Quinidine-Related Mortality in the Short-to-Medium-Term Treatment of Ventricular Arrhythmias
A Meta-Analysis

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Background. The interim results of the Cardiac Arrhythmia Suppression Trial requires physicians to use a higher threshold for employing antiarrhythmic agents in the treatment of benign or potentially lethal ventricular arrhythmias. Many have managed patients by switching to the traditional class I quinidine despite its known proarrhythmic tendency.

Methods and Results. To evaluate the relation between quinidine therapy and mortality in patients with benign or potentially lethal ventricular arrhythmias, we performed a meta-analysis on four randomized double-blind active controlled parallel trials evaluating 1,009 patients in which quinidine (n=502) was compared to flecainide (n=141), mexiletine (n=246), tocainide (n=67), and propafenone (n=53). All four trials had similar patient selection, protocols, and methodology (e.g., placebo lead-in and Holter monitoring) but varying lengths of drug exposure. A total of 12 deaths were reported on quinidine and four deaths on the other drugs: two on mexiletine, one on flecainide, and one on tocainide. The statistical analysis of the mortality rates was based on techniques for combining data across separate strata. Based on maximum likelihood estimation, the combined risk of dying on quinidine was statistically significantly higher compared to the other four drugs with a risk difference of 1.6%. The 95% confidence interval was 0–3.1% (p=0.05). The likelihood ratio test for uniformity of the risk difference across strata showed the trials to be homogeneous (p=0.88). There was one death recorded for the placebo lead-in period (2 weeks’ exposure for 624 patients and 1 week for 385 patients), and seven deaths were reported within 2 weeks on active drug therapy—six on quinidine and one on mexiletine. Furthermore, proarrhythmia was reported in 20 patients on quinidine versus 11 patients on the four other drugs (p=0.09).

Conclusions. These data suggest that quinidine may have an adverse effect on mortality as compared to other class I antiarrhythmic agents and that individualized patient selection for the use of this agent be carefully weighed relative to its potential for harm and benefit. (Circulation 1991;84:1977–1983)

Before April 1989, cardiologists frequently used class I antiarrhythmic agents for the suppression of potentially lethal ventricular arrhythmias.1–3 This prescribing pattern was probably motivated by the hope that the increased risk of sudden cardiac death in this group of patients could be reduced. However, cardiologists were also aware that quinidine, encainide, and flecainide were more likely than other class I agents to be associated with the early development of proarrhythmia.3 With the release of the interim Cardiac Arrhythmia Suppression Trial results, physicians have been cautioned not to use antiarrhythmic agents with class Ic action specifically, and to employ a higher threshold for the use of all antiarrhythmic agents in the treatment of chronic ventricular arrhythmias.4,5

Because increased risk of sudden cardiac death from the coexistence of ventricular arrhythmias and structural heart disease remains a major concern in the management of these patients, many physicians have switched their patients to the traditional class I antiarrhythmic agent, quinidine, or to the more recently available drug, mexiletine (Figure 1).5,6 Quinidine is the most commonly prescribed and oldest of

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the antiarrhythmic drugs available in the United States; therefore it has been selected as the principal comparative agent for the assessment of new antiarrhythmic drug efficacy.7

Due to the increased use and reliance by physicians on quinidine and its known proarrhythmic tendency, we conducted a meta-analysis of the four randomized controlled trials satisfying our strict eligibility criteria that used quinidine as the active control in the treatment of ventricular arrhythmias. The purpose of our investigation was to examine the combined mortality of quinidine compared to other class I antiarrhythmic agents.

Methods

A MEDLINE search of the English based literature through August 1990 was conducted for the purpose of identifying all studies that assessed oral quinidine therapy for chronic ventricular arrhythmias. Manual searches of references, review articles, and querying experts complemented the search. All comparative randomized trials utilizing quinidine in the treatment of benign or potentially lethal ventricular arrhythmias were evaluated and divided into two sets. The criteria for inclusion into the primary analysis set included 1) trials that established quantitatively at baseline, using a placebo lead-in, the presence and frequency of ventricular arrhythmias using long-term ambulatory ECG (Holter) monitor-

