Ambulatory Ventricular Arrhythmias in Patients With Heart Failure Do Not Specifically Predict an Increased Risk of Sudden Death

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Background—Ventricular arrhythmias are a frequent finding in congestive heart failure (CHF) patients and a cause of concern for physicians caring for them. Previous studies have reached conflicting conclusions regarding the importance of ventricular arrhythmias as predictors of sudden death in patients with CHF. This study examined the independent predictive value of ventricular arrhythmias for sudden death and all-cause mortality in PROMISE (Prospective Randomized Milrinone Survival Evaluation).

Methods and Results—Ventricular arrhythmias were analyzed and quantified by use of prespecified criteria on baseline ambulatory ECGs from 1080 patients with New York Heart Association (NYHA) class III/IV symptoms and a left ventricular ejection fraction ≤35% enrolled in PROMISE. The relationship of ventricular arrhythmias and other clinical parameters to overall mortality and sudden death classified by an independent, blinded mortality committee was determined. There were 290 deaths, of which 139 were classified as sudden. Of the several measures of ventricular ectopy that were univariate predictors, the frequency of nonsustained ventricular tachycardia (NSVT) was the most powerful predictor and remained a significant independent predictor when included with other clinical variables in multivariate models of both sudden death mortality and non–sudden death mortality. However, multiple logistic analysis with models including the clinical variables with and without the NSVT variable demonstrated that the frequency of NSVT did not add significant information beyond the clinical variables.

Conclusions—This study demonstrates that ventricular arrhythmias do not specifically predict sudden death in patients with moderate-to-severe heart failure. Thus, the finding of asymptomatic NSVT on ambulatory ECG does not identify specific candidates for antiarrhythmic or device therapy. (Circulation. 2000;101:40-46.)

Key Words: arrhythmia □ death, sudden □ heart failure □ inotropic agents □ prognosis

The management of patients with congestive heart failure (CHF) and asymptomatic ventricular arrhythmias continues to present a challenge for the practicing physician. This dilemma reflects the juxtaposition of 2 observations. First, patients with CHF have a high prevalence of ventricular ectopy and ventricular tachycardia. Second, sudden death is responsible for 30% to 50% of the high mortality rate in patients with CHF. However, it remains unclear as to whether and how well these dysrhythmias predict sudden death in individual patients.

Several recent studies1–5 have suggested that ventricular arrhythmias detected by ambulatory electrocardiography (AECG) may identify patients at high risk for sudden death. However, these studies have a number of limitations, including post hoc hypotheses, retrospective analyses, AECGs in only a subset of patients, small sample size and number of events, and lack of predesignated criteria for mechanism of death and interpretation of arrhythmias. Thus, several critical questions remain unresolved: Do the presence or characteristics of baseline ventricular arrhythmias specifically identify patients at high risk for sudden death? Do they provide additional prognostic information beyond that of readily available clinical variables? Can these ventricular arrhythmias guide selection of therapeutic interventions directed against reducing sudden death?

These questions have assumed new importance with the evolving role of implantable cardioverter defibrillators (ICDs) as an approach to preventing sudden death.6 although

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not without significant cost and morbidity. Thus, it has become increasingly important to identify patients at high risk for sudden arrhythmic death. AECG monitoring has the potential to fulfill this role by detecting and quantifying the nature, frequency, and duration of ventricular arrhythmias, but in the absence of evidence that these arrhythmias are specific predictors of outcomes or that they can guide therapy, current guidelines discourage the use of this procedure.8,9

The present study was undertaken to determine whether ventricular arrhythmias were independent and specific predictors of sudden death with data from the Prospective Randomized Milrinone Survival Evaluation (PROMISE).10 PROMISE enrolled 1088 high-risk CHF patients, all of whom underwent 24-hour baseline AECG, and of the 290 deaths during follow-up, 139 were classified as sudden by an end-point committee, thus providing the largest cohort to date of CHF patients who experienced sudden death after AECG monitoring. The goal of the present study was to provide information for the practicing clinician on the significance of ventricular arrhythmias in patients with CHF.

Methods

Study Design

The PROMISE study evaluated the safety and efficacy of oral milrinone in patients with advanced CHF. A description of the design, conduct, and primary results of this trial has been published previously.10 Prespecified analyses of the AECG data were defined before the initiation of the study, and the present report consists of 1080 patients in whom technically adequate 24-hour AECGs were recorded before randomization to double-blind treatment with either placebo or matching placebo.

Patient Population

The inclusion and exclusion criteria for PROMISE have been described elsewhere10 and required that patients have New York Heart Association (NYHA) class III or IV symptoms for ≥3 months and a left ventricular ejection fraction ≤35% as measured by radionuclide ventriculography. All patients were required to be receiving treatment with a diuretic, an ACE inhibitor, and digoxin. The protocol was approved by the institutional review boards at all participating centers, and patients gave informed written consent before they entered the study.

