achieved pharmacological conversion on quinidine.

The main measure of efficacy of quinidine therapy was objective determination of rhythm status at preset follow-up times. Although some studies had many time points for follow-up, only the data at 3, 6, and 12 months were used for the calculations. Kaplan-Meier estimates of the proportion of patients in sinus rhythm are shown in Table 3 for each trial along with the RD for individual trials at each interval (a measure of treatment effect). Although all six trials had 3-month follow-up data, only four had 6-month data, and three followed patients for 1 year. Three months postcardioversion, 69.4% of quinidine-treated patients and 45.1% of control patients remained in sinus rhythm. The calculated pooled RD (after correcting for individual study variiances) was 23.6%, indicating treatment benefit in favor of the quinidine-treated group. At 6 months postcardioversion, 57.7% and 33.3% of patients were in sinus rhythm in the quinidine and control groups, respectively. The pooled RD of 23.4% was virtually the same as at the 3-month time interval. Data at 12 months revealed 50.2% of quinidine-treated patients and 24.7% of control patients in sinus rhythm. The 1-year pooled RD was 24.4% in favor of quinidine. Figure 1 displays the pooled estimates of the proportion of patients in sinus rhythm and 95% confidence interval for quinidine and control groups at 3, 6, and 12 months. Despite a continual decrease in the percentage of patients remaining free of AF, quinidine maintained a significant treatment advantage over control (p<0.001 at all time intervals).

As noted in "Methods," patients who withdrew from the trial or died were treated as recurrences of AF unless their rhythm was known to be sinus at or near the time of withdrawal or death, so the RDs noted above represent the minimal treatment benefit of quinidine in maintaining sinus rhythm. Seventeen patients (2.3% of total study group) were potentially misclassified by this algorithm, because no information was available about their cardiac rhythm at the time of withdrawal or death. Reclassifying these 17 patients (14 quinidine and three control) as remaining in sinus rhythm (censored in Kaplan-Meier analysis) yields the maximum potential treatment benefit of quinidine with RDs of 26.4% at 3 months, 28.3% at 6 months, and 29.0% at 12 months.

In pooling the RD results from the six trials, a factor adjusting for study heterogeneity, was calcu-
lateral. At 3, 6, and 12 months after cardioversion, the calculation of \( \tau \) indicated that no adjustment to the pooled RD was required because of relative study homogeneity.

### Adverse Reactions to Treatment

Side effects related to quinidine were common and included diarrhea, syncope, and pyrexia. Sixty-six of the 373 (18%) patients receiving quinidine in the long-term treatment group reported adverse reactions, and 32 (9%) discontinued use of the medication.

Deaths were observed in both treatment and control groups. In the full-exposure group, 12 patients randomized to the quinidine group and three patients randomized to the control group died, yielding an unadjusted mortality rate of 2.9% for the quinidine group and 0.8% for the control group. Mortality data and calculations are shown in Table 4. The precise cause of death in the quinidine-treated patients was known in seven of 12 cases and included sudden cardiac death \((n=3)\), myocardial infarction \((n=1)\), cerebrovascular accident \((n=2)\), and suicide \((n=1)\). In the other five fatalities in the quinidine group, the precise mode of death was unclear, but important concurrent medical illnesses were present in some patients, including carcinoma \((n=2)\), pneumonia \((n=1)\), and hepatic failure \((n=1)\). Two other cardiac arrests were reported in patients receiving quinidine, but neither is included in the 12 deaths listed above for the following reasons: successful resuscitation in one case\(^1\) and sudden cardiac death in one case during open-label “test dosing” with quinidine before randomization.\(^2\) The cause of death in two of the control group patients was known to be myocardial infarction \((n=1)\) and cerebrovascular accident \((n=1)\), and it was unknown in one case.