FIGURE 1. This figure details a change in prescribing habits for antiarrhythmic drug use in the United States by year from June 1986 through June 1990. The number, in millions of new prescriptions (Rx), are displayed for the 3 years before CAST (before the interim results of the Cardiac Arrhythmia Suppression Trial in April 1989) and for the year after CAST. The number at the top of each of the bars represents the estimates of prescriptions (IMS data base, Plymouth Meeting, Pa.), and the number at the top of the inside of the bar represents the percent change in total prescriptions from the previous year. Within each bar is the distribution by percent in drugs in class Ia (Q, quinidine; P, procainamide; D, disopyramide), class Ib (M, mexiletine; T, tocainide), and class Ic (E, encainide; F, flecainide).

ing; 2) a randomized double-blind parallel group trial design; and 3) explicit reporting of deaths in the trial report. Any comparative trials that did not meet these criteria were classified as appropriate for a quantitative sensitivity analysis or were used for a qualitative review to verify the logical consistency of findings. Searches and review of the articles were conducted independently by both authors. The primary outcome measure was the presence or absence of death as reported in these studies. In addition, the articles were carefully reviewed for the occurrences of the exacerbation or provocation of ventricular arrhythmias (early proarrhythmic response).5

Various statistical methods were applied to the mortality data extracted from the trials. We had to assume that the data were accurately reported. These methods allowed the data to be combined across studies in a conceptual and statistically meaningful manner rather than simple aggregation of the individually reported results.8 The parameters used for analysis were the risk difference, relative risk, and the odds ratio.9 Parameter estimates, corresponding 95% confidence intervals, and tests of homogeneity across the various studies are presented. Various statistical methods and parameters (risk difference, relative risk, and odds ratio) are reported because 1) a single approach has not clearly been chosen to be superior,10,11 2) comparing the estimates by different statistical models allows an assessment of the robustness of the findings, including separating potential methodological variations from those associated with the data themselves, and 3) other meta-analyses that are important to understanding the clinical significance of our results used varying methods for reporting their results. The risk difference parameter was selected to receive primary attention because of its direct clinical interpretation; that is, it is the difference in proportions of deaths in patients exposed to quinidine compared to the other class I antiarrhythmic agents. The Mantel-Haenszel χ2 statistic was used to test the hypothesis of equal mortality and early proarrhythmic events between quinidine and the comparative agents combined across studies.12 Maximum likelihood, direct weighting by reciprocal variances, Mantel-Haenszel weighting, and Mantel-Haenszel-Peto methods were used for parameter estimations, deriving 95% confidence intervals and reporting of exact probability values.12–16 To allow computation of weights and parameter estimates in the presence of 0 count frequencies, 0.5 was added to each cell in the 2×2 table, or in the case of maximum likelihood implicated 0 counts were replaced with 0.01.

Results

Four parallel placebo lead-in controlled trials were identified meeting the eligibility criteria as required for the primary analysis. The trials comprised a total of 1,009 patients in which 502 were treated with quinidine and 507 treated with either flecainide (n=141), mexiletine (n=246), tocainide (n=67), or propafenone (n=53).17–20 One parallel trial with 124 patients assigned to quinidine (n=62) and disopyra-
mide (n=62) was excluded from the primary analysis because a placebo lead-in baseline period was not used and an explicit description of deaths was not reported.21 This trial was conducted in the early to mid 1970s before the advent of currently used Holter monitoring and regulatory practices. The data from this trial were combined with the data from the four trials in the primary analysis to provide an estimate of the risk difference, consequently allowing an assessment of the sensitivity of our results by excluding this trial from our primary analysis. To perform this analysis, an assumption that no deaths occurred on either drug was made. Six crossover studies were also identified and excluded from the primary analysis.22-27

The population characteristics of the four parallel studies are detailed in Table 1. These data suggest that the patient populations studied were similar among the four trials. All four trials used the same central laboratory to define quantitatively the frequency and type of ventricular arrhythmias and the change on therapy (Cardio-Data Systems Inc., Haddonfield, N.J.). The four trials also used comparable efficacy criteria as well as evaluation of adverse drug reactions. Mortality data were available by time on drug (in days), and quinidine sulfate was used as the form of quinidine in all four trials. The active drug exposure days in these trials is considered short-term to medium-term, ranging from 2 to 12 weeks: two studies dosing for 2 weeks, one for 8 weeks, and one for 12 weeks. Three studies included an escalation component and one used a fixed dose for 8 weeks. All four trials were conducted in the mid 1980s, and full medical reports were written.17-20

