Relation of Baseline Characteristics to Suppression of Ventricular Arrhythmias During Placebo and Active Antiarrhythmic Therapy in Patients After Myocardial Infarction

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In the Cardiac Arrhythmia Pilot Study (CAPS), patients early (6–60 days) after acute myocardial infarction (MI) with ventricular premature complexes (VPCs) of over 10 per hour were randomized to receive, unaware, therapy with one of four antiarrhythmic drugs (n=402) or placebo (n=100). Treatment success was defined as 70% or more decrease in VPC rate and 90% or more decrease in VPC runs. If the first active drug was ineffective, a second drug was given. If placebo was ineffective, a second placebo was given. To determine whether or not baseline clinical characteristics predict the response to antiarrhythmic therapy, 10 baseline variables were selected for investigation: age, prior MI, time from CAPS MI to randomization, ejection fraction, baseline VPC frequency, presence of runs (≥3 consecutive VPCs, ≥100 beats/min), β-blocker therapy, digitalis therapy, MI transmurality, and MI location. At the end of the first drug treatment, apparent treatment success in patients receiving placebo was associated with univariate analysis with absence of prior MI, with trends for younger age and Q wave MI, whereas in patients receiving active therapies, higher ejection fraction and younger age were associated with better suppression. In the encainide and flecainide treatments, where the greatest response was observed, absence of prior MI, higher ejection fraction, and younger age were associated with more successful treatment. In a multivariate analysis with these variables, ejection fraction and age remained significant for all active therapies, absence of prior MI and ejection fraction remained significant in the encainide and flecainide treatments, and absence of prior MI in the placebo treatment. Few variables except ejection fraction were associated with VPC suppression during the 1-year follow-up, and only lower ejection fraction and older age related to loss of long-term suppression. Thus, there are only a few independent baseline clinical variables (notably, ejection fraction) that substantially affect antiarrhythmic drug efficacy in suppressing VPCs in patients early after MI. Some variables, however, may be associated with spontaneous arrhythmia variability, leading to an apparent (placebo) response. These findings will be helpful in designing and interpreting treatment studies in patients after MI. (Circulation 1989;79:610–619)

Several clinical studies over the past 2 decades have indicated that the risk of cardiac mortality, especially from sudden arrhythmic death, is increased in patients after myocardial infarction (MI) who have frequent or complex ventricular arrhythmias.1–5 Although treatment of these patients with antiarrhythmic agents other than β-blockers6–9 has not yet been shown to reduce this risk,10 substantial interest in this possibility currently exists.11 A better understanding of patient characteristics associated with MI in the placebo treatment. Few variables except ejection fraction were associated with VPC suppression during the 1-year follow-up, and only lower ejection fraction and older age related to loss of long-term suppression. Thus, there are only a few independent baseline clinical variables (notably, ejection fraction) that substantially affect antiarrhythmic drug efficacy in suppressing VPCs in patients early after MI. Some variables, however, may be associated with spontaneous arrhythmia variability, leading to an apparent (placebo) response. These findings will be helpful in designing and interpreting treatment studies in patients after MI. (Circulation 1989;79:610–619)

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characteristics that may influence the ability of antiarrhythmic agents to suppress arrhythmias would be useful in developing effective strategies for management of individual patients and for the design of clinical trials. Further, knowledge of the variables that may be associated with increased spontaneous arrhythmia variability and that might cause a false-positive (or placebo) response would also be useful.

The Cardiac Arrhythmia Pilot Study (CAPS) was conducted to test the feasibility of suppressing arrhythmias effectively and safely in patients after MI. The careful characterization of baseline clinical variables and arrhythmia response in CAPS allowed us to test prospective hypotheses regarding relations between baseline variables and arrhythmia suppression.

Methods

The Cardiac Arrhythmia Pilot Study

CAPS tested the comparative efficacy of four antiarrhythmic regimens and placebo in patients after MI. A detailed summary of study design and primary results is presented elsewhere. Briefly, 502 patients from 10 centers were enrolled in CAPS. Patients who were early (6–60 days) after MI and who had 10 or more ventricular premature complexes (VPCs) per hour on a 24-hour ambulatory monitor recording and a left ventricular ejection fraction of 20% or greater were eligible. Patients with runs of 10 or more beats of ventricular tachycardia were excluded. Enrolled patients were randomly assigned to receive, unaware, one of five drug treatments: placebo, encainide, flecainide, imipramine, and moricizine. Treatment success was defined as at least a 70% decrease in VPC rate and 90% or more suppression of VPC runs of 3–9 beats at 100 beats/min or more.

