Prevalence, Characteristics and Significance of Ventricular Premature Complexes and Ventricular Tachycardia Detected by 24-Hour Continuous Electrocardiographic Recording in the Cardiac Arrhythmia Suppression Trial

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The prevalence, characteristics and significance of ventricular arrhythmias detected by ambulatory electrocardiography were evaluated in 1,498 patients who were randomized to encainide, flecainide or placebo in the Cardiac Arrhythmia Suppression Trial. The mean ventricular premature complex (VPC) frequency at baseline was 133 ± 257 VPCs/hour. Nonsustained ventricular tachycardia (VT) (rate ≥120 beats/min) was present in 22% of patients. Accelerated idioventricular rhythm (rate <120 beats/min) occurred in 22% of subjects. There were 63 deaths/resuscitated cardiac arrests in the active treatment (encainide/flecainide) group and 26 in the placebo group. In the treatment group mortality increased with increasing VPC frequency, ($p = 0.006$), whereas in the placebo group such a relation was not present. Mortality/resuscitated cardiac arrest increased in patients with ≥2 VT episodes than in those with ≤1 episode in the active treatment group ($p = 0.04$). There was no significant association between VT and mortality/resuscitated cardiac arrest in the placebo group. The presence of accelerated idioventricular rhythm was not associated with increased mortality/resuscitated cardiac arrest in either the active treatment or placebo groups. However, mortality was lower in patients with accelerated idioventricular rhythm rates <100 beats/min than in those with rates ≥100 beats/min ($p = 0.05$).

Thus, in the Cardiac Arrhythmia Suppression Trial the previously described association between mortality/resuscitated cardiac arrest and ventricular arrhythmias (VPC and VT) were only observed in the active treatment group. In addition, based on the results obtained in this highly selected population, it is suggested that the definition of accelerated idioventricular rhythm should be a rate <100 beats/min, and at a rate ≥100 beats/min it should be categorized as VT.

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During the first year after an acute myocardial infarction, there is an increased risk of death from cardiac causes, both sudden and nonsudden.[1–5] Ventricular arrhythmias detected on Holter monitoring are associated with an independent risk for death from cardiac causes.[6–9] The Cardiac Arrhythmia Suppression Trial (CAST), a multicenter, randomized, placebo-controlled study, was designed to test the hypothesis that suppression of asymptomatic ventricular dysrhythmias after myocardial infarction would reduce the rate of cardiac death related to arrhythmias.[10]

Using data from the CAST, we undertook a study of ventricular arrhythmias detected during baseline ambulatory electrocardiographic recordings with the following aims: (1) to examine the mean frequency and frequency distribution of ventricular premature complexes (VPCs); (2) to examine the characteristics of ventricular tachycardia (VT); (3) to examine the characteristics of accelerated idioventricular rhythm; and (4) to examine if a correlation exists between VPC frequency, VT and accelerated idioventricular rhythm characteristics at baseline Holter and outcome (total mortality/resuscitated cardiac arrest). We analyzed the placebo and active treatment groups separately because of the significant effect of the active drug treatment on mortality.

METHODS

Patient population: Twenty-seven centers in Canada, Sweden and the USA participated in this study.

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TABLE I Frequency Distribution of Ventricular Premature Complexes and Mortality/Resuscitated Cardiac Arrest Associated with Ventricular Arrhythmias

	No. of Pts. (%)	Total Mortality/ Cardiac Arrest (%)	
		Active	Placebo
VPCs/hour*			
<10	227 (15.0)	3.6	1.7
>10–50	594 (40.0)	6.5	4.7
>50–100	249 (16.5)	12.2	2.5
>100–200	177 (12.0)	13.3	4.6
>200	249 (16.5)	9.4	2.5
VT runs/24-hour Holter†			
0	1172 (78.5)	7.7	3.4
1	169 (11.5)	7.3	2.3
2–5	90 (6.0)	14.6	7.1
>5	64 (4.0)	13.2	3.8
AIVR rate (beats/min)‡			
<100	148 (46.0)	6.8	2.7
100–119	175 (54.0)	10.3	5.7

*Data missing in 2 patients with VPC.
†Data missing in 3 patients with VT.
‡Data missing in 6 patients with AIVR.
AIVR = accelerated idioventricular rhythm; VPCs = ventricular premature complexes; VT = ventricular tachycardia.