No data detailing precise measures or estimates of left ventricular function were collected, but the patient characteristics, demography, and the similar drug response rates suggest likely comparability. Table 2 details the mortality data on quinidine versus the four other active class I antiarrhythmic agents. Individually for each study, the proportion of deaths on quinidine is at least as large as the comparative agent. These data yield a combined estimated risk difference of dying on quinidine compared to the patients exposed to flecainide, mexiletine, tocainide, or propafenone of 0.016 (1.6%) with a 95% confidence interval of 0.00 to 0.03 (p=0.05), using the maximum likelihood method. The direct weighting method yields the same results. A visual presentation of the individual and combined results using the risk difference parameter is given in Figure 2, and results obtained using the other parameters are given in Table 3. The Mantel-Haenszel test statistic yields a probability of 0.04. As might be expected, more deaths occurred in the study of longest duration.8,11 Also early proarrrhythmia occurred more commonly in this study.18 There were 20 such events reported on quinidine compared to a total of 11 events on the three other active agents (Table 4). These data yield a Mantel-Haenszel test with a probability of 0.09.
Among the four trials in the primary analysis set, 624 patients had exposure to placebo for 2 weeks and 385 patients had a 1-week exposure. One death was reported among these 1,009 patients during this 1–2-week exposure to placebo. In contrast, there were seven deaths on the four active agents that occurred within 2 weeks of drug exposure, six of which occurred on quinidine and one on mexiletine. The actual days on drug to death as well as the reported cause of death are detailed in Table 5. Inclusion of the disopyramide study into the analysis yields a maximum likelihood, and a direct weighting estimate, of risk difference of 0.013 (1.3%) with both methods yielding a 95% confidence interval of 0.00 to 0.03 \( (p=0.05) \). The likelihood ratio test of homogeneity among trials for the maximum likelihood method is a probability of 0.49.

**Discussion**

Our analysis of the published comparative trials raises serious concern as to the safety of quinidine in the treatment of ventricular arrhythmias. The analysis suggests that quinidine therapy should not be a commonly used treatment for patients at risk with ventricular arrhythmias (as suggested by Figure 1) because it was found to be associated with at least as high a proportion of adverse events, such as death and early proarrhythmia, as the class Ic agents, flecainide and propafenone, and the class Ib agents.

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**Figure 2.** This figure details the individual study and combined risk differences with 95% confidence intervals for each of the four parallel quinidine comparative trials. In addition, the combined data are demonstrated using the maximum likelihood (ML) and direct weighting (DW) methods.
TABLE 4. Proarrhythmic Data Comparing Quinidine With Four Other Class I Antiarrhythmic Agents

<table>
<thead>
<tr>
<th>Study</th>
<th>Quinidine</th>
<th>Comparative drug</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of proarrhythmia events (% of exposed)</td>
<td>No. of patients exposed</td>
</tr>
<tr>
<td>Q-F</td>
<td>2 (1.4)</td>
<td>139</td>
</tr>
<tr>
<td>Q-M</td>
<td>18 (7.3)</td>
<td>245</td>
</tr>
<tr>
<td>Q-T</td>
<td>0 (0.0)</td>
<td>66</td>
</tr>
<tr>
<td>Q-P</td>
<td>0 (0.0)</td>
<td>52</td>
</tr>
</tbody>
</table>

Q, quinidine; F, flecainide; M, mexiletine; T, tocainide; P, propafenone.

mexiletine and tocainide. When the data are combined, the risk difference of dying from quinidine versus the other class I antiarrhythmic agents reached a statistical difference of a probability of 0.05. Comparing quinidine to two agents with class Ic action and two with class Ib action provides meaningful information when viewed in the context of enhanced mortality data for such class I drugs.