The treatment approach included an initial dose-finding period in which up to three incremental doses of the assigned drug (1 dose/wk) were given until efficacy was achieved or until intolerable side effects occurred. Therapy during the first 2 days of the dose-finding period for each drug occurred during in-hospital monitoring. For inefficacious treatments or for those associated with significant adverse effects, a crossover to a second drug was undertaken. Patients receiving imipramine or moricizine were crossed over by a prerandomization design, if necessary, to receive either encainide or flecainide and vice versa. Patients receiving placebo were “crossed over” to placebo. The first drug regimen that achieved effectiveness was then continued for 1 year after randomization, regardless of later VPC counts.

Summary of Cardiac Arrhythmia Pilot Study Treatment Response

Table 1 summarizes the results at the end of the dose-finding period with the first drug assigned in CAPS. These results show a superior response to encainide and flecainide, an intermediate response to moricizine and imipramine, and the lowest, yet still substantial, response to placebo. All treatments showed a low initial proarrhythmic response. Tolerance was excellent for all treatments except for imipramine, in which 32% of the patients experienced intolerable adverse effects. Response and intolerance rates during long-term (1 year) therapy paralleled initial rates for the five treatments and are presented elsewhere.

Baseline Characteristics and Treatment Response

Selected baseline variables. The purpose of the present investigation was to assess the potential of selected baseline clinical characteristics to predict a successful antiarrhythmic response during the initial dose-finding phase in CAPS. In the first approach, the investigators prospectively selected 10 baseline variables that they thought could influence the efficacy of treatment. These included patient age, history of more than one MI, the time from CAPS MI to initiation of treatment, the left ventricular ejection fraction (determined by radionuclide ventriculography [in 86% of patients] or angiography [14%]), average VPC frequency per hour, the presence of runs of ventricular tachycardia (VT) of 3–9 beats (rate ≤100 beats/min) on the qualifying 24-hour recording, therapy with a β-blocker, therapy with digitalis, MI location (whether anterior or inferior), and MI transmurality (whether Q wave ["transmural"] or non–Q wave ["nontransmural"]). Continuous variables (age, ejection fraction, VPC frequency, and time from CAPS MI) were continuous covariates in the analysis.

Because of the substantial differences in observed VPC suppression and group size between the active therapy (n = 402) and placebo (n = 100) cohorts, analyses were performed separately for these two groups. Additional analyses were performed for the combined encainide and flecainide treatments (the most successful therapies).

Endpoints of analysis. Primary analysis was based on the outcome at the end of the dose-finding phase of drug 1 (up to three dose increments were allowed). Secondary analyses were based on outcomes after the first dose of the first drug, at the end of the dose-finding period in the placebo group, and during long-term therapy as measured by average VPC suppression at 3, 6, 9, and 12 months of follow-up. Analysis of outcome at the end of the dose-finding

<table>
<thead>
<tr>
<th>Drug (n)</th>
<th>Efficacy (%)</th>
<th>Proarrhythmia (%)</th>
<th>Other* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flecainide (103)</td>
<td>83</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Encainide (99)</td>
<td>79</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Moricizine (98)</td>
<td>66</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Imipramine (102)</td>
<td>52</td>
<td>1</td>
<td>32</td>
</tr>
<tr>
<td>Placebo (100)</td>
<td>37</td>
<td>3</td>
<td>11</td>
</tr>
</tbody>
</table>

*Other cardiac and noncardiac effects leading to discontinuation.
period in the actively treated cohort was not used in
the primary analysis because true relations (those
presumably present for most patients suppressed on
dose 1 of drug 1) and false relations (those that may
occur on the basis of spontaneous variability, espe-
cially in patients undergoing up to six evaluations
on two drugs) would be more difficult to untangle.

Analytic approaches. The univariate relations
between each of these 10 factors and the outcome
variables were examined for significance based on
logistic regression. A p value of 0.05 or less (with
two-tailed tests) was considered potentially signifi-
cant, and a p value of 0.005 or less was considered
definitively significant, given the multiple compar-
sions. A multivariate logistic analysis was per-
formed on these investigator-selected variables with
a stepwise logistic approach in which the individual
variables were selected sequentially to form an
overall predictive model for successful suppression.

In a second approach, all 61 recorded baseline
clinical and laboratory variables (Appendix 2) were
screened to explore the possible importance to
arrhythmia suppression of factors other than those
selected by the investigators. In the first 251 patients,
these variables were examined in a univariate man-
ner for 1) active therapy, 2) placebo, and 3) enca-
idine and flecainide treatment groups. Variables that
yielded nominal significance (p≤0.15) were included
in a multivariate stepwise regression analysis that
was run on the second 251 patients. In this way, the
potential for chance associations was reduced.

Variables related to false suppression were also
looked for in actively treated patients who were
initially suppressed by regressing these variables, in
a stepwise linear fashion, on the loss of suppression
outcome during follow-up. For the purposes of this
analysis, loss of suppression was defined as suppres-
sion on 3, 6, 9, and 12 months of follow-up Holter
electrocardiographic recordings averaging less than
half of that determined initially at the end of success-
ful dose titration (i.e., <50% if initial suppression was
100%, <35% if initial suppression was 70%, etc.).