The entry criteria to the CAST included: (1) ≥6 VPCs/hour, (2) age <80 years, and (3) impaired left ventricular function (left ventricular ejection fraction ≤0.55 for myocardial infarction ≤90 days and ejection fraction ≤0.40 for infarcts 90 days to 2 years). Criteria for adequate suppression included ≥80% suppression of VPCs and a ≥90% suppression of runs of VT. Patients who met the entry criteria and achieved adequate suppression during the open-label titration entered the main CAST study. Patients with symptomatic ventricular arrhythmias or VT of ≥15 beats' duration at a rate ≥120 beats/min were excluded.

Analysis of Holter recordings: An ambulatory electrocardiographic recording (Holter) with a minimum of 18 hours of analyzable data was obtained an average of 97 ± 155 days (mean ± standard deviation) after admission for the index myocardial infarction. The Holters were analyzed by computer with manual overread at each participating center. As part of ongoing quality control procedures, Holter technicians were required to read gold standard tapes provided by the quality control subcommittee. The percent discrepancy for VPCs/hour was calculated as the absolute value of the formula:

$$\frac{\text{Tape reading} - \text{"Gold standard"}}{\text{"Gold standard"}} \times 100\%$$

The average percent discrepancy from all sites reading gold standard tapes (n = 1,012 tapes) was 7.7%. Intracenter quality control was assessed by having the chief Holter technician at each center over-read tapes analyzed by other technicians. The average percent discrepancy of VPCs/hour was 10.5% (n = 399). In addition, 197 tapes read by the chief technicians at the participating centers were selected at random by the data coordinating center for a second computer analysis performed by an external center (Cardiodata Inc., New Jersey). The overall inter-center average discrepancy of VPCs/hour was 12.7% (n = 296).

For VT and accelerated idioventricular rhythm reading, the computed percent discrepancy first mentioned is less meaningful since a large percentage of the tapes do not have these arrhythmias. The quality control measures are expressed instead in terms of the false-positive and false-negative rates.

The false-positive rate for VT on the gold standard tapes (n = 967) was 4%, for the intercenter tapes (n = 42), 4%. The corresponding figures for false-positive rates for accelerated idioventricular rhythm were 7% (n = 737 tapes) and 5% (n = 325 tapes), respectively.

The false-negative rates for VT on the gold standard tapes (n = 104) was 29% and for intercenter tapes (n = 241), 27%. The corresponding false-negative rates for accelerated idioventricular rhythm were 51% (n = 334 tapes) and 43% (n = 35 tapes), respectively.

Follow up: The groups were stratified according to clinical center, left ventricular ejection fraction (≥ or <0.30) and time between qualifying Holter recording and myocardial infarction (≥ or <90 days). After randomization, follow-up visits were scheduled at 4-month intervals. At every visit, data were collected on secondary end points such as new or worsened congestive heart failure, sustained VT, recurrent myocardial infarction, various cardiac procedures and quality of life. The primary CAST end point is death from arrhythmia or resuscitated cardiac arrest.[10]

Definitions: VT was defined as ≥3 consecutive VPCs at a rate ≥120 beats/min. Accelerated idioventricular rhythm was defined as ≥3 consecutive VPCs at a rate <120 beats/min. The end point used for analysis in this report is total mortality and resuscitated cardiac arrest.