The O–E value for each study was greater than zero, indicating a consistent trend toward increased mortality in the quinidine group. The OR of dying on quinidine as compared with control for each study varied from 1.81 to 8.03, with a typical (pooled) OR of 2.98 (95% confidence interval, 1.1–8.3; \(p<0.05\); \(\chi^2\) for heterogeneity=1.6, df=5, \(p=0.9\)). The summary OR calculated by the method of Mantel and Haenszel was 3.51 (95% confidence interval, 0.99–12.45; \(p=0.05\)). The above results suggest that the odds of dying on exposure to quinidine are approximately

![Figure 2. Odds ratios (Quinidine:Control) for total mortality in full-exposure groups of six randomized control trials (RCT) (see References 17–22) are depicted (small squares) along with pooled (“typical” odds ratio) result from all trials (large square). Horizontal lines depict 95% confidence interval. Pooled odds ratio and its 95% confidence interval fall to the right of the vertical line, indicating a significant increase in total mortality in quinidine-treated group as compared with control group (\(p<0.05\)).](image-url)
three times greater than on no antiarrhythmic therapy and that a relatively homogeneous observation was made among the six trials (Figure 2). If only mortality from the long-term treatment group were analyzed, the unadjusted mortality rate was 2.4% for the quinidine group and 0.6% for the control group. The typical OR was 3.1 (95% confidence interval, 0.9–10.4; \( p = 0.07 \)). Although this value did not reach conventional statistical significance, it too indicates a strong trend toward increased mortality in the group assigned to quinidine.

**Discussion**

The relatively new technique of meta-analysis of RCTs is a particularly valuable tool for pooling data from several trials when the answer to a clinical question is not available in any single report in the literature, usually because of inadequate power to test for statistically significant differences among treatment groups. Pooling of information from these six RCTs of quinidine therapy for suppression of AF was considered appropriate because of consistency of trial design and data presentation (objective end point of ECG evidence of recurrence of AF), similarity of patient populations (Table 2), minimal variation in control group findings (Table 3), and homogeneity of the treatment results (Table 3). Selection bias was avoided by analyzing only those reports from trials in which patients were randomly allocated to treatment groups (n=6); data from the other 46 trials found in our search were not included because of the possibility of bias in assignment to treatment groups. The effects of interstudy variability were accounted for by combining the results of differences between treatment and control groups only after comparisons had been made within individual RCTs. Measurements of treatment effects obtained by meta-analysis, in which all available data meeting stringent criteria for pooling are used, provide a more precise estimate of the results of therapy and reduce the chance of a Type II error.

**Suppression of Atrial Fibrillation and Mortality Risk**

This meta-analysis of RCTs reveals a statistically significant treatment benefit of quinidine in preventing recurrences of AF. The treatment effect is apparent 3 months after restoration of sinus rhythm and persists throughout the 1-year follow-up period. The risk of recurrence of AF is greatest during the first 3 months after cardioversion, and quinidine appears to diminish that risk. For these six studies, approximately 69%, 58%, and 50% of quinidine-treated patients remained in sinus rhythm 3, 6, and 12 months postcardioversion. The proportion of control patients remaining in sinus rhythm at these same intervals was 45%, 33%, and 25%, representing an absolute reduction of approximately 24% compared with the quinidine-treated group at each interval.

The play of chance is an unlikely explanation for the results observed in this study. Although the total number of patients analyzed is small compared with other meta-analyses, such as those studying the use of beta-blockers after myocardial infarction, the treatment benefit observed is large and relatively consistent from study to study. Unfortunately, not enough data were available to analyze the maintenance of sinus rhythm in subsets of patients with various underlying cardiac diagnoses. This study also does not allow for comparison of short- and long-acting quinidine preparations. Another limitation of this meta-analysis is the relatively short follow-up period. Few data concerning maintenance of sinus rhythm are available from nonrandomized trials beyond 2–3 years after cardioversion, but available data suggest dismal results. Because patients are at risk for emboli and development of symptoms anytime AF recurs, long-term data may be useful to collect in the future.

As noted by Yusuf et al., a meta-analysis of clinical trials is most representative of the true treatment effect both qualitatively and quantitatively when nearly all randomized patients are available for analysis. Potential sources of incomplete data collection include: 1) failure to identify one or more randomized clinical trials (published or unpublished because of negative results), 2) inappropriate withdrawal of some randomized patients from the final report, and 3) failure to report important clinical events such as mortality or clinical status when patients are withdrawn from the trial. Regarding the first point, our method of collection of trials probably identified all published reports but would have overlooked unpublished reports from sources such as pharmaceutical firms and scientific symposia. However, if there were a publication bias, we would have expected trials with a larger sample size to show systematically a smaller RD, and this was not observed in our analysis. In response to the second point, 22 randomized patients in this meta-analysis were withdrawn (13 quinidine, nine control) from the long-term treatment group because of a combination of quinidine intolerance, death after randomization and treatment, pharmacological conversion to sinus rhythm, and loss to follow-up. Even if all 22 patients were considered to have sustained recurrences of AF and the pooled RD were recalculated, a slightly reduced but still significant treatment benefit in favor of quinidine would be present at all time intervals analyzed (22.3% at 3 months, 20.8% at 6 months, and 22.0% at 12 months). Lastly, in response to the third point, our assumption of recurrent AF on withdrawal from the trial unless otherwise specified by the authors might have contributed to a systematic underestimation of the true treatment benefit of quinidine, but the qualitative results would be unchanged.