Some baseline variables may also be important
predictors of certain adverse events during antiar-
rhythmic therapy. Accordingly, the following analy-
ses were performed with baseline variables as they
related to other cardiac events. First, the number of
events of proarrhythmia, ventricular tachyarrhyth-
my (whether or not proarrhythmic), recurrent MI,
heart failure (grade II or III [14]), and noncardiac
side effects were determined for several major period-
group combinations (i.e., drug 1 dose-finding and
1-year follow-up intervals, for active and placebo
therapies, and for encaidine and flecainide treat-
ments by both initial and total, including crossover
assignment). Next, logistic regressions were per-
formed of the specific adverse events on the 10
covariates for combination sets with enough events
to be remotely meaningful (> 5 events), likely mean-
ingful (> 10 events), and most likely meaningful (> 15
events). The p value and odds ratio results of analy-

ses for sets with fewer than 15 events should be
viewed with some skepticism because of the substan-
tial change in model fitting that can occur in these
instances by shifting as few as one event.

Results

Univariate Analysis of Variables
Selected Prospectively

Relation of baseline variables to initial responses. Table 2 lists the results of the univariate analysis of
baseline variables (n = 10) selected prospectively by
the investigators. Arrhythmia suppression at the
end of the dose-finding phase with the first drug was
significantly related to some of the baseline vari-
ables in placebo and active drug groups. In the
placebo group, only history of previous MI was a
predictor, with trends for age and MI transmurality.
In the combined experience with all active antiar-
rhythmic agents, only ejection fraction and age
were significant predictors. When analysis was
restricted to encaidine and flecainide treatments,
significant relations between arrhythmia suppres-
sion and history of prior MI, ejection fraction, and
age were observed.

Age and response. Figure 1 shows antiarrhythmic
efficacy at end of treatment with drug 1 as a function
of age for active and placebo therapies. A small (but
significant) decrease in responsiveness to active
therapy was observed with increasing age, and a
progressive decrease in responsiveness to placebo
was observed with increasing age.

History of myocardial infarction and response. A
history of prior MI (before the CAPS qualifying MI)
as a significant baseline predictor of response to
placebo (p≤0.014) and to active therapy with enca-
dine or flecainide (p≤0.001). As shown in Figure 2,
the chance of "responding" to placebo at the end of
drug 1 treatment was reduced from 44% to 23% in
the presence of a prior MI. Similarly, treatment
efficacy with encaidine or flecainide was reduced
from 88% to 68%. When experience with all four
active drugs was combined, however, the trend was
no longer significant (p≤0.20). The effects of prior
MI on variability were independent of baseline
frequency of VPCs, which were similarly distrib-
uted in those with (n = 151 patients; mean, 143±252
VPCs/hr; median, 41/hr) and without prior MI
(n = 35 patients; mean, 136±224 VPCs/hr; median,
51/hr).

Ejection fraction and response. Ejection fraction
was an important determinant of response to active
therapy at the end of dose-finding with drug 1
(p≤0.009). The decreasing response rate observed
for therapy with encaidine or flecainide (p≤0.012)
with decreasing ejection fractions is shown in
Figure 3. In these treatments, response was 68% for
patients in the lowest decile bracket of ejection
fraction and 90% in patients in the highest. In the
placebo group, a lower response rate trend was
observed only in those with ejection fractions less
Table 2. Significance Levels for Univariate Tests: Effects of 10 Selected Baseline Variables on Efficacy of First Assigned Drug

