Effect of Empiric Antiarrhythmic Therapy in Resuscitated Out-of-Hospital Cardiac Arrest Victims with Coronary Artery Disease

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The effect of empiric antiarrhythmic therapy with quinidine and procainamide on long-term mortality was examined in 209 patients with coronary artery disease resuscitated after out-of-hospital cardiac arrest. The antiarrhythmic agent used was determined by the patient's private physician without knowledge of the study ambulatory electrocardiogram. Of the 209 patients, procainamide was prescribed in 45 (22%), quinidine in 48 (23%) and no antiarrhythmic therapy in 116 (55%). Digoxin therapy was initiated in 101 patients. The 2-year total survival rate for the quinidine, procainamide and nontreated patients was 61, 57 and 71% ($p < 0.05$), and for sudden death was 69, 69 and 89% ($p < 0.01$), respectively. These observations suggest that empiric antiarrhythmic therapy in survivors of out-of-hospital cardiac arrest did not affect total mortality and was associated with an increased frequency of sudden death.

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The efficacy of antiarrhythmic agents in patients with cardiovascular disease is currently being re-evaluated in the light of new clinical data.[1] Although these drugs are effective in suppressing ventricular arrhythmias, they have not been shown to prolong life in a randomized controlled trial. The recent reports of the Cardiac Arrhythmia Suppression Trial indicate that certain drugs may actually be associated with an accelerated mortality despite their ability to suppress ventricular ectopy. Victims resuscitated after out-of-hospital cardiac arrest are known to be at an increased risk of another cardiac arrest. Frequent ventricular ectopy is known to be a characteristic of these patients,[2,3] and it is presumed that treatment with antiarrhythmic agents may have a salutary effect on their mortality rate. Several studies in patients with frequent ventricular ectopy using a variety of antiarrhythmic agents with and without electrophysiologic guidance report a decrease in mortality rate when compared to historical controls.[4–6]

In a previous report by us, the most significant clinical predictor of total mortality in this group of resuscitated out-of-hospital survivors was a history of digoxin therapy; for sudden death it was quinidine therapy.[3] Frequent and repetitive ventricular ectopy was also demonstrated to be predictive of total mortality in this population.[7] The increased mortality rate associated with digoxin and quinidine therapy was thought to be due either to the adverse effect of the drugs or to the presence of heart failure for which digoxin therapy could be considered a surrogate. This study retrospectively compares the effect of empiric therapy with quinidine, procainamide or placebo, with and without concurrent digoxin therapy, on survival in patients who have been resuscitated after an out-of-hospital cardiac arrest.

METHODS

This is a retrospective analysis of the effect of empiric antiarrhythmic therapy in previously reported patients resuscitated after out-of-hospital cardiac arrest[3] from July 1, 1975, through June 30, 1982. Informed consent was obtained and eligible patients were registered. Laboratory and electrocardiographic data were collected. Hospital and Emergency Medical Service records were reviewed for clinical information relating to medical history. Because study ambulatory electrocardiographic data were not available at the time of dis-

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charge or at any time during the follow-up, the medical management of patients in regard to treatment of cardiac failure and arrhythmias was determined by each patient's private physician without regard to this information.

The patients were classified using previously described methodology.[3] Of the 274 patients successfully resuscitated, 227 (83%) were classified as having significant coronary heart disease, based on the presence of a previous myocardial infarction, angina pectoris or coronary angiographic evidence of significant coronary arterial obstruction. Of these 227 patients, complete data regarding digoxin and antiarrhythmic drug therapy were available in 209 (76%) patients. This group of 209 patients is the population analyzed in this study. Eighty-six (41%) of these patients were classified as having an acute myocardial infarction, 79 (38%) an ischemic event and 44 (21%) primary arrhythmic events. Patients were interviewed by the study nurse 2 months after discharge, and every 4 months thereafter. After each visit the clinical status of the patient was evaluated and compliance for all medication was established.