The total mortality rate of the full-exposure group was 2.9% in quinidine-treated patients and 0.8% in control patients, yielding a pooled OR of 2.98. Ideally, the above mortality data would have been analyzed by a comparison of survival curves using the log-rank test. Because the primary data were not
presented in a time-to-failure format, the OR method was used. The tendency toward increased mortality in the quinidine-treated group was noted in each individual study but was a more powerful observation when the data were pooled. Although it is theoretically possible that the mortality difference could have arisen as a result of bias in the treatment groups, this seems unlikely for the following reasons: 1) The trials were all randomized, 2) the total sample size was approximately 800 patients, 3) there was no significant difference in the distribution of cardiac diagnoses and simple measures of degree of illness (in those RCTs in which such information was available), and 4) the trend toward increased mortality in the quinidine group was a consistent finding among all six RCTs ($\chi^2$ for heterogeneity=1.6, df=5, $p=0.9$). The mechanism of increased mortality was known to be sudden cardiac death in three of seven quinidine-treated patients in which the cause of death was specified by the authors. A lethal ventricular arrhythmia may have been the cause of death in some or all of the five other quinidine-treated patients in which the mode of death was unclear. The two other cardiac arrests occurring in patients receiving quinidine (but not included in the analysis as noted above) highlight the potential role of quinidine in precipitating serious ventricular arrhythmias and support the concept that sudden death may be an important component of the increased total mortality in patients receiving quinidine.

**Clinical Implications**

By pooling data regarding the maintenance of sinus rhythm and drug-related mortality, clinicians may make more appropriate treatment decisions based on a clearer estimate of quinidine’s effectiveness and toxicity. Quinidine is more effective than no suppressive antiarrhythmic therapy in keeping patients in sinus rhythm, but this effectiveness appears to be obtained at the cost of at least a 3% annual incidence of mortality. A slightly increased risk of mortality might be considered acceptable if evidence were overwhelming that suppression of AF by quinidine clearly reduced the risk of thromboembolic events and/or alleviated symptoms, but such data are lacking in the literature despite a general clinical impression that quinidine therapy is beneficial. The risks of long-term anticoagulation in a patient with chronic AF also may provide an impetus for the decision to use quinidine.

The potential implications of an increased risk of mortality are far-reaching. In the Cardiac Arrhythmia Suppression Trial, the number of patients who died or experienced a cardiac arrest was 16 of 315 (5.1%) in the flecainide group versus seven of 309 (2.3%) in its matched placebo group during an average follow-up of 10 months. The corresponding values for the encainide-treated patients were 40 of 415 (9.6%) versus 15 of 416 (3.6%) in the matched placebo group. These events occurred despite the fact that there was a documented decrease in ventricular ectopic activity on those drugs before randomization. Since the information from the Cardiac Arrhythmia Suppression Trial has been made available, it has been suggested that physicians modify their prescribing practices related to type IC antiarrhythmic agents. Hine et al recently performed a meta-analysis of RCTs in which a variety of antiarrhythmic agents was administered empirically to patients with a recent myocardial infarction. They noted an adverse effect of drug treatment on mortality (typical OR, 1.38; 95% confidence interval, 1.09–1.74) and concluded that treatment of unselected patients at moderate risk of sudden cardiac death after myocardial infarction with the currently available type I antiarrhythmic agents is unwarranted.