<table>
<thead>
<tr>
<th>Baseline variable</th>
<th>Placebo (p)</th>
<th>All active (p)</th>
<th>Encainide and flecainide (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>A. 0.11</td>
<td>0.40</td>
<td>0.48</td>
</tr>
<tr>
<td></td>
<td>B. 0.076</td>
<td>0.020 (-)</td>
<td>0.031 (-)</td>
</tr>
<tr>
<td></td>
<td>C. 0.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior MI</td>
<td>A. 0.21</td>
<td>0.32</td>
<td>0.019 (-)</td>
</tr>
<tr>
<td></td>
<td>B. 0.014 (-)</td>
<td>0.20</td>
<td>0.001 (-)</td>
</tr>
<tr>
<td></td>
<td>C. 0.046</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time after MI</td>
<td>A. 0.57</td>
<td>0.51</td>
<td>0.61</td>
</tr>
<tr>
<td></td>
<td>B. 0.40</td>
<td>0.97</td>
<td>0.68</td>
</tr>
<tr>
<td></td>
<td>C. 0.70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>A. 0.23</td>
<td>0.002 (+)</td>
<td>0.006 (+)</td>
</tr>
<tr>
<td></td>
<td>B. 0.91</td>
<td>0.009 (+)</td>
<td>0.012 (+)</td>
</tr>
<tr>
<td></td>
<td>C. 0.062</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VPCs/hr</td>
<td>A. 0.65</td>
<td>0.21</td>
<td>0.70</td>
</tr>
<tr>
<td></td>
<td>B. 0.25</td>
<td>0.96</td>
<td>0.79</td>
</tr>
<tr>
<td></td>
<td>C. 0.42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VPC runs present</td>
<td>A. 0.30</td>
<td>0.52</td>
<td>0.77</td>
</tr>
<tr>
<td></td>
<td>B. 0.46</td>
<td>0.20</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>C. 0.26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blocker use</td>
<td>A. 0.01 (+)</td>
<td>0.075</td>
<td>0.77</td>
</tr>
<tr>
<td></td>
<td>B. 0.14</td>
<td>0.35</td>
<td>0.80</td>
</tr>
<tr>
<td></td>
<td>C. 0.54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digitalis use</td>
<td>A. 0.48</td>
<td>0.16</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>B. 0.36</td>
<td>0.36</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td>C. 0.20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI transmurality</td>
<td>A. 0.18</td>
<td>0.82</td>
<td>0.83</td>
</tr>
<tr>
<td>(Q wave MI)</td>
<td>B. 0.097 (+)</td>
<td>0.47</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>C. 0.08 (+)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI location</td>
<td>A. 0.51</td>
<td>0.28</td>
<td>0.41</td>
</tr>
<tr>
<td>(Anterior)</td>
<td>B. 0.47</td>
<td>0.89</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td>C. 0.73</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A, Drug 1, dose 1 determinations; B, end of dosing determinations for drug 1 (three possible determinations, one for each drug increment). Average number determinations: all active drugs, 1.3±0.6; encainide and flecainide, 1.3±0.5; placebo, 1.7±0.7. B was prospectively defined as the primary parallel comparison point. C, end of dosing for placebo (two possible “drugs,” six possible determinations, one for each placebo dose step). Average number determinations: all placebo, 2.9±1.8.

(-), less efficacy; (+), more efficacy in presence of factor or larger values of factor.

than 30%, but the overall response was not significantly different by a linear test of trends.15

Multivariate Variables Predicting Initial Response

When a multivariate analysis was performed on the 10 prospectively selected variables by stepwise logistic regression, the results in Table 3 were obtained. Ejection fraction and age were selected as multivariate predictors of response to the combined active treatments at the end of drug 1 dose-finding. History of previous MI, ejection fraction, and age were selected as predictors for encainide and flecainide, which were the most effective treatments. (The odds ratio of responding was 0.32 in patients who had unfavorable entries for all three of these variables). History of previous MI was the only multivariate predictor in the placebo group.

Relation of Selected Baseline Variables to Long-term (1-Year) Response

Relations of baseline variables with long-term (1-year) response differed slightly from that for short-term response (Table 4). For the prospectively defined CAPS efficacy endpoint of 70% or more average VPC suppression, selected multivariate baseline predictors included ejection fraction and VPC runs for patients in all active treatment groups and, likewise, ejection fraction and VPC runs for patients receiving encainide and flecainide. No long-term predictors emerged in the placebo group.

Baseline variables predicting loss of initial suppression. Among actively treated patients with an initial successful response (≥70% VPC suppression) during dose titration on active therapy, lower ejection fraction (p=0.007) and older age (p=0.025) were significant predictors of reduced VPC suppression during long-term follow-up, by a multivariate stepwise logistic regression of these 10 selected baseline variables on reduced suppression outcome (Table 5).

Relation of Baseline Variables to Adverse Reactions

The relation of baseline variables to the development of proarrhythmic events, heart failure, and dose- or drug-altering side effects was also investigated. None of the variables predicted an altered risk of proarrhythmic events, during either the dose-finding or follow-up periods. In contrast, the occurrence of ventricular tachyarrhythmia not fulfilling the criteria for proarrhythmia occurred with increased frequency in patients with depressed ejection fraction treated with either active drugs or placebo, both during the dose-finding period (on drug 1) and during long-term follow-up (active therapy during dose-finding: odds ratio, 4.0, p<0.001; active therapy during follow-up: odds ratio, 1.8, p=0.001; placebo therapy during dose-finding: odds ratio, 2.1, p=0.034; placebo therapy during follow-up: odds ratio, 2.5, p=0.003, both for a 10-point decrement in ejection fraction). An increased risk of heart failure during active therapy was also predicted by a lower ejection fraction, during dose-finding (odds ratio, 2.0, p=0.013) and during long-term follow-up (odds ratio, 1.5, p=0.001); an equivalent risk was also observed in patients receiving placebo (drug 1 dose-finding: odds ratio, 2.4, p=0.036; long-term follow-up: odds ratio, 1.7, p=0.013). Other predictors of heart failure during
active therapy included digitalis use (dose-finding, odds ratio, 2.1, \( p = 0.034 \); long-term follow-up, odds ratio, 1.6, \( p \leq 0.002 \)), entry time closer to MI (dose-finding: odds ratio, 1.5, \( p = 0.007 \), for 10 days earlier; long-term follow-up: odds ratio, 1.2, \( p = 0.006 \)), and presence of baseline runs (long-term follow-up: odds ratio, 1.3, \( p = 0.034 \)). An increased incidence of noncardiac side effects during active therapy was predicted by greater age but only during the initial dose-finding period (odds ratio, 1.9 for 10-year increase in age, \( p = 0.002 \)).