Statistical methods: Continuous data are presented as mean ± standard deviation. Two-way contingency tables were analyzed with the standard chi-square test. The survival curves are shown using the Kaplan-Meier method[11] and the curves were compared by the log-rank test. The exposure time began at the time of randomization to blinded therapy and patients who were still alive on April 19, 1989, had censored exposure time. The association between mortality/resuscitated cardiac arrest and VPC frequency is analyzed using the Cox regression. The log VPC scale is used to reduce skewness. The relative risk of treatment in defined subgroups was calculated to evaluate the consistency of the drugs' effects across subgroups. Confidence intervals for relative risk were computed using the method de-

TABLE II Frequency Distribution of Ventricular Tachycardia Characteristics

	No. of Pts. (%)	Total Mortality/ Cardiac Arrest (%)	
		Active	Placebo
VT length (beats)			
3–5	238 (73.0)	8.1	3.5
6–9	62 (19.0)	17.6	7.1
10–14	26 (8.0)	16.7	0.0
Total	326 (100)	10.7	3.8
VT rate (beats/min)*			
120–149	188 (60.0)	9.4	3.3
150–199	112 (35.5)	15.5	1.9
>200	14 (4.5)	0	16.7
Total	314 (100)	11.1	3.3

*Twelve patients had missing or values out of range, or both.
VT = ventricular tachycardia.

TABLE III Frequency Distribution of Accelerated Idioventricular Rhythm Characteristics

	No. of Pts. (%)
AIVR runs/24-hour Holter*	
0	1,168 (78.0)
1	143 (9.5)
2–5	105 (7.0)
>5	79 (5.5)
Total	1,495 (100)
AIVR length (beats)*	
3–5	259 (79.0)
6–9	44 (13.5)
10–15	14 (4.5)
>15	10 (3.0)
Total	327 (100)

*Three patients had missing values.
AIVR = accelerated idioventricular rhythm.

TABLE IV Mode of Deaths for Both Groups

	Active	Placebo
Number of patients	755	743
Mean exposure time (days)	290	300
Arrhythmic death/cardiac arrest	43	16
Other cardiac death	17	5
Noncardiac death	3	5
Total	63	26

scribed by Fleiss.[12] Nominal p values <0.05 are reported but we caution their interpretation because of the multiple comparison problem. Discrepancies observed between the total number of patients in the study and the number of cases reported in individual tables are due to missing information or the exclusion of out of range values, or both.

RESULTS

Prevalence and characteristics of ventricular premature complexes: By definition, all patients entered in the CAST study had ≥6 VPCs/hour on the baseline (qualifying) Holter. The mean VPC frequency for the 1,498 patients entering the main study was 133 ± 257 VPCs/hour (range 6 to 2,328). The frequency distribution for VPCs is listed in Table I. Almost half (45%) of all patients had >50 VPCs/hour.

Prevalence and characteristics of nonsustained ventricular tachycardia: Of the 1,498 patients, 326 (22%) had ≥1 runs of VT. Mean number of VT runs per Holter in this subgroup was 9.02 ± 30 (range 1 to 321). The frequency distribution of VT runs is listed in Table I. Most patients with VT had ≤5 runs of VT on their Holter. Mean VT length of the longest episode was 4.8 ± 2.4 beats (range 3 to 14, which is the allowable range in the study protocol). The frequency distribution of VT length is listed in Table II. Most VTs (73%) were ≤5 beats in duration. Mean rate of the longest VT episode was 148 ± 24 beats/min (range 120 to 281). The frequency distribution of VT rate is listed in Table II. Most VTs (96%) had rates <200 beats/min.

Prevalence and characteristics of accelerated idioventricular rhythm: Of the 1,498 patients, 330 (22%) had ≥1 runs of accelerated idioventricular rhythm on the Holter recording. Mean number of accelerated idioventricular rhythm episodes per Holter was 10.3 ± 31 (range 1 to 389). The frequency distribution of accelerated idioventricular rhythm runs is listed in Table III. More than half (56%) of patients with accelerated idioventricular rhythm had ≥2 runs on their Holter.

