Declining Incidence of Ventricular Fibrillation in Myocardial Infarction

Implications for the Prophylactic Use of Lidocaine

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Background. The purposes of the present investigation were 1) to track the incidence of primary ventricular fibrillation (VF) in the control and lidocaine-treated groups in the randomized control trials (RCTs) of lidocaine prophylaxis against primary VF in acute myocardial infarction, with particular emphasis on the time frame of the randomized trial, and 2) to estimate the number of patients who must receive lidocaine currently to prevent one episode of VF.

Methods and Results. The following variables from RCTs published between 1969 and 1988 were entered into logistic regression models to predict the percent of patients developing VF: year of publication of the RCT, method of data analysis used in the RCT, route and technique of lidocaine administration, duration of monitoring for VF, and exclusion criteria before randomization (congestive heart failure/cardiogenic shock, ventricular tachycardia/VF, or bradycardia/atrioventricular block). Year of publication was a significant predictor of VF in both the control and lidocaine groups (p ≤ 0.002) even after adjusting for other covariates. Based on a univariate logistic regression model with year as the predictor variable, it was estimated that the incidence of primary VF in the control group fell from 4.51% in 1970 to 0.35% in 1990 and from 4.32% down to 0.11% for the lidocaine group over the same time period. Thus, about 400 patients would currently need prophylaxis with lidocaine to prevent one episode of VF.

Conclusions. Present estimates of the risk-benefit ratio of lidocaine prophylaxis should consider the low risk of VF in control patients and the large number who need lidocaine prophylaxis to prevent one episode of VF. When added to the previously reported trend toward excess mortality in lidocaine-treated patients, these data argue against the routine prophylactic use of lidocaine in patients with acute myocardial infarction. (Circulation 1992;86:764-773)

Key Words • lidocaine • myocardial infarction, acute • ventricular fibrillation • trials, randomized control

Since the introduction of coronary care units in the 1960s, a considerable portion of the clinical literature dealing with acute myocardial infarction (MI) has addressed the concept of lidocaine prophylaxis against primary ventricular fibrillation (VF). Recommendations for the prophylactic use of lidocaine have evolved in three broad stages: 1) an initial proposal that individuals with "warning" ventricular arrhythmias required treatment with lidocaine in a prophylactic fashion to prevent primary VF,\(^1\) 2) expansion of the profile of patients to be treated prophylactically to include all individuals with known or suspected acute MI because warning arrhythmias were shown to have limited predictive value in identifying patients at risk for primary VF,\(^2,3,4\) 3) a proposal that patients be targeted for lidocaine prophylaxis based on epidemiological markers of increased risk for primary VF other than warning arrhythmias (e.g., age less than 70 years, admission to the coronary care unit within 6–12 hours of the onset of chest pain, and high clinical index of suspicion of an MI actually having occurred).\(^5\)

To investigate the efficacy and safety of prophylactic lidocaine, a number of randomized control trials (RCTs) have been performed over the last two decades. A recent meta-analysis has confirmed that lidocaine administration is associated with a statistically significant 35% reduction in the incidence of VF in comparison with the control group (relative risk, 0.65).\(^6\) However, two independent meta-analyses have observed that the pooled data for lidocaine-treated patients demonstrate a trend toward increased total mortality compared with control patients, possibly because of an excess of fatal bradycardic or asystolic arrests in the lidocaine groups.\(^6,7\) This trend toward excess mortality in lidocaine-treated patients persists even when the meta-analysis is restricted only to those RCTs that specifically excluded patients with congestive heart failure or cardiogenic shock before randomization (unpublished observation). Thus, although lidocaine may serve to prevent VF, it may also predispose the patient to bradycardia and asystole because of excess slowing of conduction, especially in the setting of ischemia. If the risks of bradycardia and asystole are greater than the
risk of VF, one would anticipate an excess mortality in patients treated with lidocaine despite the fact that VF may occur less frequently in the treated group.