Death within 1 hour of new or accelerating symptoms was classified as sudden death. The follow-up period ranged from a minimum of 6 months to a maximum of 93 months with an average of 35 months. Quinidine was prescribed as quinidine gluconate or sulfate 3 to 4 times daily for a total average dose of 1.14 g (range 0.6 to 2.6). The average daily dose of procainamide was 2.0 g (range 0.75 to 3.0) administered every 4 to 6 hours. Digoxin was prescribed in a dose of 0.125 or 0.25 mg. Blood concentrations of the drugs were not obtained.

The cumulative mortality graphs for antiarrhythmic agents were based on assignment of antiarrhythmic

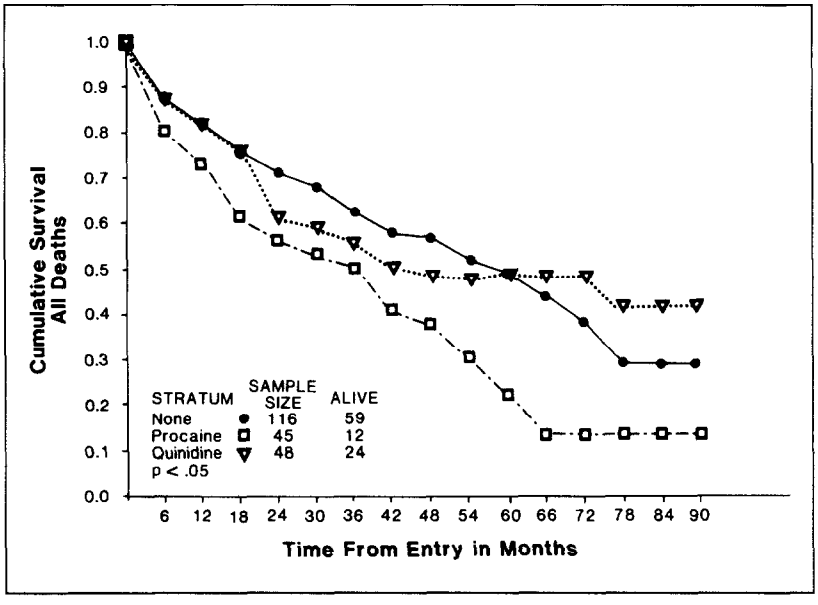

FIGURE 1. Cumulative total survival for the study population.

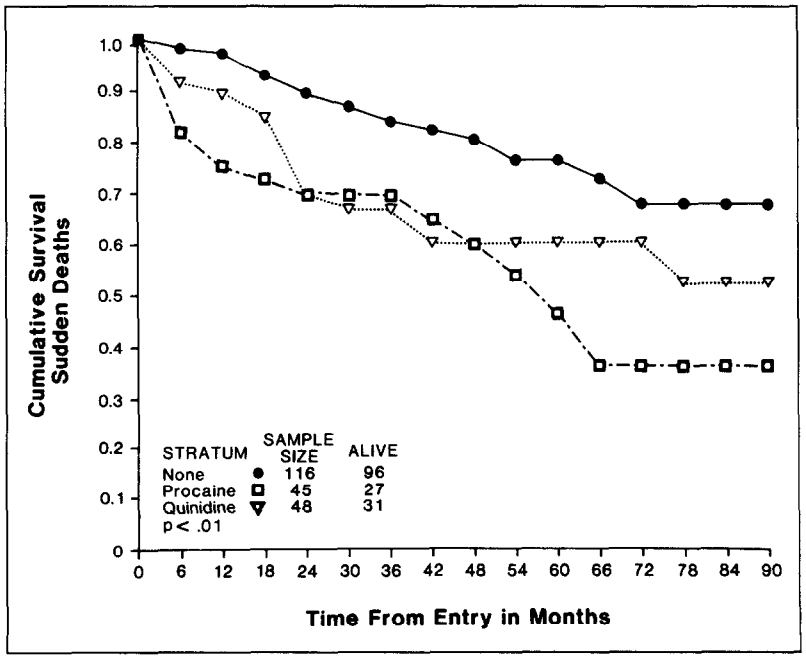

FIGURE 2. Cumulative sudden death survival for the study population.