Mean accelerated idioventricular rhythm length was 4.9 ± 4.8 beats (range 3 to 61 beats). The frequency distribution of accelerated idioventricular rhythm length of the longest run is listed in Table III. Most (79%) accelerated idioventricular rhythms had length between 3 and 5 beats. Fifty-four percent of the patients with accelerated idioventricular rhythm had rates between 100 and 119 beats/min.

Ventricular arrhythmias and mortality: Of the 1,498 patients, 755 were assigned to active therapy (encainide/flecainide) and 743 to placebo. The average exposure time for patients treated with active drugs was 290 and 300 days for the placebo group. Total deaths, including arrhythmic death, resuscitated cardiac arrests, and other cardiac and noncardiac deaths for the active and placebo groups, are listed in Table IV. The mortality rate for the active treatment group exceeded that of the placebo group. The relative risk of mortality for the active and placebo groups was 2.4 (95% confidence interval 1.5 to 4.1) and remained constant for the subgroups analyzed. The association between ventricular arrhythmias and mortality/resuscitated cardiac arrests was analyzed separately for the placebo and active treatment groups, given the significant effect of active treatment on the mortality observed in this study.

The mortality/resuscitated cardiac arrest rate related to VPC frequency for the active treatment and pla-

cebo groups is shown in Figure 1. In the active treatment group there was a significant association between mortality and log VPC frequency ($p = 0.006$), analyzed as a continuous variable. The mortality rate appeared to increase with increasing VPC frequency and reached a plateau around 100 to 200 VPCs/hour. (Figure 1, top) There was no significant association between mortality/resuscitated cardiac arrest and VPC frequency in the placebo-treated group (Figure 1, bottom).

The presence of VT was associated with higher mortality in the active treatment group, but this difference (7.7 vs 10.7%) was not significant. Figure 2 shows the association between mortality/resuscitated cardiac arrest for patients taking an active drug having ≤ and >1 VT episodes. The mortality for patients having >1 VT episode when compared with those with no VT or only 1 VT episode on a 24-hour Holter was significantly increased (7.5 vs 13.8%; $p = 0.04$) (Table I). The presence of VT was not associated with a significantly higher mortality/resuscitated cardiac arrest in the placebo-treated group (3.4 vs 3.8%) (Table I). The effect of VT length and VT rate on mortality/resuscitated cardiac arrest is shown in Table II. There was no significant association between VT length or rate and mortality/resuscitated cardiac arrest. We also examined the mortality/resuscitated cardiac arrest associated with accelerated idioventricular rhythm. Of the 330 patients with accelerated idioventricular rhythm, 136 (42%) also had VT on their Holter recording. There is a strong association between the presence of VT and accelerated idioventricular rhythm (odds ratio 3.5:1) ($p = <0.001$). To determine whether the presence of accelerated idioventricular rhythm had a significant contribution to mortality/resuscitated cardiac arrest, we compared the outcome of patients with accelerated idioventricular rhythm only (193 patients) to those with VPCs only (979 patients) in the placebo and active treatment groups. There was no difference in mortality/resuscitated cardiac arrest between patients with