Dramatic improvements in the general care of acute MI patients have occurred since the 1960s. These interventions, largely of a pharmacotherapeutic nature (e.g., β-blockers, aspirin, anticoagulants, nitrates, thrombolytic agents), have led to a reduction in the short-term mortality associated with acute MI. The mechanisms of the reduction in mortality remain speculative but include such possibilities as limitation of infarct size, a decrease in the number of recurrent myocardial ischemic episodes, and reduction in the incidence of potentially lethal ventricular arrhythmias.8

**See p 1033**

In light of the meta-analytic results indicating that prophylactic lidocaine therapy is associated with a reduction in the risk of primary VF but possibly at the cost of increased total mortality, it seems important to reevaluate the risk:benefit ratio of lidocaine prophylaxis in the present coronary care era, when numerous other drug interventions are used concurrently. The RCTs of lidocaine prophylaxis against primary VF afford an excellent opportunity to perform such an analysis because these trials span two decades of coronary care medicine. The purposes of the present investigation were to track the incidence of primary VF in the control and lidocaine-treated groups in the RCTs of lidocaine prophylaxis against primary VF in acute MI, with particular emphasis being placed on the time frame of the randomized trial and to estimate the number of patients who must now receive lidocaine to prevent one episode of VF.

**Methods**

**Selection of Trials for Review and Acquisition of Data**

To identify all RCTs of lidocaine prophylaxis against primary VF in acute MI, the English and non-English language literature were searched from 1966 to 1990 using the MEDLINE data bases of the National Library of Medicine. Additional sources included references from studies identified in the above searches and the reference lists of several large meta-analyses dealing with this topic.6,7,9 The criteria for inclusion of an RCT in this review were: 1) patients with known or suspected acute MI were randomized to lidocaine or control treatment groups; 2) the trial followed patients longitudinally to assess the efficacy of lidocaine in preventing primary VF, and these data were available in a form that permitted calculation of the percent of patients remaining free of VF during the course of the trial; 3) the minimum follow-up time was 1 hour after randomization; 4) lidocaine was the only permissible antiarhythmic agent that was administered prophylactically.

The following data were extracted from each RCT included in this report and later coded as potential predictor variables for regression analysis: year of publication of the RCT, method of data analysis used in the RCT (intention to treat versus exclusion of randomized patients if acute MI was not confirmed), route of administration of lidocaine (intramuscular versus intravenous), technique of lidocaine administration (single dose versus maintenance infusion), duration of monitoring for VF after randomization, and a statement by the investigators indicating whether patients were excluded if congestive heart failure cardiogenic shock, ventricular tachycardia/VF, or bradycardia/atrioventricular block was present before randomization. For each RCT, the number of patients allocated to the lidocaine and control groups was noted along with the number of patients in each group who experienced at least one episode of primary VF during the monitoring period of the trial. No special effort was made to contact the original investigators of the RCTs.

**Statistical Analyses**

The data were entered into a SYSTAT file for various computations. The analytic methods used in this investigation included the generation of univariate and multivariate logistic regression models (LOGIT, Salford Systems, San Diego, Calif.) predicting the proportion of patients experiencing VF in the control and lidocaine groups, based on the predictor variables retrieved from the RCTs.10,11 Because the incidence of primary VF after acute MI falls exponentially as time elapses from the onset of chest pain,3,12 the natural logarithm of the duration of monitoring (in hours) was used in constructing logistic regression models. The general form of the logistic regression models used to predict the percent of patients experiencing VF in the control and lidocaine groups was

\[
\text{Percentage of patients experiencing VF} = \frac{1}{1 + e^{-\left(\beta_0 + \beta_1 x_1 + \ldots + \beta_k x_k\right)}} \times 100
\]

where \(\beta_0\) equals the parameter estimate for the constant in the logistic function and \(\beta_1, \ldots, \beta_k\) are the parameter estimates for the predictor variables (covariates) having values \(x_1, \ldots, x_k\), respectively. Confidence intervals for the predicted percent of patients experiencing VF were also obtained using the LOGIT statistical package.10

For each predictor variable \(x\), the multiplicative change in the odds of VF occurring (odds ratio) is given in the general form \(e^{\beta x}\). In the case of the two continuous variables (year of RCT, duration of monitoring), the odds ratios describe the change in the odds of VF for each increase in the respective unit of measurement (year, hour). For the other dichotomous variables, the odds ratios describe the change in the odds of VF when the latter of the two conditions is present (e.g., intention-to-treat analysis versus analysis only of patients with proven infarction) or when a condition is present compared with when it is absent (e.g., exclusion for congestive heart failure cardiogenic shock). For example, suppose \(x_1=0\) if only a single dose of lidocaine was administered and \(x_1=1\) if a maintenance dose of lidocaine was used. Then the term \(e^{\beta x_1}\) represents the odds ratio comparing the odds of VF in single-dose studies with the odds of VF in those studies using a maintenance infusion. The logistic models inherently give weight to studies in direct proportion to the number of subjects included (i.e., inversely proportional to the variability within the study).10