The mortality rates in the control groups in the 10 postinfarction RCTs analyzed by Hine et al ranged from 2% to 22% and are higher than the mortality rates in the control groups of the six RCTs in AF patients reported herein (range, 0–2.6%). Nevertheless, an apparent adverse effect on mortality was observed in the quinidine-treated patients in this meta-analysis. This disturbing observation is of borderline statistical significance in part because of the low event rate in the AF patients, as would be expected in comparison with postinfarction patients. To confirm this observation, a randomized trial with a large sample size and long enough follow-up would need to be performed. Based on the rates in this meta-analysis, approximately 1,500 patients would need to be randomized to detect the difference between a 1% mortality in the control group and a 3% mortality in the quinidine group ($\alpha=0.05$, power=90%). Because of the ethical concerns raised by this meta-analysis, one would want to include a sequential stopping rule.

Although reports of death in patients on quinidine have been available for more than 15 years, many physicians may not be fully aware of the data and many do not inform their patients of the potential dangers of quinidine. At least part of the mortality in patients taking quinidine is related to sudden cardiac death. Prolongation of the QT interval has been observed in patients before sudden death, and patients receiving quinidine who develop hypokalemia may be particularly prone to serious ventricular rhythm disturbances. Although not specified by the authors, some of the mortality in the quinidine-treated patients may have resulted from hypokalemia from diuretic use or concurrent medical illnesses (e.g., pneumonia, carcinoma). In addition, because at least four of the trials were conducted before reports of a quinidine-digoxin pharmacokinetic interaction, some of the arrhythmia-related deaths may have been a result of digoxin toxicity. Furthermore, it is unclear whether quinidine produced exacerbation of underlying ventricular arrhythmias, particularly with exercise, as has been reported recently for flecainide.

Clinical decisions based on the results of a meta-analysis are most appropriate if the patient under
question has a clinical profile similar to that of the patients in the meta-analysis. Contemporary patients with AF are less likely to have rheumatic heart disease and are more likely to be older and have coronary artery disease. Changes in clinical practice that have developed subsequent to the publication date of the RCTs analyzed may not be reflected in this meta-analysis. Careful monitoring of the electrocardiogram, prompt correction of hypokalemia, and awareness of potential drug interactions have been integrated into modern-day care of patients with AF when they are treated with quinidine. The potential effect of the above change in the predominant underlying cardiac disorder and modifications in arrhythmia management on the relative safety of quinidine requires further investigation.

These observations also highlight the need to examine the effects of other antiarrhythmics, such as disopyramide and procainamide, commonly used to maintain sinus rhythm postcardioversion. In addition, they emphasize the need to find safer and more effective pharmacological agents. Initial estimates of the efficacy of the investigational antiarrhythmics propafenone and sotalol are encouraging; additional safety data need to be accumulated.32–36 Until more data are available, it now seems prudent to be more circumspect when considering the initiation of quinidine treatment for AF.

Appendix

Calculation of Pooled Proportion of Patients Remaining in Sinus Rhythm at Time t for Quinidine and Control Groups12,13

\[ \bar{p}_t = \frac{\sum (S_i \cdot W_i)}{\sum W_i} \]

where \(\bar{p}_t\) = pooled proportion of patients remaining in sinus rhythm at time t, \(S_i\) = the Kaplan-Meier estimate of the proportion of patients remaining in sinus rhythm at time t for each individual study, and \(W_i = 1/(\text{variance of } S_i)\), where the variance as per Greenwood's formula is equal to

\[ \left(\frac{1}{n_i}\right) \left(\frac{d_i}{n_i - d_i}\right) \]

where \(d_i\) = the number of patients reverting to AF in the interval \((t-1)\) to \(t\), and \(n_i\) = the total number of patients at risk during the same interval.

Techniques for Pooling Treatment Differences13

For k clinical trials, each trial provides the number of patients in each treatment group (\(N_{\text{quin}}\) and \(N_{\text{cont}}\)) and the rate at which some event occurs within that group (\(S_{\text{quin}}\) and \(S_{\text{cont}}\)). For each trial, the rate difference (RD) is equal to \(S_{\text{quin}} - S_{\text{cont}}\). The variance of RD is the sum of the variances of the rates calculated for the quinidine and control groups and is calculated as follows:

\[ \text{Var}_{RD} = \frac{S_{\text{quin}} \cdot (1 - S_{\text{quin}})}{N_{\text{quin}}} + \frac{S_{\text{cont}} \cdot (1 - S_{\text{cont}})}{N_{\text{cont}}} \]

and \(W_{RD}\) is calculated as follows:

\[ W_{RD} = \frac{1}{\text{Var}_{RD}} \]