drug at the time of discharge. The survival distributions of the 3 treatment groups overall and within digoxin status categories were calculated using the product-limit method and compared using the log rank test.[8,9] The Cox-Breslow life table procedure, as implemented in the BMDP series, was used to examine the importance of possible covariates.[10]

RESULTS

Characteristics of study patients are listed in Table I. Patients were classified at the time of discharge into 6 groups based on the prescription of quinidine and procainamide and whether or not digoxin therapy was used in each of these groups.

When the patients prescribed digoxin were compared to those who were not, a significant ($p < 0.001$) difference was observed in some factors. Patients prescribed digoxin were older (65 vs 60 years), and had an increased incidence of previous myocardial infarction, pulmonary congestion and diuretic intake. The antiarrhythmic prescription, however, was not significantly different. At the 3-month follow-up visit, 96.4% of those prescribed quinidine and 92.3% of those prescribed procainamide were still taking their original drug. At 6 months, 76.7% and 78.6%, respectively, of patients continued with their initial drug therapy.

When concomitant digoxin therapy was disregarded, cumulative total (Figure 1) and sudden death (Figure 2) survival rates were significantly lower for patients treated with procainamide and quinidine, compared to those who did not receive these drugs. The 2-year cumulative total survival rates (Figure 1) for quinidine, procainamide and no therapy were 61, 57 and 71%, respectively ($p < 0.05$). The 2-year sudden death survival