To provide a clinically useful measure of the treatment effect of lidocaine in preventing VF that incorporated the baseline risk in the control group as well as the risk reduction associated with lidocaine prophylaxis, we calculated the number of patients who would require
TABLE 1. Characteristics of Randomized Control Trials Included for Analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Reference</th>
<th>Year</th>
<th>Data analysis method</th>
<th>Route</th>
<th>Dosing pattern</th>
<th>Duration of monitoring (hours)</th>
<th>Exclusion criteria before randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15</td>
<td>1969</td>
<td>AMI</td>
<td>IV</td>
<td>Maint</td>
<td>48</td>
<td>CHF/shock = Yes, VT/VF = Yes</td>
</tr>
<tr>
<td>2</td>
<td>16</td>
<td>1970</td>
<td>AMI</td>
<td>IV</td>
<td>Maint</td>
<td>48</td>
<td>CHF/shock = Yes, VT/VF = Yes</td>
</tr>
<tr>
<td>3</td>
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<td>1971</td>
<td>AMI</td>
<td>IV</td>
<td>Maint</td>
<td>48</td>
<td>CHF/shock = Yes, VT/VF = Yes</td>
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<td>4</td>
<td>19</td>
<td>1971</td>
<td>ITT</td>
<td>IV</td>
<td>Maint</td>
<td>48</td>
<td>CHF/shock = Yes, VT/VF = Yes</td>
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<tr>
<td>5</td>
<td>20</td>
<td>1971</td>
<td>AMI</td>
<td>IV</td>
<td>Maint</td>
<td>48</td>
<td>CHF/shock = Yes, VT/VF = Yes</td>
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<td>6</td>
<td>21</td>
<td>1972</td>
<td>AMI</td>
<td>IV</td>
<td>Maint</td>
<td>48</td>
<td>CHF/shock = Yes, VT/VF = Yes</td>
</tr>
<tr>
<td>7</td>
<td>23</td>
<td>1973</td>
<td>ITT</td>
<td>IV</td>
<td>Maint</td>
<td>48</td>
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<td>AMI</td>
<td>IV</td>
<td>Maint</td>
<td>48</td>
<td>CHF/shock = Yes, VT/VF = Yes</td>
</tr>
<tr>
<td>9</td>
<td>34</td>
<td>1988</td>
<td>ITT</td>
<td>IV</td>
<td>Maint</td>
<td>48</td>
<td>CHF/shock = Yes, VT/VF = Yes</td>
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<td>AMI</td>
<td>IM</td>
<td>Single</td>
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<td>CHF/shock = Yes, VT/VF = Yes</td>
</tr>
<tr>
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<td>ITT</td>
<td>IM</td>
<td>Single</td>
<td>3</td>
<td>CHF/shock = Yes, VT/VF = Yes</td>
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<tr>
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<td>29</td>
<td>1978</td>
<td>AMI</td>
<td>IM</td>
<td>Single</td>
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<td>CHF/shock = Yes, VT/VF = Yes</td>
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<td>31</td>
<td>1985</td>
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<td>IV</td>
<td>Single</td>
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<td>32</td>
<td>1985</td>
<td>ITT</td>
<td>IM</td>
<td>Single</td>
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<td>CHF/shock = Yes, VT/VF = Yes</td>
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<td>1970</td>
<td>AMI</td>
<td>IV</td>
<td>Maint</td>
<td>24</td>
<td>CHF/shock = Yes, VT/VF = Yes</td>
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<tr>
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<td>24</td>
<td>1973</td>
<td>AMI</td>
<td>IV</td>
<td>Maint</td>
<td>120</td>
<td>CHF/shock = Yes, VT/VF = Yes</td>
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<tr>
<td>17</td>
<td>22</td>
<td>1972</td>
<td>ITT</td>
<td>IV</td>
<td>Maint</td>
<td>48</td>
<td>CHF/shock = Yes, VT/VF = Yes</td>
</tr>
<tr>
<td>18</td>
<td>30</td>
<td>1982</td>
<td>ITT</td>
<td>IM</td>
<td>Single</td>
<td>3</td>
<td>CHF/shock = Yes, VT/VF = Yes</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Maint</td>
<td>12</td>
<td>CHF/shock = Yes, VT/VF = Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CHF/shock = Yes, VT/VF = Yes</td>
</tr>
</tbody>
</table>

CHF, congestive heart failure; VT/VF, ventricular tachycardia/ventricular fibrillation; AV, ativoventricular; AMI, acute myocardial infarction; ITT, intention-to-treat method of data analysis; IV, trial contained an intravenous lidocaine component in treatment regimen; IM, trial contained only an intramuscular lidocaine component in treatment regimen; Single, therapeutic regimen of trial consisted only of a single dose of lidocaine given prophylactically; Maint, therapeutic regimen of trial contained a maintenance phase of lidocaine administration.