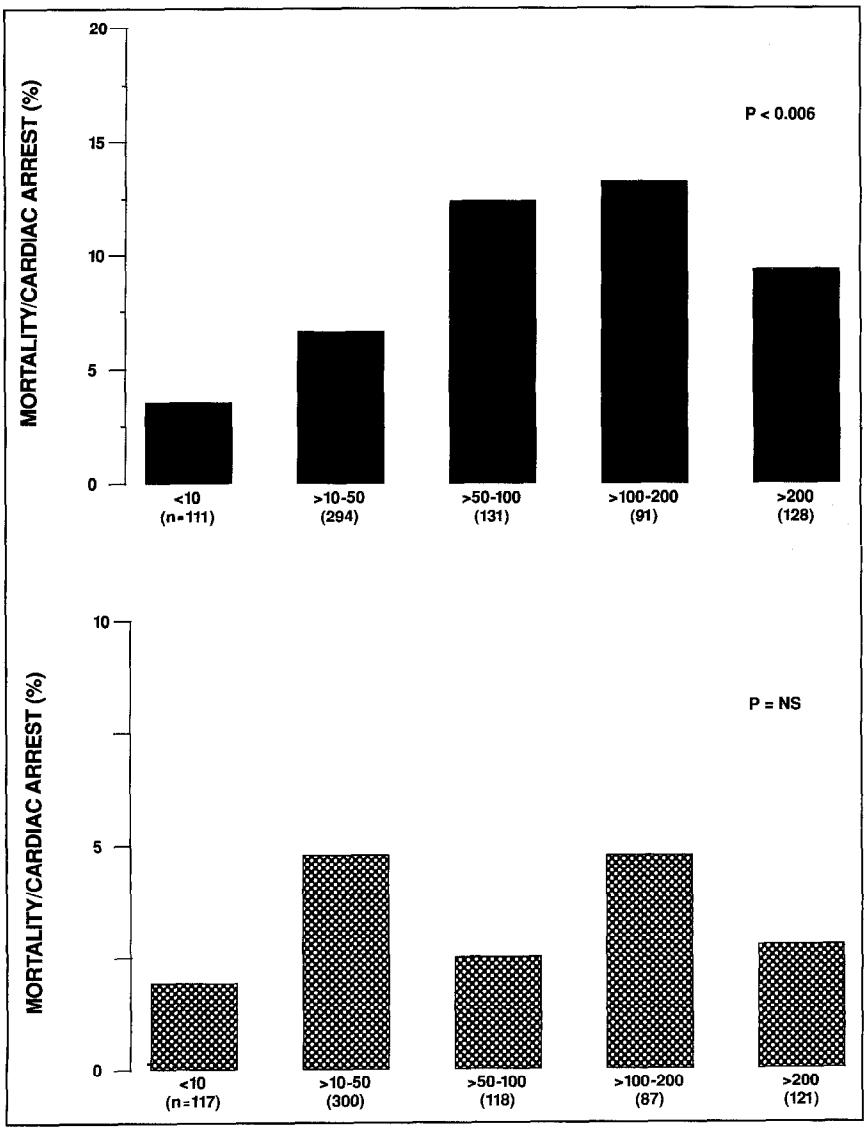

FIGURE 1. Frequency of ventricular premature complexes and mortality/cardiac arrest. *Upper panel,* percent mortality/cardiac arrest in active treatment group according to ventricular premature complex (VPC) frequency. Mortality increased significantly with increasing VPC frequency ($p < 0.006$). *Lower panel,* percent mortality/cardiac arrest in placebo group according to VPC frequency. NS = not significant.

VPC only and those with VPC plus accelerated idioventricular rhythm in the active-treated (7.9 vs 6.5%) or placebo-treated (3.3% vs 4.0%) groups. When the relation between individual characteristics of accelerated idioventricular rhythm and mortality/resuscitated cardiac arrest was examined, no statistically significant relation was found between mortality/resuscitated cardiac arrest and the number of accelerated idioventricular rhythm runs or the length of the runs. However, a decreased mortality was found in the accelerated idioventricular rhythm group with rate <100 than in those with rates 100 to 119 ($p = 0.05$) (Figure 3). This difference in mortality/resuscitated cardiac arrest between accelerated idioventricular rhythm < and ≥100 to <120 showed similar trends when the active treatment and placebo groups were analyzed separately (Table I).