AECG Monitoring

The 24-hour AECG recordings were obtained within 7 days before randomization. The tapes were scanned and analyzed by experienced technicians and overseen by supervisors at an independent laboratory (Clinical Data, Inc, Boston, Mass), and 10% of the recordings were validated by an independent cardiologist. The results were not available to the treating physician. The total number of ventricular ectopic beats and the numbers of single ventricular ectopic beats, paired ventricular beats, and ventricular tachycardia events (defined as ≥3 consecutive ventricular ectopic beats with mean R-to-R cycle length <600 ms) were determined. Several prospectively defined qualitative (ie, presence or absence) and quantitative indices of ventricular ectopy were derived from the AECG and examined as predictors of outcome.

Outcome Definitions and Determination

The primary end point of the study was mortality due to all causes. The mode of death was reviewed in a prospectively defined, blinded fashion by a mortality committee and classified as sudden or nonsudden. Sudden death was defined as an unexpected circulatory collapse resulting in death within 1 hour in a previously clinically stable patient.

Data Analysis and Statistical Methods

The baseline characteristics of the treatment groups were compared by the t statistic for continuous variables and by the χ² statistic for noncontinuous variables. To test the hypothesis that ambulatory ventricular ectopy is predictive of outcome in patients with CHF, a number of prespecified analyses were performed, including a χ² analysis of selected dichotomous AECG variables. Univariate and multivariate Cox proportional hazards analyses were then used on selected AECG and clinical variables. Because of the nonnormal distribution of some continuous AECG variables, a logarithmic transformation was performed on the number of ventricular ectopic beats per hour, the number of episodes of nonsustained ventricular tachycardia (NSVT), and the number of successive beats of NSVT. The AECG variable with the greatest predictive power was analyzed in a logistic survival model with sensitivity and specificity analyses. In addition, 2 multivariate logistic models were then developed that used the clinical variables with and without the most powerful AECG variable to assess the incremental additive information from this variable. Sensitivity and specificity analyses were performed on both of these models, and receiver operating characteristic (ROC) curves were generated. Analyses were performed with the SAS statistics package (version 6.12). Results of analyses were considered significant at a level of P<0.05.

Results

General

Patients were enrolled from January 24, 1989, to October 4, 1990, when the trial was stopped on the recommendation of the Data and Safety Monitoring Board. Some of the baseline characteristics of these patients and the prevalence of ventricular arrhythmias on the prerandomization AECG are given in Table 1. Although the multivariate analyses control for the presence of milrinone, data are also provided for each of the individual treatment groups. There were no significant baseline differences between the placebo and milrinone groups.

<table>
<thead>
<tr>
<th>TABLE 1. Characteristics of the Patient Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=525)</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Males, %</td>
</tr>
<tr>
<td>CAD, %</td>
</tr>
<tr>
<td>NYHA III/IV, %</td>
</tr>
<tr>
<td>Ejection fraction</td>
</tr>
<tr>
<td>Amiodarone therapy, %</td>
</tr>
<tr>
<td>Other antiarrhythmic, %</td>
</tr>
<tr>
<td>PVCs &gt;30/h, %</td>
</tr>
<tr>
<td>Couplets, %</td>
</tr>
<tr>
<td>NSVT, %</td>
</tr>
<tr>
<td>NSVT &gt;5 episodes, %</td>
</tr>
<tr>
<td>NSVT &gt;10 beats, %</td>
</tr>
</tbody>
</table>

CAD indicates patients with coronary artery disease as cause of heart failure; EF, ejection fraction. There were no statistical differences between treatment groups for any variable. Results are expressed as mean±SEM unless otherwise noted.
AECG Variables Are Univariate Predictors of Overall Mortality and Sudden Death

Two hundred ninety (27%) patients died, of whom 139 (13%) were classified as sudden deaths, representing 48% of the total deaths that occurred during the trial. Frequent premature ventricular contractions (PVCs; >30/h), NSVT, and NSVT of >10 beats’ duration identified groups with 55%, 68%, and 60% increased all-cause mortality, respectively (Table 2). Clinical predictors also defined groups at significantly increased risk of all-cause mortality.

Frequent PVCs (>30/h), the presence of couplets, and the presence and frequency (>5 episodes) of NSVT each defined groups with an ≈50% increased risk of sudden death. Age, NYHA class, and ejection fraction also defined groups at significantly increased risk of sudden death (42%, 70%, and 78%, respectively).

The presence of coronary artery disease was not a significant predictor of sudden death. Milrinone treatment was associated with a 60% increase in sudden death in this analysis.