Discussion

Summary of Predictors of Ventricular Premature Complex Suppression

Analysis of the CAPS experience shows a paucity of independent relations between baseline clinical factors in patients after MI and the ability of an antiarrhythmic drug to effectively reduce spontaneous ventricular ectopy and to sustain long-term suppression. A low ejection fraction was the most consistent, though not a particularly strong, predictor of a poor response. Clinical and laboratory evidence for poor left ventricular function is also a strong predi-

Figure 1: Bar graph of percentage of patients achieving initial antiarrhythmic efficacy (Cardiac Arrhythmia Pilot Study criteria) for placebo and active drug therapy as a function of patient age.

Figure 2: Bar graph of percentage of patients achieving initial antiarrhythmic efficacy for therapy with placebo, all active drugs, and encainide (Enc) or flecainide (Flec) according to the presence or absence of a history of prior myocardial infarction (before the Cardiac Arrhythmia Pilot Study qualifying Myocardial Infarction).

Figure 3: Bar graph of percentage of patients achieving initial antiarrhythmic efficacy for therapy with placebo compared with encainide (Enc) or flecainide (Flec) as a function of baseline radionuclide left ventricular ejection fraction (%).

tor of mortality risk in other studies\(^{16-18}\) and in CAPS (unpublished observations from this study). This suggests that the ability to suppress VPCs may be largely independent of baseline clinical characteristics for patients qualifying to enter CAPS (i.e., those with left ventricular ejection fraction >20\% and without severe heart failure). Another observation is that successive Holter monitoring does run a certain risk of showing an apparent drug "response" because of arrhythmia spontaneous variability or natural history (spontaneous improvement) as shown by responses in the placebo group.

Of the 10 univariate predictors selected by the investigators, only absence of previous MI related significantly to an apparent initial response to placebo therapy at the primary comparison endpoint (end of drug 1 dose-finding), with trends for younger age and Q wave MI. The strength of these relations was inconsistent upon secondary placebo analyses (Table 2) (i.e., not as strong on the first recording on placebo and again becoming weaker during long-term observations). Predictors of success for active antiarrhythmic therapy were limited to ejection fraction, prior MI, and age for encainide and flecainide, the most effective therapies, and to only ejection fraction and age for all active therapies. The association of prior MI and probably age with response in both placebo and active therapy groups indicates that these relations may primarily relate to greater arrhythmia variability or natural history (spontaneous change) early after MI rather than to true drug effect.

Although ejection fraction appears to emerge as one of the sole predictors of true response to active therapy, the difference in response between patients in the lowest entry bracket of ejection fraction (20–30\%) and patients in the highest (>60\%) was rather modest (response difference, approximately 20\%). Thus, in patients with low ejection fractions (but >20\%), a fair-to-good response to therapy can still be achieved. Ejection fraction was also the most
consistent variable to emerge as a predictor of long-term response, with presence of VPC runs at baseline also suggested in some of the analyses. Finally, low ejection fraction and advanced age were associated with an increased risk of losing an initially successful VPC suppression response during long-term follow-up.

Although the 10 baseline variables were carefully selected, other important predictors may have existed among the 61 recorded characteristics. Thus, an exploratory (screening) analysis of all 61 baseline variables was performed (data not presented). Other than ejection fraction, this screening analysis did not reveal important and consistent predictors of initial (or long-term) response. Ejection fraction again emerged as a predictor of initial response to all active therapies, and ejection fraction and the related function variable, New York Heart functional class, predicted response to encainide and flecainide. An apparent relation of bypass surgery to long-term (but not initial) response in this screening analysis is viewed with caution, given the lack of other supporting observations and the multiplicity of tests. Height of the creatine kinase peak, a measure of infarct size, positively correlated with initial response to placebo, but no factors predicted long-term response.