DISCUSSION

This study examines the prevalence, characteristics and significance of ventricular arrhythmias detected on baseline 24-hour Holter monitoring in the CAST for

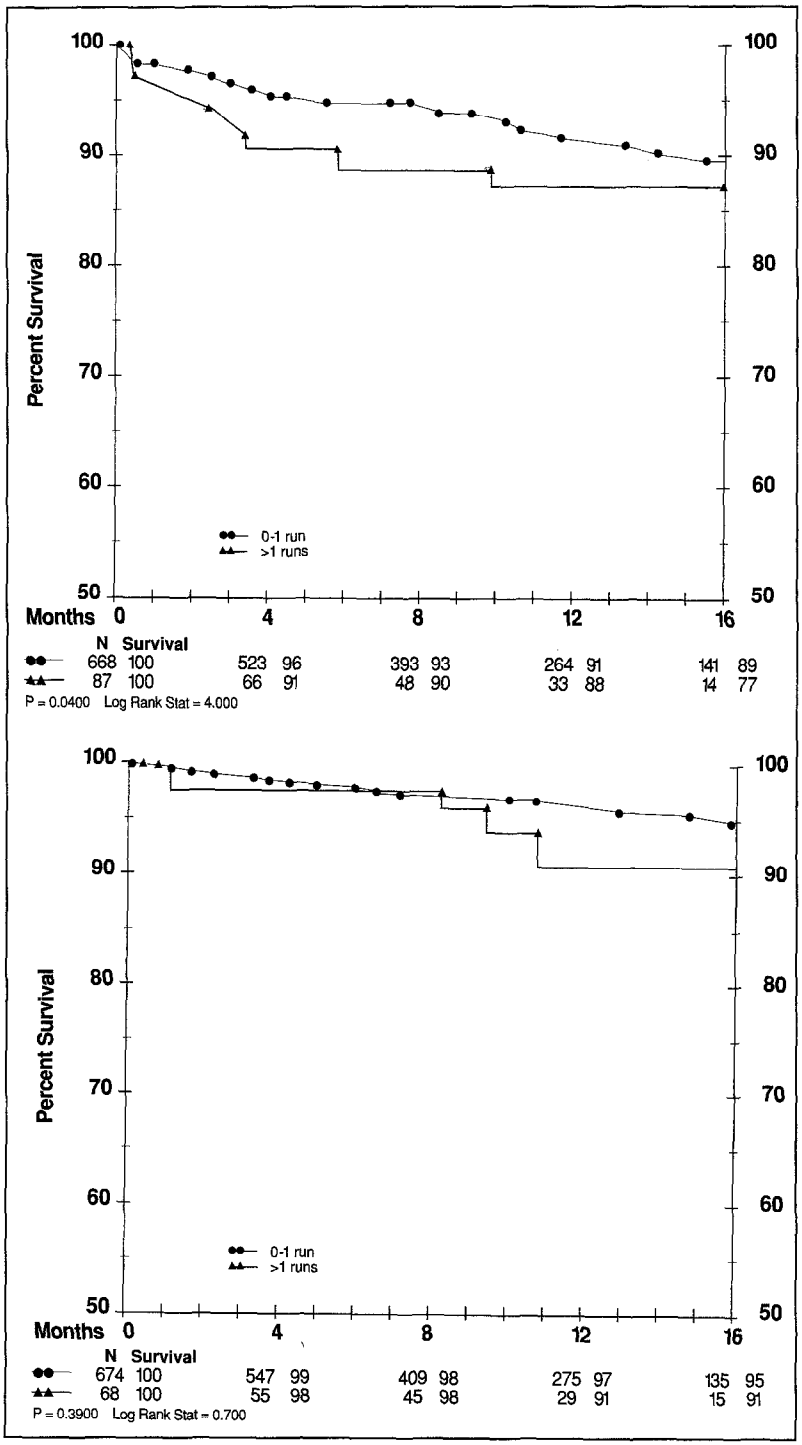

FIGURE 2. Frequency of the number of ventricular tachycardia (VT) runs and mortality/cardiac arrest. Survival curve according to VT frequency. *Upper panel,* survival in the active treatment group was greater in patients with ≤1 run of nonsustained VT ($p < 0.05$). *Lower panel,* survival in the placebo group did not differ based on VT frequency.

patients randomized to active treatment (encainide/flecainide) and placebo. In the CAST, patients were preselected for having ventricular arrhythmias (VPC rate ≥6/hour) at entry, associated with impaired left ventricular function. In this report, we included only patients whose ventricular arrhythmias were suppressible by encainide/flecainide and subsequently were assigned to active treatment or placebo. These study population characteristics contrast with the previous reports on ventricular arrhythmias in postinfarction patients.[1-9] The previous studies included patients with and without ventricular arrhythmias and the patients were not preselected for the suppressibility of their ventricular arrhythmias. The treatment effect in most previous studies was not analyzed but treatment varied among patients.