The Cardiac Arrhythmia Suppression Trial clearly demonstrated enhanced risk of death on flecainide compared to placebo in patients with potentially lethal ventricular arrhythmias after myocardial infarction. In that trial, there were 16 (5.1%) deaths among the 315 patients on flecainide compared to seven deaths out of 309 patients (2.3%) on placebo. Encainide, another class Ic agent used in the Cardiac Arrhythmia Suppression Trial, demonstrated a similar effect. Unfortunately, no mortality data regarding propafenone compared to placebo are available, but because of its similar class Ic action, the Food and Drug Administration has insisted on the same warnings for its clinical use as flecainide and encainide.

A meta-analysis performed by Furberg and Mendlane, as reported by Anderson, showed that data on 6,177 patients randomized to class Ib agents and 6,076 patients randomized to placebo resulted in an odds ratio for enhanced mortality due to active therapy of 1.29 (95% confidence interval 1.04 to 1.62, p=0.02). Mexiletine and tocainide are agents with class Ib action. Thus, as reported here, quinidine's enhanced risk of mortality is being compared to agents on which there are data that documented an absolute elevation of death compared to placebo (the class Ic drugs) and to agents on which the suspicion of increased risk is moderate to high (the class Ib drugs).

Our study also shows a trend toward an increased rate of proarrhythmia on quinidine compared to a combined rate on the other four class I agents (p=0.09). These data give an empirical basis for the general impression of cardiologists who subsequently ranked quinidine as the most proarrhythmic drug in their experience when given to patients with benign or potentially lethal ventricular arrhythmias.3

The results of the current study are further strengthened when considered co-jointly with that of an analysis performed by Coplen et al29 in 800 patients in which quinidine was compared to placebo in the treatment of atrial fibrillation. In their meta-analysis, 12 out of 413 (2.9%) patients exposed to quinidine died versus three deaths out of 387 (0.8%) patients given placebo, in a 3–12-month follow-up. These investigators reported a Mantel-Haenszel odds ratio of 3.51, with a 95% confidence interval of 0.99 to 12.45 (p=0.05). The Mantel-Haenszel-Peto method yielded an odds ratio of 2.98 with a 95% confidence interval of 1.1 to 8.3 (p<0.05). These results are highly suggestive of increased mortality on quinidine. In our analysis, the odds of dying on quinidine was also about three times that compared to the odds of dying on an active comparative agent; the respective estimates being 3.08 and 2.78 (Table 3).

Examining the mortality results available in the crossover trials, out of approximately 230 patients exposed to quinidine, and either moricizine, acetyltolol, encainide, or lorcanide, only two deaths were reported, both on encainide.22–27 When these two deaths are added to the primary analysis there is a total of 12 deaths reported on quinidine and now six on comparative agents. Although the crossover trial data cannot be formally combined with the previous results, the overall data strongly suggest that quinidine therapy results in at least as many deaths. Additional supporting evidence concerning harmful effects of quinidine are the results reported by Moosvi et al.30 They demonstrated an increase in mortality on quinidine when used empirically for the treatment of ventricular arrhythmias in postmyocardial infarction patients compared to untreated patients. Additional data on quinidine's effect are documented in the meta-analysis report by Hine et al.31 This study reported on the use of type I antiarrhythmic agents compared to placebo during long-term (3–24 months) therapy after myocardial infarction. A

TABLE 5. Number of Days on Drug to Death and Cause of Death

<table>
<thead>
<tr>
<th>Study</th>
<th>Days on quinidine (cause of death)</th>
<th>Days on comparative drug (cause of death)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q-F</td>
<td>3 (SCD), 2 (VF), 3 (SCD)</td>
<td>36 Hours off flecainide (SCD)</td>
</tr>
<tr>
<td>Q-M</td>
<td>3 (SCD), 3 (CAD), 4 (ARRH), 19 (SCD), 32 (VF), 35 (AMI), 82 (SCD)</td>
<td>7 (CA), 47 (SCD)</td>
</tr>
<tr>
<td>Q-T</td>
<td>21 (SCD)</td>
<td>21 (SCD)</td>
</tr>
<tr>
<td>Q-P</td>
<td>7 (SCD)</td>
<td></td>
</tr>
</tbody>
</table>

Q, quinidine; F, flecainide; M, mexiletine; T, tocainide; P, propafenone; SCD, sudden cardiac death; VF, ventricular fibrillation; CAD, coronary artery disease; ARRH, arrhythmia; AMI, acute myocardial infarction; CA, cardiac arrest.
statistically significant adverse risk difference on quinidine of 1.8% (p=0.05) was reported.