The calculation was based on the univariate logistic regression model with year as the predictor variable and was performed as follows:

Number of patients = 100

\[
\frac{\% \text{ VF control} - \% \text{ VF lidocaine}}{\% \text{ VF lidocaine}}
\]

where \% VF control equals predicted percent of patients experiencing VF in the control group in 1990 and \% VF lidocaine equals predicted percent of patients experiencing VF in the lidocaine group in 1990.

We used the Wilcoxon rank sum procedure for independent samples to examine the data for any association between year of publication of the RCT and dichotomous study characteristics to evaluate the potential for multicollinearity problems in logistic regression models. For example, the average year of publication for RCTs using intramuscular lidocaine was compared with that for RCTs using intravenous lidocaine. The association between year of publication and duration of monitoring for VF was assessed using Spearman's \( r \), a rank-based correlation statistic. The tests noted above were considered important because severe multicollinearity in the predictor variables is well known to cause problems in the estimation of regression models. In general, problems of collinearity are manifested by extraordinarily large estimated standard errors and sometimes by unduly large estimated coefficients as well.

To assess the trend over time in the relative benefit of lidocaine treatment in reducing VF, a weighted least-squares regression was performed with the natural logarithm (ln) of the within-study odds ratio (OR) as the outcome variable. The weight assigned to each lnOR was the inverse of its variance. A predicted value of the lnOR for a theoretical RCT conducted in 1990 was also calculated. With a relatively rare occurrence such as primary VF in acute MI, the OR is an accurate estimate of the relative risk of VF in the treated compared with the untreated group. This analysis, which preserves the randomization within each study, also allowed us to validate the calculation of the number of patients needing treatment to prevent one episode of VF.

Results were considered statistically significant when associated with a probability value of less than 0.05.

Results

Twenty RCTs were initially identified, but two were excluded because they provided data only on the number of deaths in the control and lidocaine-treated groups but not on the number of episodes of VF. The characteristics of the 18 RCTs included for analysis are summarized in Table 1. Only one RCT specifically investigated the benefits of lidocaine prophylaxis in the prehospital phase of acute MI, whereas the other 17 studied patients after arrival in the hospital with treatment initiated either in the emergency room or in the coronary care unit. The RCTs were published over a span of 19 years and were nearly equally divided between those that analyzed patients on an intention-to-treat method and those that only analyzed data on patients in whom an acute MI was confirmed. About three fourths of the RCTs included an intravenous
route of lidocaine administration (72%), and two thirds incorporated a maintenance phase of lidocaine therapy in the treatment regimen. Over 80% of the RCTs excluded patients with left ventricular failure/cardiogenic shock or ventricular tachycardia/VF before randomization; two thirds excluded patients with bradycardia/atrioventricular block before randomization. In 10 of 18 RCTs (56%), there was a concordant pattern in all three of the exclusion criteria, and the remaining eight RCTs were concordant in at least two of the three exclusion criteria listed in Table 1.

Important associations were detected between the year of publication of the RCT and several of the other predictor variables. RCTs conducted more recently had a greater tendency to use an intention-to-treat method of data analysis compared with exclusion of patients in whom an MI was not confirmed \((p=0.03)\), to use only a single dose of lidocaine versus a maintenance infusion \((p=0.006)\), to use only an intramuscular route of lidocaine administration \((p=0.03)\), and to have a shorter duration of monitoring for VF \((p=0.02)\). Other sources of multicollinearity were evident as well. With one exception,\(^{31}\) studies that used intravenous delivery of lidocaine included a maintenance dose, and studies using intramuscular lidocaine administered only a single dose of drug. The observations above regarding the concordance of exclusion criteria in the majority of RCTs and significant associations between year of RCT publication and other predictor variables imposed some limitations on attempts to develop logistic regression models using the available data set because of sample-based multicollinearity (overspecification of the model).\(^{11}\) This produced very large standard errors for the parameter estimates in some of the multivariable models. In extreme cases, models failed to converge on a solution. Nevertheless, in all models that did converge, the coefficient for year of publication of the RCT retained its statistical significance (see below).