Ventricular premature complexes, characteristics and associated mortality: Kotler et al,[13] in 1973, examined the effect of VPC frequency on mortality in 160 male survivors of acute myocardial infarction using 12-hour Holter recording. The incidence of sudden death was 2.9% in patients with VPC frequency of <10/hour compared with 19.2% in those with VPC ≥10/hour. Moss et al[14] found a significant association during the initial 4 months of follow-up between cardiac mortality and VPC frequency (3.2% for patients with <20 VPCs/hour and 15% for those with >30/hour) in postinfarction patients using 6-hour Holter recordings. Ruberman et al,[6] using 1-hour Holter recording in 1,739 men who had had myocardial infarction, also noted that the 3-year sudden death mortality in patients with frequent (≥10/hour) and complex VPCs was significantly higher than in those with complex but less frequent (<10/hour) VPCs (6.42 vs 18.7%, sudden death). Bigger et al[8] evaluated 766 postmyocardial infarction patients with 24-hour Holter monitoring and also showed a correlation between the 2-year mortality and VPC frequency. The CAST study showed a similar statistically significant association between VPC frequency and mortality/resuscitated cardiac arrest in the group receiving active treatment. In the placebo-treated group an association between VPC frequency and mortality was not observed (Table I and Figure 1). However, the number of events in the placebo group was quite small.

Ventricular tachycardia, characteristics and associated mortality: There is much less information available on the prevalence, characteristics and significance of ventricular runs (≥3 consecutive VPCs). The largest study, reported by Bigger et al,[9] included 90 patients (11%) with ventricular runs from a total of 867 participants in the Multicenter Post-Infarction Program. The 3-year cumulative mortality rate was 23% for patients with and 15% for patients without VT. VT had a strong and statistically significant association with all-cause mortality and arrhythmic mortality independent of other risk variables associated with VT. There were no statistically significant associations between individual VT characteristics and mortality. The CAST study defined VT as ≥3 consecutive VPCs at an average rate of ≥120 beats/min. Ventricular runs at a rate <120 beats/min were defined as accelerated idioventricular rhythm. The CAST included 326 patients with VT and 329 patients with accelerated idioventricular rhythm. It is the largest number of patients reported with nonsustained VT and the first study to report on the preva-