Univariate Cox proportional hazards models demonstrated that many clinical and AECG variables predicted overall mortality (Figure 1A), sudden death (Figure 1B), and non–sudden death mortality. All of the AECG variables were significant predictors of overall mortality and sudden death. These variables were also significant predictors of non–sudden death mortality, which indicates their nonspecificity for mode of death.

Multivariate Predictors of All-Cause Mortality and Sudden Death

Multivariate general linear proportional hazards models were used to identify independent predictors of mortality while
controlling for the effects of the other variables. Important clinical variables (age, NYHA class, presence of coronary artery disease, ejection fraction, systolic blood pressure, and PROMISE treatment arm) that were significant univariate predictors were entered into separate models for all patients and each separate treatment arm (placebo and milrinone). Antiarrhythmic drug therapies (all antiarrhythmics, amiodarone, and other antiarrhythmics) were not significant univariate predictors of any form of mortality, nor did they alter the multivariate models; consequently, they were not included in any further analyses. These analyses demonstrated that all of the selected clinical variables were significant independent predictors of overall mortality and that ejection fraction was the most powerful clinical predictor of sudden death (Table 3). The relative risks in the analysis of the placebo group alone were almost identical to those of the combined group, which suggests that milrinone was not responsible for these results. The one exception was NYHA class, for which an interaction effect with milrinone was noted: NYHA class IV patients had greater excess mortality with milrinone than did class III patients.

Because the main purpose of this study was to assess the additional predictive value of ventricular arrhythmias in the context of important clinical variables, the AECG variables were included in multivariate models with the clinical variables. When the variables of frequency of PVCs (ln PVC/h), presence of NSVT, frequency of NSVT (ln NSVT episodes), and duration of longest run of NSVT (ln NSVT beats) were added individually to the 6 clinical variables, each was a significant independent predictor of both overall mortality and sudden death, with the frequency of NSVT being the most powerful. An additional analysis was performed with both a forward and backward elimination procedure in a multivariate Cox proportional hazards model that included all of the clinical variables and the 4 AECG variables; these analyses converged on the same variable set, and the results of the backward elimination procedure are shown in Table 4. The number of NSVT episodes was a significant predictor of overall mortality, sudden death, and non–sudden death mortality and was the most powerful predictor of sudden death. These analyses support the hypothesis that AECG variables, especially the frequency of NSVT episodes, are significant independent predictors of sudden death, non–sudden death mortality, and overall mortality.

Ventricular Arrhythmias Are Not Specific Predictors of Sudden Death

Although it is clear that AECG variables are significant predictors of sudden death in patients with CHF, the sensitivity and specificity of these findings are the clinically relevant issue. To address this issue, the best of the AECG variables (ln NSVT episodes) was entered into a univariate logistic analysis, which yielded false-positive rates of >80% at all sensitivity levels of ≥50% for predicting sudden death. The ROC curve (Figure 2) demonstrates that this variable has poor sensitivity and specificity, because it did not discriminate between sudden death and all-cause mortality.

Multivariate logistic regression models were developed to further investigate the ability of AECG variables to specifically predict sudden death. A logistic model was developed

<table>
<thead>
<tr>
<th>Variable</th>
<th>RR</th>
<th>CI</th>
<th>P</th>
<th>RR</th>
<th>CI</th>
<th>P</th>
<th>RR</th>
<th>CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.03</td>
<td>1.02–1.04</td>
<td>0.001</td>
<td>1.02</td>
<td>1.01–1.04</td>
<td>0.011</td>
<td>1.02</td>
<td>1.00–1.04</td>
<td>0.02</td>
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<tr>
<td>NYHA</td>
<td>1.57</td>
<td>1.22–2.00</td>
<td>0.001</td>
<td>1.22</td>
<td>0.84–1.79</td>
<td>NS</td>
<td>1.34</td>
<td>0.95–1.91</td>
<td>0.10</td>
</tr>
<tr>
<td>Etiology (CAD)</td>
<td>1.32</td>
<td>1.04–1.67</td>
<td>0.020</td>
<td>1.35</td>
<td>0.94–1.93</td>
<td>0.10</td>
<td>1.22</td>
<td>0.87–1.71</td>
<td>NS</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>1.03</td>
<td>1.02–1.05</td>
<td>0.001</td>
<td>1.03</td>
<td>1.00–1.06</td>
<td>0.055</td>
<td>1.06</td>
<td>1.03–1.09</td>
<td>0.001</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>1.02</td>
<td>1.01–1.03</td>
<td>0.001</td>
<td>1.02</td>
<td>1.01–1.04</td>
<td>0.001</td>
<td>1.01</td>
<td>0.99–1.02</td>
<td>0.12</td>
</tr>
<tr>
<td>Milrinone therapy</td>
<td>1.36</td>
<td>1.08–1.72</td>
<td>0.009</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>1.72</td>
<td>1.22–2.44</td>
<td>0.002</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease; BP, blood pressure.