**Summary of Predictors of Adverse Events**

Successful antiarrhythmic therapy depends not only on successful arrhythmia suppression but also on avoiding treatment-related adverse effects. Increasing age, but no other variables, predicted a higher incidence of noncardiac side effects; this variable lost significance, however, when analysis was restricted to only treatment with encainide or flecainide, which are both well-tolerated agents. Proarrhythmia did not relate to any baseline factor although spontaneously appearing ventricular tachyarrhythmia was more frequent in those with depressed ejection fraction. Similarly, heart failure occurred with a greater incidence in those with a depressed ejection fraction, but this applied equally to those on active and placebo therapy, suggesting that natural history of disease rather than antiarrhythmic therapy was the cause of heart failure. In summary, few adverse effects specifically related to

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Variable</th>
<th>p</th>
<th>Odds ratio</th>
<th>Direction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All active</td>
<td>Ejection fraction</td>
<td>0.008</td>
<td>0.77Δ10 points</td>
<td>Lower EF results in less suppression</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>0.014</td>
<td>0.71/decade</td>
<td>Older age results in less suppression</td>
</tr>
<tr>
<td>Encainide and flecainide</td>
<td>Prior (&gt;1) MI</td>
<td>0.002</td>
<td>0.63</td>
<td>Prior MI results in less suppression</td>
</tr>
<tr>
<td></td>
<td>Ejection fraction</td>
<td>0.038</td>
<td>0.71Δ10 points</td>
<td>Lower EF results in less suppression</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>0.051</td>
<td>0.63/decade</td>
<td>Older age results in less suppression</td>
</tr>
<tr>
<td>Placebo (&quot;drug&quot; 1)</td>
<td>Prior (&gt;1) MI</td>
<td>0.011</td>
<td>0.45</td>
<td>Prior MI results in less suppression</td>
</tr>
<tr>
<td>Placebo (&quot;drug&quot; 1 and 2)†</td>
<td>Prior (&gt;1) MI</td>
<td>0.044</td>
<td>0.63</td>
<td>Prior MI results in less suppression</td>
</tr>
</tbody>
</table>

MI, myocardial infarction; EF, ejection fraction.
*Multivariate analysis, using stepwise logistic regression, of variables related to efficacy for various treatments at the end of dose-finding for drug 1, in order of significance with incremental p values.
†Analysis at the end of placebo (includes "drug 1" and "drug 2" placebo testing).

---

**Table 3. Multivariate Predictors Among 10 Selected Baseline Variables of Initial Arrhythmia Suppression***

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Univariate predictors</th>
<th>Direction</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>VPC suppression (CAPS) criteria*</td>
<td>EF (0.008)</td>
<td>-†</td>
<td>0.80†</td>
</tr>
<tr>
<td>All Active</td>
<td>Runs (0.02)</td>
<td>(0.02)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>History of MI (0.07)</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>Floxacinide and encaainide</td>
<td>EF (0.02)</td>
<td>(0.06)</td>
<td>-†</td>
</tr>
<tr>
<td>By primary assignment</td>
<td>Runs (0.02)</td>
<td>(0.02)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>β-blocker (0.03)</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td></td>
<td>Q Wave MI (0.10)</td>
<td>(0.06)</td>
<td>+</td>
</tr>
<tr>
<td>Placebo exposure</td>
<td>EF (0.07)</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Runs (0.03)</td>
<td>(0.03)</td>
<td>-</td>
</tr>
</tbody>
</table>

* ≥70% average reduction if 0.7 ≤[(VPC/hr at EOD+VPC/hr at 3 mo+6 mo+9 mo+12 mo)/5]/[(VPC/hr at baseline+VPC/hr at 12 mo washout+VPC/hr at any other washout)/(2+number of other washouts)]. Patients analyzed by intention to treat.
†For Δ=10-point decrease.
EF, ejection fraction; MI, myocardial infarction; VPC, ventricular premature complex.

---

**Table 4. Univariate and Multivariate Predictors Among 10 Selected Baseline Variables of Long-term (1 year) Response**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients analyzed (n)</th>
<th>Univariate predictors (p)</th>
<th>Multivariate predictors (p)</th>
<th>Direction of effect</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>VPC suppression (CAPS) criteria*</td>
<td>EF (0.008)</td>
<td>(0.008)</td>
<td>-†</td>
<td>0.80†</td>
<td></td>
</tr>
<tr>
<td>All Active</td>
<td>Runs (0.02)</td>
<td>(0.02)</td>
<td>-</td>
<td>0.76</td>
<td></td>
</tr>
<tr>
<td></td>
<td>History of MI (0.07)</td>
<td>. . .</td>
<td>. . .</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Floxacinide and encaainide</td>
<td>EF (0.02)</td>
<td>(0.06)</td>
<td>-†</td>
<td>0.74†</td>
<td></td>
</tr>
<tr>
<td>By primary assignment</td>
<td>Runs (0.02)</td>
<td>(0.02)</td>
<td>-</td>
<td>0.68</td>
<td></td>
</tr>
<tr>
<td></td>
<td>β-blocker (0.03)</td>
<td>. . .</td>
<td>. . .</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Q Wave MI (0.10)</td>
<td>(0.06)</td>
<td>+</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Placebo exposure</td>
<td>EF (0.07)</td>
<td>None</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Runs (0.03)</td>
<td>(0.03)</td>
<td>-</td>
<td>0.72</td>
<td></td>
</tr>
</tbody>
</table>