The incidence of VF in the control and lidocaine groups for each RCT is shown in Table 2. There was a general trend toward a smaller percentage of patients experiencing VF in both the control and lidocaine groups in RCTs conducted more recently.

### Control Group

The results of the univariate logistic regression analyses for prediction of the development of VF in the control group are summarized on the left side of Table 3. Because the route of administration and dosing pattern for lidocaine would not be anticipated to be predictive of the probability of VF in the control group, these two variables were not assessed in any logistic regression models. Year of publication of the RCT was strongly predictive of the development of VF \((\chi^2_{df \ 1}=42.47, p<0.001)\). Other variables that were significantly predictive of the development of VF were the method of data analysis in the RCT \((\chi^2_{df \ 1}=29.65, p<0.001)\), the duration of monitoring for VF \((\chi^2_{df \ 1}=39.95, p<0.001)\), and exclusion of patients with a history of congestive heart failure/cardiogenic shock before randomization \((\chi^2_{df \ 1}=5.76, p=0.02)\).

Multivariate logistic regression models were constructed to examine the ability of each of the independent variables to predict the proportion of patients experiencing VF in the control group after adjusting for the year of publication of the RCT (Table 4). When year of publication is in the model, only exclusion of patients with bradycardia and/or atrioventricular block

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### Table 2. Incidence of Ventricular Fibrillation in Control and Lidocaine Groups of Randomized Control Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No. of patients (VF/total)</th>
<th>%VF (95% CI)</th>
<th>No. of patients (VF/total)</th>
<th>%VF (95% CI)</th>
</tr>
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<tr>
<td>1</td>
<td>1969</td>
<td>0/31</td>
<td>0 (0,9.2)</td>
<td>0/34</td>
<td>0 (0,8.4)</td>
</tr>
<tr>
<td>2</td>
<td>1970</td>
<td>7/125</td>
<td>5.6 (2.3,11.2)</td>
<td>16/249</td>
<td>6.4 (3.7,10.2)</td>
</tr>
<tr>
<td>3</td>
<td>1971</td>
<td>2/23</td>
<td>8.7 (1.1,28.0)</td>
<td>0/21</td>
<td>0 (0,13.3)</td>
</tr>
<tr>
<td>4</td>
<td>1971</td>
<td>0/43</td>
<td>0 (0,6.7)</td>
<td>1/39</td>
<td>2.6 (0.1,13.5)</td>
</tr>
<tr>
<td>5</td>
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<td>0/114</td>
<td>0 (0,2.6)</td>
<td>1/108</td>
<td>0.9 (0,02,5.0)</td>
</tr>
<tr>
<td>6</td>
<td>1972</td>
<td>3/100</td>
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<td>4/103</td>
<td>3.9 (1,13,9)</td>
</tr>
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<td>1973</td>
<td>10/331</td>
<td>3.0 (1,5,5.5)</td>
<td>9/328</td>
<td>2.7 (1,3,5,1)</td>
</tr>
<tr>
<td>8</td>
<td>1974</td>
<td>11/105</td>
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<td>0/107</td>
<td>0 (0,2,8)</td>
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<td>9</td>
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<td>0/168</td>
<td>0 (0,1,8)</td>
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<td>0/90</td>
<td>0 (0,3,3)</td>
<td>0/91</td>
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<td>0/27</td>
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<td>0/27</td>
<td>0 (0,10,5)</td>
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<tr>
<td>12</td>
<td>1978</td>
<td>4/153</td>
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<tr>
<td>13</td>
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<td>0/79</td>
<td>0 (0,3,7)</td>
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VF, ventricular fibrillation; 95% confidence intervals are calculated by an exact method.
remained a significant predictor of the development of VF (χ² = 11.35, p = 0.001). In a forward stepwise logistic regression model (p = 0.05 to enter and p = 0.05 to remain in model), the only variables that were found to be significantly predictive of VF in the control group were year of publication of the RCT and the three exclusion criteria listed in Table 1 (p < 0.0001 for all variables). In all multivariate models tested, including stepwise logistic regression, the year of publication of the RCT remained highly predictive of the development of VF in the control group. In Table 5, results of two models including both year of publication and a single additional variable demonstrate that year remains an important predictor even after adjustment for length of monitoring or method of data analysis (intention to treat versus proven acute MI only).