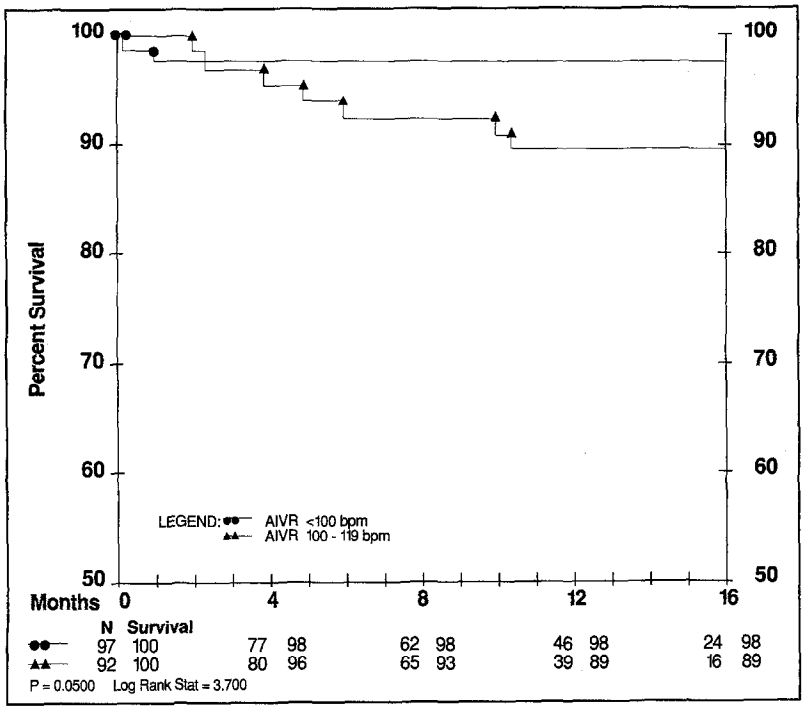

FIGURE 3. Rate of accelerated idioventricular rhythm (AIVR) and mortality/cardiac arrest. In patients with AIVR rates ≥100 beats/min, survival rates decreased compared with patients with AIVR rates <100 beats/min (p = 0.05).

lence, characteristics and significance of accelerated idioventricular rhythm in the postmyocardial infarction population. The prevalence of VT in the CAST study was 22%, which is higher than the prevalence previously reported in other studies (1 to 17%).[2,9,14-17] Our study demonstrated a higher mortality/resuscitated cardiac arrest in the presence of nonsustained VT in the actively treated patients — 7.7% for patients without and 10.7% for patients with VT — although this difference was not statistically significant. However, patients with VT runs of ≥2 had a higher mortality/resuscitated cardiac arrest than those with a single run of VT or no VT ($p = 0.04$) (Figure 2, top). There was no significant association between VT and mortality/resuscitated cardiac arrest in the placebo-treated group (Figure 2, bottom). There were no statistically significant associations between VT length and rate and mortality/resuscitated cardiac arrest.

No previous study in postmyocardial infarction patients evaluated the association of accelerated idioventricular rhythm with mortality. Half of the patients with accelerated idioventricular rhythm had rates from 100 to 119 beats/min. Of the 330 patients with accelerated idioventricular rhythm, 137 (42%) also had VT. The overall mortality/resuscitated cardiac arrest of patients with accelerated idioventricular rhythm in the active- and placebo-treated groups was not significantly different from patients who had only VPCs on their 24-hour Holter recording. This finding confirms a previously held impression that accelerated idioventricular rhythm does not confer a worse prognosis. The CAST finding also suggests that the definition of accelerated idioventricular rhythm should include rates up to 100 beats/min only because the mortality/resuscitated cardiac arrest associated with accelerated idioventricular rhythm of rates 100 to 119 beats/min was higher than those with rates <100 (Figure 3 and Table I).

Study limitations: The data described in this study are primarily a descriptive analysis of the characteristics of ventricular arrhythmias in the main CAST. Patients were preselected by having frequent ventricular arrhythmias at entry associated with impaired left ventricular function. Also, all patients included in the study had ventricular arrhythmias that were suppressible by the antiarrhythmic drugs used in the trial. Therefore, much of the information obtained derives from a very selective group of post-myocardial infarction patients. The conclusions obtained may not be applicable to the post-myocardial infarction population at large. Other technical or design-related limitations include the fact that Holter recordings were obtained at varying intervals after acute myocardial infarction. The quality control data for evaluating the accuracy of ventricular arrhythmia quantitation meets the expected standards for VPC counting. However, the false-negative rates for VT and accelerated idioventricular rhythm detection are high. Previously published studies did not specifically address the difficulties related to VT and accelerated idioventricular rhythm quantitation. The CAST is the first study to point out this potential problem. The false-positive rates for detection of VT and accelerated idioventricular rhythm were acceptably low; therefore, the differences regarding VT and accelerated idioventricular rhythm are probably more significant than described in this study.

The small number of end-point events in the placebo group limits the statistical power of the associations. This may account for the lack of demonstrable relationships between ventricular arrhythmias and mortality/resuscitated cardiac arrests in the placebo-treated patients.

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APPENDIX

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