* ≥70% average reduction if 0.7 ≤[(VPC/hr at EOD+VPC/hr at 3 mo+6 mo+9 mo+12 mo)/5]/[(VPC/hr at baseline+VPC/hr at 12 mo washout+VPC/hr at any other washout)/(2+number of other washouts)]. Patients analyzed by intention to treat.
†For Δ=10-point decrease.
EF, ejection fraction; MI, myocardial infarction; VPC, ventricular premature complex.
antiarrhythmic therapy were predicted by baseline variables in the CAPS population. Thus, predictors of antiarrhythmic efficacy are also likely to predict overall antiarrhythmic success, defined as successful suppression without limiting adverse effects, especially when well-tolerated agents such as encainide, flecainide, and moricizine are considered.

**Predicting Mortality Risk**

In contrast to the weak or inconsistent value of baseline variables to predict response of ambulatory ventricular arrhythmia frequency, measures of ventricular dysfunction have strongly and consistently predicted mortality in studies in patients after MI, including studies in which patients were not selected for ventricular arrhythmia or treatment status.2-5,16-25

**Previous Studies Evaluating Baseline Predictors**

Little previous information is available about the role of baseline clinical characteristics in determining antiarrhythmic drug response for patients after MI with unsustained ventricular arrhythmias although some has been forthcoming for patients with sustained arrhythmias. In patients with sustained ventricular tachyarrhythmias in whom treatment is directed electrophysiologically by programmed electrical stimulation, predictors of treatment success have been assessed and have included young age and otherwise little organic heart disease.22,23 Predictors of treatment failure have included indexes of poor left ventricular function (and left ventricular aneurysm) in the setting of coronary artery disease and frequently occurring, readily induced ventricular tachyarrhythmia.22,23 The nature of the spontaneous and induced arrhythmia and the number of previous empiric drug trials are other predictors of outcome for patients with these more malignant ventricular arrhythmias.22-24

In patients having a history of sustained ventricular tachyarrhythmias in whom therapy is guided by noninvasive measures, a recent study found that arrhythmia density on ambulatory monitoring and left ventricular function were independent predictors of the ease of arrhythmia suppression.25 Long-term outcome correlated with left ventricular dysfunction and the responsiveness of monitored arrhythmias to antiarrhythmic drugs. Thus, indexes of poor ventricular function consistently predict a suboptimal response to antiarrhythmic therapy and to cardiac arrest or death, both in patients with a history of unsustained (but prognostically important) ventricular arrhythmias (this study) and the patients with sustained (malignant) ventricular tachyarrhythmias.22-25

**Implications for Future Studies**

The observation that treatment response of unsustained ventricular arrhythmias is not highly dependent on baseline patient characteristics is useful for the planning of further and larger scale intervention trials in patients after MI who have spontaneous ventricular arrhythmias. The Cardiac Arrhythmia

---

### Table 5. Predictors Among 10 Selected Baseline Variables of Loss of Initial VPC Suppression

<table>
<thead>
<tr>
<th>Baseline variable*</th>
<th>Loss of response % (n)</th>
<th>Multivariate p</th>
<th>Direction</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yr)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 55</td>
<td>19 (19/100)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>55–64</td>
<td>28 (37/132)</td>
<td>0.025</td>
<td>+</td>
<td>1.32†</td>
</tr>
<tr>
<td>≥ 65</td>
<td>32 (34/107)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prior MI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>33 (30/90)</td>
<td>NS</td>
<td>. .</td>
<td>. .</td>
</tr>
<tr>
<td>No</td>
<td>24 (60/244)</td>
<td>NS</td>
<td>. .</td>
<td>. .</td>
</tr>
<tr>
<td><strong>Time after MI (wk)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 6</td>
<td>29 (66/224)</td>
<td>NS</td>
<td>. .</td>
<td>. .</td>
</tr>
<tr>
<td>≥ 6</td>
<td>21 (24/115)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ejection fraction (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 35</td>
<td>42 (32/77)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35–50</td>
<td>21 (28/133)</td>
<td>0.007</td>
<td>-</td>
<td>0.78‡</td>
</tr>
<tr>
<td>&gt; 50</td>
<td>23 (30/129)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>VPC runs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>34 (36/105)</td>
<td>NS</td>
<td>. .</td>
<td>. .</td>
</tr>
<tr>
<td>No</td>
<td>28 (52/231)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>β-Blockade</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>22 (30/139)</td>
<td>NS</td>
<td>. .</td>
<td>. .</td>
</tr>
<tr>
<td>No</td>
<td>30 (60/200)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*MI, myocardial infarction; VPC, ventricular premature complex.

*VPC rate/hour (5), digitalis therapy (8), and MI location (10) had no effect.

†For age increase of 10 years.