The mechanism of the potential enhanced mortality of quinidine is not known. Torsade de pointes as identified by Ruskin et al. and Rodin et al. may be the likely mechanism of enhanced quinidine mortality. This late occurring proarrhythmic response in patients who were otherwise stable early after starting antiarrhythmic drugs is comparable to the late proarrhythmia seen in the Cardiac Arrhythmia Suppression Trial. Late proarrhythmia is not obviously predicted by the occurrence of early proarrhythmia.

The potential interaction of digoxin and quinidine may contribute to late proarrhythmia. The trials included in this report were conducted when this interaction was well known, and the protocols clearly recommended a reduction in digoxin dosage. However, in the quinidine versus mexiletine trial there were two deaths among the 185 patients who were on quinidine without digoxin use versus five deaths in the 60 patients in the group on quinidine plus concomitant digoxin. Overall, 60 of 245 (24.5%) patients randomized to quinidine compared to 56 of 246 (22.8%) patients assigned to mexiletine were being treated with digoxin. Also, in the flecainide versus quinidine trial, there was one death in the 103 patients on quinidine without concomitant digoxin compared to two deaths among the 36 patients who were on both quinidine and digoxin. Thus, the increased deaths on quinidine may be related to concomitant digoxin use or to an enhanced mortality risk when quinidine is used in patients treated with digoxin presumably due to the coexistence of poor left ventricular function.

The meta-analysis provided in this report satisfies the characteristics required for valid use of this technique. The four parallel trials had comparable study designs and data presentation as well as enrolling similar patient populations. In addition, all studies were conducted within a specific drug class (class I). Although 53% of the data were contributed by the 12-week quinidine-mexiletine study, the results are consistent over the other three shorter-term trials. Moreover, the combining of all the data is logical due to the similar class I status of the comparative agents and the statistical finding of homogeneity across the separate trials.

The effect of suppression of benign or potentially lethal ventricular arrhythmias has been previously reported in 446 patients in 17 trials by a meta-analysis of Salerno et al. The percentage of patients responding to quinidine was 53% with a range of 43 to 63%. The efficacy rate demonstrated in the four trials reported here ranged between 32 to 83% of patients responding. In the meta-analysis of Salerno et al., the average percent of responders for 100% suppression of nonsustained ventricular tachycardia was 57% with a range of 21 to 92% in 158 treated patients in nine studies. In the four studies reported here, the response rates ranged between 43 and 80%.

Our analysis of quinidine's effect is limited to the short-to-medium-term drug exposure from 2 to 12 weeks, which is typical for ventricular arrhythmia treatment studies. The deaths reported in the original clinical trials were not considered for their potential as a late occurring proarrhythmic event and often were ascribed to natural occurrences. This retrospective analysis, in view of the mortality results of the Cardiac Arrhythmia Suppression Trial, necessitated that the deaths be more closely inspected and presented (Table 5).

The results of this meta-analysis do not address the concern of the use of antiarrhythmic agents in the treatment of life-threatening or sustained ventricular tachyarrhythmias, but similar caution in the use of quinidine over the long term should be considered. It is also clear that no quinidine versus placebo comparative trials, in any form of ventricular arrhythmias, are likely to occur in the future, although this would be the only definitive way of defining the true rate of late proarrhythmic mortality from quinidine therapy. Clearly the results of the Cardiac Arrhythmia Suppression Trial cautioned against the prophylactic use of antiarrhythmic therapy for sudden cardiac death prevention in postmyocardial infarction patients with asymptomatic potentially lethal ventricular arrhythmias. Currently, β-blockers are the only "antiarrhythmic" agents that have been shown to demonstrate long-term safety in this regard. The only current class I agent with adequate long-term safety data appears to be moricizine because it continues to be studied in Phase II of the Cardiac Arrhythmia Suppression Trial. The implications of our findings complement and support the growing literature on the enhanced risk of mortality from quinidine and provides further impetus to the cautious use of any antiarrhythmic agents in which the benefit has not been shown to outweigh the potential harm.

References


**KEY WORDS** • class I antiarrhythmic drugs • quinidine • ventricular arrhythmias • sudden cardiac death • proarrhythmia

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