Using the unadjusted parameter estimate for year of publication of the RCT from the univariate logistic regression model with that variable and applying a range of values corresponding to the years 1969–1990, the predicted percent of patients experiencing VF was calculated along with its 95% confidence intervals and is depicted in Figure 1A. There was a decline in the percent of patients estimated to experience VF in the control group from 4.51% (3.16%, 6.40%) in 1970 to 0.35% (0.14%, 0.86%) in 1990.

**Lidocaine Group**

The results of the univariate logistic regression analyses for prediction of the development of VF in the lidocaine group are summarized on the right side of Table 3. Year of publication of the RCT was again strongly predictive of the development of VF (χ² = 64.79, p < 0.001). All other variables with the exception of exclusion for ventricular tachycardia/VF before randomization were significantly predictive of the development of VF when examined in a univariate logistic regression model.

Multivariate logistic regression models were constructed to examine the ability of each of the independent variables to predict the proportion of patients experiencing VF in the lidocaine group after adjusting for the year of publication of the RCT (Table 4). None of the other variables were significantly predictive of VF in the lidocaine group. In a forward stepwise logistic regression model (p = 0.05 to enter and p = 0.05 to remain in model), once again only the year of publication of the RCT was identified as a significant predictor of VF (p < 0.0001). As with the control group data, in all multivariate models tested including stepwise logistic regression, the year of publication of the RCT remained highly predictive of the development of VF in the lidocaine group. Two important examples are presented in Table 5.

Using the unadjusted parameter estimate for year of publication of the RCT, the predicted percent of patients experiencing VF in the lidocaine group was calculated along with its 95% confidence interval in a manner similar to that for the control group (Figure 1B). There was a decline in the percent of patients...
TABLE 5. Odds Ratio for Ventricular Fibrillation as Predicted by Year of Publication of Randomized Control Trial Before and After Adjustment for Other Covariates

<table>
<thead>
<tr>
<th>Model</th>
<th>Control group</th>
<th>Lidocaine group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year of RCT</td>
<td>0.88 (0.84–0.91)</td>
<td>0.83 (0.79–0.87)</td>
</tr>
<tr>
<td>Year of RCT after adjustment for method of data analysis</td>
<td>0.90 (0.85–0.95)</td>
<td>0.82 (0.77–0.88)</td>
</tr>
<tr>
<td>Year of RCT after adjustment for duration of monitoring</td>
<td>0.93 (0.86–1.00)</td>
<td>0.74 (0.66–0.85)</td>
</tr>
</tbody>
</table>

RCT, randomized control trial.

Discussion

Our results indicate an important relation between the year of publication of RCTs of lidocaine prophylaxis and the predicted incidence of primary VF in both the control and lidocaine-treated groups. This relation remained significant even after adjusting the predictor variable, year, for each of the other covariates. Although not precisely equivalent to the year(s) of enrollment of patients into an RCT, the year of publication of the RCT was selected because it allowed a single value to be applied for each RCT in the logistic regression analyses and was considered reasonably reflective of the general medical practice during the conduct of the RCT.

Reasons for Declining Incidence of VF

There are several possible explanations for the observation of a reduced incidence of VF in more recently conducted RCTs as noted below:

1) Application of broader admission criteria and availability of a larger number of coronary care unit beds compared with more restrictive entry criteria for admission to a limited number of coronary care unit beds may have resulted in admission of less critically ill patients with smaller MIs in more recent years.35

2) Administration of β-blockers to acute infarction patients became an accepted part of coronary care practice progressively over the last two decades.36 In addition, greater use of β-blockers for hypertension, angina pectoris, and cardiac arrhythmias over the last 20 years has increased the probability that a patient will enter the coronary care unit in the 1990s already receiving a β-blocker.37 These agents have been shown
to reduce the incidence of primary VF in patients with acute MI in several RCTs.\textsuperscript{38,39} It is also possible that β-blockers may help to reduce the tendency to VF by reducing infarct size, episodes of recurrent myocardial ischemia/MI and pain associated with infarction and by reducing the tendency to hypokalemia seen in the first 4 hours after the onset of acute infarction.\textsuperscript{40}