‡For ejection fraction increase of 10 percentage points.
Suppression Trial (CAST), which was initiated in 1987, is one such study. In CAST, the hypothesis that suppressing ventricular arrhythmias reduces cardiac mortality, especially sudden (arrhythmic) death, is being tested. For these studies, our findings indicate that a high response rate to certain antiarrhythmic agents (such as encainide and flecainide) may be expected, independent of baseline clinical variables, with the exception that patients with very poor left ventricular function or clinical heart failure or both may show a moderately lower rate of true drug response. However, patients with poor left ventricular function, though responding less well to therapy, have a higher overall mortality, justifying their inclusion despite greater difficulty in suppressing arrhythmia. Those with better function respond very well and show this antiarrhythmic response in the absence of limiting adverse events, suggesting their inclusion, too, despite their lower expected sudden death rates. Thus, based on the observations of CAPS, patients at risk with relatively good, as well as poor, left ventricular function should be included in future mortality trials of antiarrhythmic therapy.

Acknowledgment
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Coordinating Center: University of Washington: A Hallstrom, PhD, *MJ Gillespie, MS, L Greene, MD.

Project Office: National Heart, Lung and Blood Institute: L Friedman, MD, J Verter, PhD, S Yusuf, MD, CE Harris, E Schron, RN, MS.

Appendix 2. Clinical Baseline Variables

Historical Factors Before Qualifying Myocardial Infarction
1. Sustained hypertension
2. Cerebrovascular disease
3. Peripheral arterial disease
4. Valvular heart disease or prior valvular surgery or both
5. Chronic pulmonary disease
6. Fainting spells or blackouts
7. History of cardiac arrest or ventricular fibrillation before day 6 or both and/or syncope
8. History of prior myocardial infarction
9. Prior coronary artery bypass graft surgery
10. Prior congestive heart failure and congestive heart failure impairment
11. Chest pain more than 7 days before myocardial infarction and type of pain
12. Nitrates taken before myocardial infarction
13. Potassium supplement taken before myocardial infarction
14. Antiarrhythmic drug taken before myocardial infarction
15. New York Heart Association activity classification

Peri-infarction Variables (From Time of Hospital Admission to Randomization)
16. Age
17. Pericardial rub with pain

*Principal Investigator
18. Vasodilator therapy on day of baseline study
19. Diuretic therapy on day of baseline study
20. Coronary artery bypass graft surgery or other cardiac surgery after CAPS myocardial infarction
21. β-blocker therapy on day of baseline study
22. Calcium entry blocker therapy on day of baseline study
23. Potassium supplement therapy on day of baseline study
24. Chest pain day 6–15 postmyocardial infarction and type of pain
25. Days onset of myocardial infarction to ambulatory electrocardiogram

Indicators of Heart Failure (Admission to Randomization)

26. Shock (oliguria and systolic blood pressure < 90 mm Hg)
27. Pulmonary edema
28. Congestive heart failure (S3, chest x-ray, rales) requiring treatment
29. Chest x-ray—cardiac enlargement
30. Chest x-ray—pulmonary venous congestion or Kerley B lines or both
31. Chest x-ray—pleural effusion

Electrocardiographic Characteristics of Myocardial Infarction

32. PR interval
33. QRS duration
34. QT interval
35. Sinus bradycardia (< 60 beats/min)
36. Sinus tachycardia (> 100 beats/min)
37. Right bundle branch block
38. Q waves diagnostic of myocardial infarction
39. CAPS myocardial infarction transmurality: Q wave, non–Q wave
40. Myocardial infarction: anterior, inferior, mixed, unknown

Major Therapeutic Interventions

41. Streptokinase infusion
42. Percutaneous transluminal coronary angioplasty
43. Coronary artery bypass graft surgery or other cardiac surgery after CAPS myocardial infarction
44. Myocardial infarction occurred after coronary artery bypass graft surgery

Findings on Physical and Laboratory Examinations

45. Supine heart rate
46. Supine systolic blood pressure
47. Jugular venous distension or hepatojugular reflux
48. Pulmonary rales
49. S3 sound
50. S4 sound
51. Mitral regurgitant murmur
52. Hepatic enlargement
53. Edema of lower extremities
54. Hematology: white cell count
55. Chemistries: chloride
56. White cell count within laboratory normal range
57. Potassium within laboratory normal range
58. Alkaline phosphatase within laboratory normal range
59. Ambulatory electrocardiogram obtained within hospital
60. Maximal creatine phosphokinase, total/upper limit of normal total creatine phosphokinase
61. Left ventricular ejection fraction

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17. Hammermeister KE, DeRouen TA, Dodge HT: Variables predictive of survival in patients with coronary disease: Selection by univariate and multivariate analyses from the clinical

**KEY WORDS** • antiarrhythmic therapy • arrhythmias • clinical trial • patient characteristics • ventricular arrhythmias
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