The weighted mean RD is given by the following equation:

\[ \text{Mean } RD = \frac{\sum (RD \cdot W_{RD})}{\sum W_{RD}} \text{ for } k \text{ studies} \]

A measure of study heterogeneity, Q, can then be calculated as follows:

\[ Q = \text{sum of } (W_{RD} \cdot [RD - \text{mean } RD]^2) \text{ for } k \text{ studies} \]

If the studies are relatively homogeneous, each separate study estimates the same mean RD, and the variance among individual studies approaches zero. If the among study variance \(= 0\), then Q follows an approximate \(\chi^2\) distribution with \(k - 1\) df. Because Q has very low power and some heterogeneity nearly always exists, the method of moments is used to calculate an estimate of among study variance, \(\tau\). As noted below, when \(\tau\) is zero, no adjustment is needed because interstudy variability is minimal:

\[ \tau = \max \left\{ 0, \frac{Q - [k - 1]}{\sum W_{RD} - \frac{\sum [W_{RD}^2]}{\sum W_{RD}}} \right\} \]

A corrected value of \(W_{RD}\) for each of \(k\) studies is calculated as follows:

\[ W_{RD_{corr}} = \frac{1}{[\text{Var}_{RD} + \tau]} \]

The corrected weighted mean rate difference is given by:

\[ \text{Mean } RD_{corr} = \frac{\sum (RD \cdot W_{RD_{corr}})}{\sum W_{RD_{corr}}} \text{ for each of } k \text{ studies} \]

and

\[ \text{SE} = \frac{1}{\sqrt{\sum W_{RD_{corr}}} \text{ with approximate 95% confidence interval given by:}} \]

\[ \text{Mean } RD_{corr} \pm 1.96 \cdot \text{SE} \]

The statistical significance of mean \(RD_{corr}\) is determined by calculation of z as follows:

\[ z = \frac{\text{Mean } RD_{corr}}{\text{SE}} \]

Mortality Comparison

<table>
<thead>
<tr>
<th></th>
<th>Quinidine</th>
<th>Control</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. dead</td>
<td>a</td>
<td>b</td>
<td>(M_1)</td>
</tr>
<tr>
<td>No. alive</td>
<td>c</td>
<td>d</td>
<td>(M_0)</td>
</tr>
<tr>
<td>Total</td>
<td>(N_1)</td>
<td>(N_0)</td>
<td>(T)</td>
</tr>
</tbody>
</table>
Calculation of Odds Ratios

In a trial of T patients, N<sub>i</sub> were randomly assigned to quinidine treatment, and M<sub>i</sub> died; the observed number of deaths, O<sub>i</sub>, is compared with the expected number, E<sub>i</sub>, where E<sub>i</sub>=(N<sub>i</sub>M<sub>i</sub>)/T. If quinidine treatment did not affect mortality, the quantity O−E would differ only randomly from zero with variance (V).

\[
V = \frac{[N_1 M_1] - [N_0]}{T} \cdot \frac{[M_0]}{T} \cdot (T-1)
\]

If quinidine treatment truly were associated with an increased mortality, that tendency might be obscured or reversed by chance in an individual study. However, the overall trend should become more apparent when the sum of the individual O−E values is determined. This sum has variance equal to the sum of the individual study variances (SIV) and has an SD equal to the square root of the total variance. Formal statistical testing is performed by calculating z where

\[
z\frac{\sum \text{individual } O-E \text{ values}}{SD}
\]

and comparing z to a table of normal distribution.

The typical odds ratio (OR) of death among those patients assigned to quinidine treatment is calculated as follows:

\[
\text{OR} = \exp \left( \frac{z}{SD} \right)
\]

with approximate 95% confidence interval given by:

\[
\exp \left( \frac{z}{SD} \pm 1.96 \right)
\]

Heterogeneity between treatment effects in different trials can be estimated by subtracting the χ² statistic for the overall result from the sum of χ² statistics for each separate trial result in a group of k trials with df=k−1. Such tests of heterogeneity are rather insensitive to real treatment differences and therefore are of limited value.

References


KEY WORDS • atrial fibrillation • quinidine • meta-analyses • clinical trials
Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion. A meta-analysis of randomized control trials.
S E Coplen, E M Antman, J A Berlin, P Hewitt and T C Chalmers

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