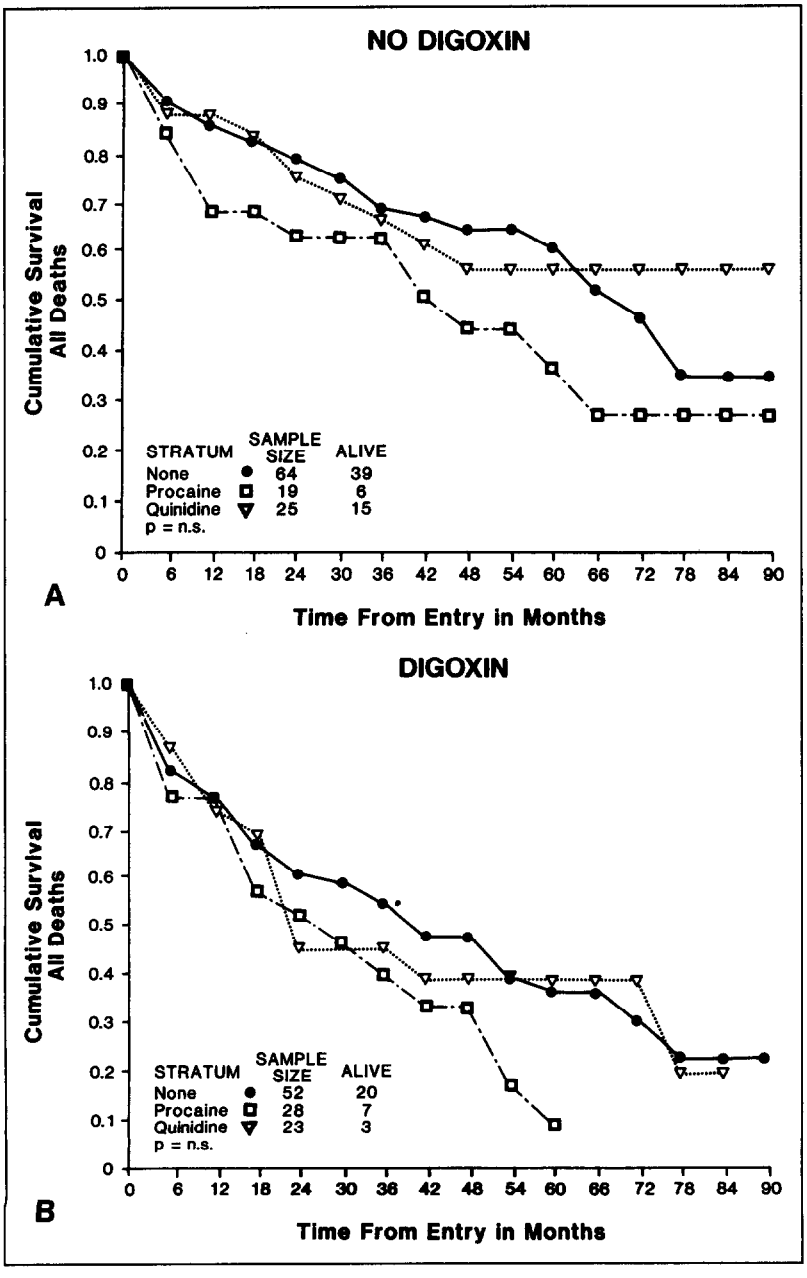

FIGURE 3. Cumulative total survival in patients not receiving digoxin (*A*) and those receiving digoxin (*B*).

rates (Figure 2) for the quinidine, procainamide and no therapy groups were 69, 69 and 89%, respectively ($p < 0.01$).

The effect of the concomitant use of digoxin with the antiarrhythmic agents on the total survival was not associated with a statistically significant difference between the 3 antiarrhythmic treatment groups (Figure 3). Patients receiving digoxin, however, generally had a worse total survival rate. The 2-year cumulative survival rates for quinidine, procainamide and no therapy groups in patients not receiving digoxin (Figure 3A) were 75, 63 and 79%, respectively ($p = 0.16$), and in patients receiving digoxin (Figure 3B) were 43, 51 and 61%, respectively ($p = 0.19$).

When sudden death survival (Figure 4) was examined, both quinidine- and procainamide-treated patients experienced a worse sudden death survival rate compared to the no treatment group, regardless of concurrent digoxin therapy. The 2-year sudden death survival rates for quinidine, procainamide and no therapy groups in patients not receiving digoxin (Figure 4A) were 79, 63 and 91%, respectively ($p < 0.05$), and in patients receiving digoxin were 57, 76 and 88%, respectively ($p < 0.05$).

While the relation of digoxin and antiarrhythmic therapy to worse survival seems clear when examined univariately, given the design of the study and the mechanism for assigning treatment, it is possible that they are not the only predictors of survival. This is indicated by the association of digoxin therapy with various other factors such as age and previous myocardial infarction (Table I). Using a stepwise model building procedure, the predictive value of age, previous myocardial infarction and pulmonary congestion, along with digox-