3) The risk of hypokalemia is probably lower now because of the availability of more effective afterload-reducing regimens (limiting the use of diuretics)\textsuperscript{8,41} and the now common clinical practice of aggressively correcting low serum potassium levels.\textsuperscript{42} It is unclear whether recent reports of the benefits of intravenous magnesium administration in reducing the risk of VF in acute infarction are reflected in the more recent RCTs of lidocaine, but if so, more aggressive use of intravenous magnesium may also be playing a role.\textsuperscript{43}

4) During the years covered by the RCTs analyzed in this report, there has been a decline in ischemic heart disease–related mortality as a result of improvements in lifestyle and medical interventions.\textsuperscript{57} Although by no means proven, the factors cited above along with the possibility of a more widespread use of anticoagulants, antiplatelet agents, and thrombolytic agents in the more recent RCTs of lidocaine may have resulted in a profile of infarction patients with less global myocardial damage, reduced tendency to hemodynamic derangements, lowered risk of recurrent ischemia/infarction, and a reduced overall tendency to VF.

5) The now commonplace use of intravenous morphine sulfate for pain relief and the introduction of the benzodiazepines and butyrophenones into the pharmacopeia may have resulted in a greater level of sedation and analgesia in patients enrolled in more recently performed RCTs of lidocaine prophylaxis.

The 18 RCTs were scrutinized for any information related to the following topics in an attempt to determine whether any of the above arguments could be confirmed in the current data set: infarct size, ventricular function, concurrent medical interventions (especially β-blockers, anticoagulants, antiplatelet agents, thrombolytic agents), and electrolyte disturbances. Unfortunately, the causes of the declining incidence of primary VF in patients with acute MI could not be determined with certainty because of inadequate primary data on these important variables in the RCTs analyzed. Although the majority of RCTs provided data on the method of diagnosis of MI, only seven\textsuperscript{17,20,25,29,30,32,34} provided any estimate of infarct size, but different measurement scales were used; only one gave an estimate of left ventricular function.\textsuperscript{34} Three RCTs reported the number of patients receiving a β-blocker at the time of admission,\textsuperscript{30,31,34} but none commented on whether intravenous β-blockers were used as part of general coronary care therapy during the trial. Only two RCTs provided the mean potassium levels in the patients studied (4.1–4.3 meq/l),\textsuperscript{20,34} Three RCTs\textsuperscript{17,24,30} published before 1983 commented that diuretics were used to treat congestive heart failure, only two\textsuperscript{20,34} commented on whether anticoagulants were used in the patients studied, none reported on the use of sedatives and anxiolytics in use in the intensive care unit during the trial, and only one RCT reported the number of patients treated with thrombolytic agents.\textsuperscript{34}

**Study Limitations**

A potential confounding effect that theoretically could have contributed in part to the progressive decline in the incidence of VF with the passage of years would be a systematic selection bias that resulted in lower-risk individuals being referred for enrollment in RCTs conducted more recently. Because the RCTs analyzed either provided no information on the patients who were screened but not enrolled or failed to describe adequately the patients who were rejected for randomization, this issue could not be extensively investigated. However, based on the data provided on the patients actually enrolled in the RCTs in which such information was available, it does not appear that individuals at lower risk of VF were selectively entered into more recently conducted RCTs. The mean age of the patients randomized in the eight RCTs reporting such information did not appear to be increasing in later studies (range, 55–66 years),\textsuperscript{20,24,25,28–30,32,34} By contrast, in the five RCTs reporting the number of hours that had elapsed from the time of onset of chest pain to administration of lidocaine, those RCTs conducted more...
recently tended to enroll patients sooner (4–6 hours elapsed) compared with those RCTs conducted in earlier years (8–15 hours). In view of the inverse relation between proximity in time to the onset of infarction and the probability of primary VF, these data would suggest that there may actually have been a bias toward higher-risk patients being enrolled in more recently conducted RCTs.

Although the 18 RCTs analyzed span two decades of coronary care medicine, the majority of the trials were performed between 1970 and 1980. Although a more limited data base was available for the decade between 1980 and 1990, the power of logistic regression methodology helps overcome this deficiency. Logistic regression of the predicted probability of VF versus year of publication of the RCT allows one to make smoothed estimates of the relative contributions from each year by borrowing information from surrounding years. In particular, it permits the prediction of risk of VF even for years in which scant information is available.

Finally, the data set used in this investigation had several examples of sample-based multicollinearity. The associations of year of publication of the RCT with the duration of monitoring and method of data analysis (intention to treat versus exclusion of randomized patients if acute MI was not confirmed) are particularly important examples because the more recent RCTs tended to use shorter durations of monitoring and the intention-to-treat method of analysis (a closer approximation to the decision-making process of clinicians when facing a patient with suspected acute infarction). Although this observation may explain some portion of the decline in the incidence of VF in more recent RCTs, it is unlikely to be playing a significant role. In view of the rapid decrease in the probability of VF as time elapses from the onset of chest pain (about 70% of episodes of VF occur within 4–6 hours and 85% within 24 hours), the value of each additional hour of monitoring decreases exponentially. Furthermore, the odds ratio for VF associated with the year of publication of the RCT changed only slightly after adjusting for the method of data analysis and duration of monitoring in both the control and lidocaine groups (Table 5).

Clinical Implications for the Prophylactic Use of Lidocaine

Based on the regression models developed from the data in these 18 RCTs, we estimated that in 1990, the incidence of primary VF on average for patients admitted to the coronary care unit would be 0.35% in the control group and about 0.10% for the lidocaine group. Thus, about 400 patients would currently need prophylaxis with lidocaine to prevent one episode of VF. These predictions are based on estimates for the average patient admitted to the coronary care unit in 1990 and are not adjusted for the gradient of risk as determined by other variables. In view of a lack of primary data on the impact of age, sex, and the duration of time from onset of chest pain to presentation for medical care, no adjustment could be made for these variables that have been determined by others to be predictive of the risk of VF. Also, no adjustments could be made for any changes in general coronary care practices that may have occurred during the conduct of the RCTs. Nevertheless, the data presented in this report are strongly indicative of a decrease in the risk of primary VF in acute MI as coronary care practice has evolved over the last two decades. Our data do not allow us to determine whether the treatment benefit of lidocaine prophylaxis is constant in patients with varying risks of primary VF. Assuming a constant relative risk of VF (i.e., treatment benefit) in all lidocaine-treated patients, for individuals who have a risk of VF currently that is three times that of the average risks noted above, approximately 130 individuals would require lidocaine prophylaxis to prevent one episode of VF.

Because the incidence of VF is decreasing in both the control and lidocaine groups as we now care for MI patients in the 1990s, estimates of the risk:benefit ratio of lidocaine prophylaxis should consider the low VF risk in control patients, the large number who need lidocaine prophylaxis to prevent one episode of VF, and the previously reported trend toward excess mortality in lidocaine-treated patients. Our observations support the contention of Ruskin that it now appears possible to reduce the risk of VF in the majority of patients (probably because of more widespread use of β-blockers and aggressive correction of hypokalemia) while avoiding the potential toxicity of lidocaine that occurs when the drug is used in a blanket prophylactic fashion for all patients. The benefits of empirical treatment with magnesium will be tested more formally in the ISIS-4 trial.

We propose that clinicians now markedly reduce the use of prophylactic lidocaine in the coronary care unit and eliminate the practice of routinely prescribing the drug simply because a patient is admitted with "rule out MI." In the absence of contraindications, β-blockers should be used intravenously early after presentation, and electrolyte disturbances should be corrected promptly in all patients. Supplemental protection against primary VF with prophylactic lidocaine should be reserved for settings in which rapid defibrillation is not possible, and even then, probably only for highly selected patients (absence of congestive heart failure or cardiogenic shock, age less than 65 years, and presentation within 6 hours of the onset of chest pain). Because of the rapidly decreasing risk of VF as time elapses from the onset of infarction, insuffusions should be of limited duration (6–12 hours). We hope that using lidocaine in such a more restricted and cost-effective fashion will still be associated with beneficial antiarrhythmic effects, no change in VF-related mortality (because of widespread availability of defibrillators), and a reduced risk of adverse drug effects.

The possibility of reperfusion ventricular arrhythmias after thrombolytic therapy has led some investigators to incorporate lidocaine prophylaxis as part of the treatment protocol. This is not a universal practice and deserves further investigation because the precise risks of primary VF in the lytic era of coronary care unit medicine are unclear, especially when β-blockers are used aggressively and electrolyte deficits are corrected promptly. Of note, preliminary data on the risk of VF in the control and treatment groups from RCTs of thrombolytic therapy for acute MI do not suggest that the decision to prescribe a thrombolytic agent should affect the threshold for administering lidocaine prophylactically, but additional information is required to answer this question more precisely.
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