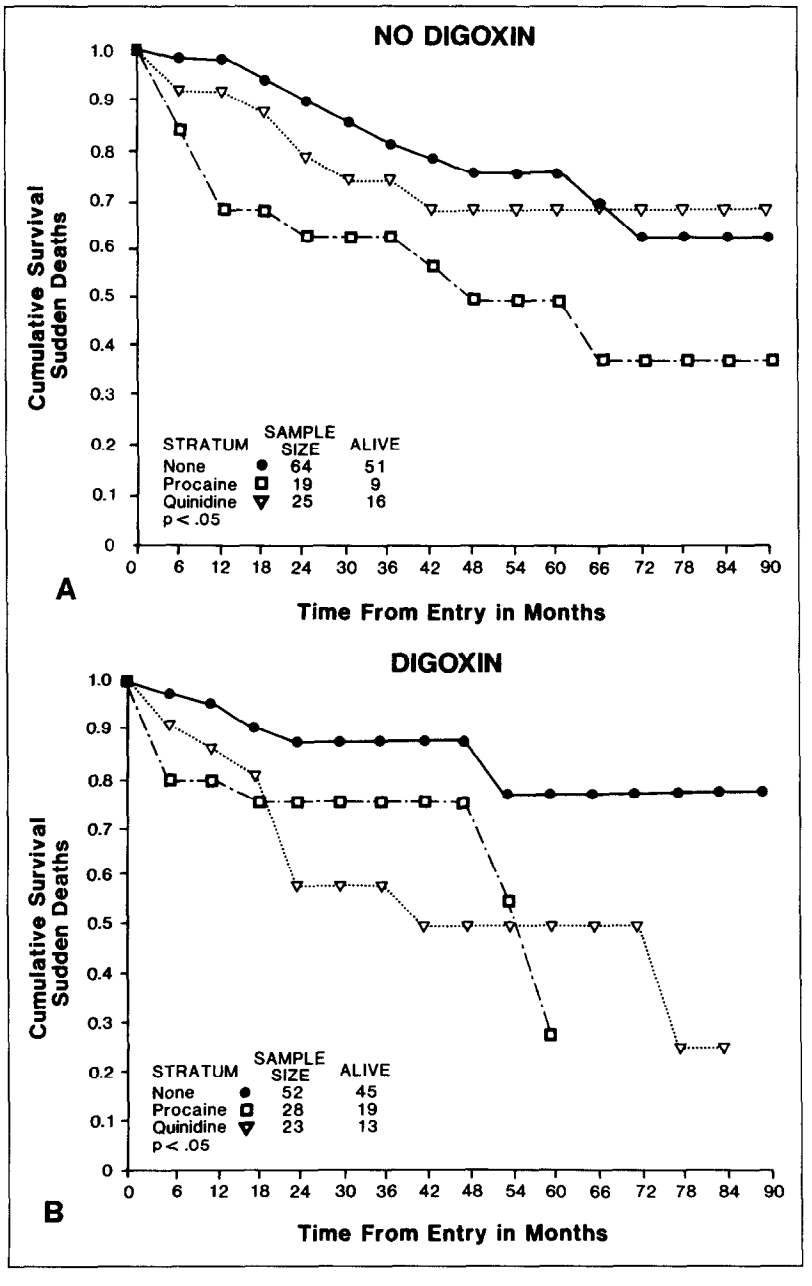

FIGURE 4. Cumulative sudden death survival for patients not receiving digoxin (*A*) and those receiving digoxin (*B*).

TABLE I Distribution of Clinical and Historical Events in Relation to Therapy at Discharge

	No Digoxin				Digoxin			
	None (n = 64)	P (n = 19)	Q (n = 25)	Both (n = 108)	None (n = 52)	P (n = 26)	Q (n = 23)	Both (n = 101)
Mean age (yrs)	59	59	61	60*	65	66	62	65*
History (%)								
Angina	47	74	60	55	52	77	65	61
Heart failure	72	58	52	65*	89	85	70	83*
Hypertension	47	37	36	43	60	54	52	56
Previous MI	25	63	36	34*	58	77	65	64*
Hospital course (%)								
Acute MI	50	37	40	45	42	19	44	37
PC	55	32	32	45	77	65	70	72
Medications at discharge (%)								
Other antiarrhythmics	0	5	0	1	0	0	4	1
Diuretics	19	21	16	19*	69	65	57	65*
Propranolol	13	5	4	9	12	0	0	6

* $p < 0.001$ no digoxin vs digoxin group.
MI = myocardial infarction; P = procainamide; PC = pulmonary congestion by x-ray; Q = quinidine.

in and antiarrhythmic status, was considered for both overall survival and sudden death survival. The strongest predictors of death were age and previous myocardial infarction, while the strongest predictors for sudden death were age, treatment with an antiarrhythmic agent and previous myocardial infarction. These results indicate that antiarrhythmic therapy is related to worse survival. However, with this study design it is difficult to determine if the poorer survival is related to the antiarrhythmic drug itself or to additional factors.

DISCUSSION

It must be emphasized that this is a retrospective analysis of a very unique patient population in whom antiarrhythmic agents were administered empirically. It is not a randomized, controlled study of antiarrhythmic therapy in this population. Nevertheless, it does raise some important issues in regard to therapy of this high risk population. The choice of antiarrhythmic therapy was made by the practicing physician, who was unaware of the results of the ambulatory electrocardiogram. It is possible that physicians identified the high risk patient by other clinical characteristics and therefore chose to initiate antiarrhythmic therapy. This could explain the higher mortality rate observed in the patients prescribed antiarrhythmic therapy. With the exception of baseline differences in patients receiving digoxin, there were no consistent differences in regard to the administration of antiarrhythmic agents. The prescribed dosage of quinidine and procainamide was in the usual dose range and drug compliance is consistent with other antiarrhythmic trials. We observed in this analysis that patients who received no therapy appeared to fare the best, although this reached statistical significance only in the sudden death group.

Our previous examination of predictors of death in resuscitated out-of-hospital cardiac arrest victims indicated that the history of digoxin therapy is associated with worse survival rate.[3] This observation suggested that heart failure was a significant predictor of subsequent death, and this has been supported by others.[1,11-13] However, digoxin therapy, left ventricular dysfunction and ventricular ectopy are so closely interrelated that it is difficult to isolate the importance of each of these factors.[13,14] The present analysis indicates that the use of digoxin was one of a number of multivariate predictors associated with an overall decreased total survival rate.

Antiarrhythmic therapy in patients resuscitated after a cardiac arrest has been generally considered advisable, if not mandatory, since a high frequency of ventricular arrhythmia is associated with an accelerated mortality rate.[3,7] The suggestion that antiarrhythmic therapy can be of benefit in this population has come from uncontrolled drug therapy directed by ambulatory electrocardiography or electrophysiologic studies. Using serial ambulatory electrocardiographic monitoring, the use of multiple antiarrhythmic agents in high risk patients appeared to show a decreased mortality compared to historical controls.[4] A major confounding variable, however, is the association of ventricular ectopy with left ventricular dysfunction. Arrhythmia suppression and the associated risks of therapy are adversely influenced by a decreased ejection fraction.[1,17,18] The Cardiac Arrhythmia Suppression Trial examined the effect of arrhythmia suppression on sudden death mortality.[1] Encainide and flecainide arms of the study were prematurely stopped when an increased rate of arrhythmic death and total mortality was observed with those drugs compared to placebo. The sudden death rate at 1 year for patients with ejection fractions <30% was 9.5% with drugs and 3.6% with placebo. In patients with ejection fractions >30%, it was 3.7% and 0.8%, respectively.

Balanced against the uncertain benefits of antiarrhythmic therapy are the well-documented proarrhythmic effects of a number of these agents.[11,19-22] Adverse reaction to antiarrhythmic agents is adversely affected by digoxin and diuretic therapy.[19] These events are presumed to occur early after the institution of drug therapy, and were observed with almost all of the currently

available agents.[21] There was a tendency in this study for an accelerated mortality early after initiation of therapy but the survival curves continued to fall throughout the follow-up period, which is similar to the observations of the Cardiac Arrhythmia Suppression Trial.

Although our data are applicable to a very unique group of patients with coronary artery disease, they also have important implications for patients with coronary artery disease in general, and they are consistent with recent studies.[1] Our present observations suggest that empiric antiarrhythmic therapy with quinidine and procainamide fails to provide protection in this high risk group. In each survival analysis, the patients who did not receive an antiarrhythmic agent fared better than those who were treated with these drugs, although this was statistically significant only in regard to sudden death. These observations should give us pause before embarking on empiric antiarrhythmic therapy in this high risk population.

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