RR was expressed as RR per unit for continuous variables (ie, for age, per year; ejection fraction, per ejection fraction unit; systolic blood pressure, per mm Hg pressure).
that included only the clinical variables, and this model was a very significant predictor of sudden death (Wald $\chi^2$ 46.6; $P<0.0001$), with 67% of the observed responses concordant with the model. However, at sensitivity levels >50%, there was a >80% false-positive rate. When the number of NSVT episodes was added to the model, it remained significant (Wald $\chi^2$ 58.4; $P<0.0001$), although as discussed above, only 69% of the observed results were concordant with the model, and there were similarly high false-positive rates. The addition of the strongest AECG predictor did not provide significant incremental prognostic information, as demonstrated by analyses that included either all patients or the placebo group alone (Figure 3, respectively). Not only were both models associated with poor sensitivity and specificity, but the ROC curves of the 2 models were essentially superimposable.

**Discussion**

This study demonstrates that in patients with CHF who were enrolled in the PROMISE trial, asymptomatic ventricular arrhythmias were not specific predictors of sudden death. Ambulatory ventricular arrhythmias were independent predictors of overall mortality, sudden death, and non–sudden death mortality. However, univariate and multivariate logistic analyses of these AECG variables demonstrated that these measures, either alone or in combination with other clinical variables, lacked the sensitivity and specificity necessary to guide therapeutic interventions. Thus, in this study population, ventricular arrhythmias did not specifically define a group at high risk for sudden death and did not provide significant incremental prognostic information beyond readily available clinical variables.

Previous studies have suggested that ventricular arrhythmias are statistically significant independent predictors of mortality, and the results of the present study support this observation. All of the selected AECG variables were significant predictors of both sudden death and overall mortality in univariate analyses, as well as in multivariate models that included the clinical variables of age, NYHA functional class, presence of coronary artery disease, ejection fraction, and systolic blood pressure. Of these AECG variables, the frequency of NSVT episodes was the most powerful predictor of sudden death, non–sudden death mortality, and overall mortality. Other studies have demonstrated the ability of AECG variables to predict both overall mortality and sudden death. These studies showed that the duration,4 frequency,2 or presence3,5 of NSVT, the presence of couplets,1,5 and the frequency of PVCs1 predicted sudden death.

Two recent studies (GESICA [Gruppo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina] and CHF-STAT [Congestive Heart Failure–Survival Trial of Antiarrhythmic Therapy]) have addressed similar issues, although with fewer patients and less rigorous methodology. In the GESICA trial,5 24-hour AECGs from 295 patients with advanced CHF were analyzed. There were 123 deaths in this subgroup, 44 of which were classified as sudden. Patients with NSVT were found to have significantly worse CHF, a higher overall mortality, and a greater incidence of sudden death. When a post hoc combined dichotomous variable of couplets and/or NSVT was used, there was an 89% sensitivity and a 42% specificity for the prediction of sudden death, with a 21% positive predictive value. Although these results indicate that ventricular arrhythmias are a marker for poor ventricular function and more severe CHF, the lack of

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**TABLE 4. Predictors of Outcome by Backward Elimination Multivariate Analysis**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall Mortality</th>
<th>Sudden Death</th>
<th>Non–Sudden Death Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk Ratio</td>
<td>CI</td>
<td>$P$</td>
</tr>
<tr>
<td>EF</td>
<td>1.03</td>
<td>1.01–1.04</td>
<td>0.004</td>
</tr>
<tr>
<td>NYHA</td>
<td>1.49</td>
<td>1.16–1.90</td>
<td>0.002</td>
</tr>
<tr>
<td>CAD</td>
<td>1.44</td>
<td>1.13–1.83</td>
<td>0.003</td>
</tr>
<tr>
<td>Age</td>
<td>1.03</td>
<td>1.02–1.04</td>
<td>0.001</td>
</tr>
<tr>
<td>Mirtironone</td>
<td>1.29</td>
<td>1.02–1.63</td>
<td>0.031</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>1.02</td>
<td>1.01–1.03</td>
<td>0.001</td>
</tr>
<tr>
<td>NSVT episodes</td>
<td>1.12</td>
<td>1.07–1.17</td>
<td>0.001</td>
</tr>
<tr>
<td>PVCs/h</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>NSVT</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>NSVT beats</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

EF indicates ejection fraction; CAD, coronary heart disease; and BP, blood pressure.

NSVT episodes and NSVT beats are ln transformed.

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Figure 2. ROC curves of sensitivity and specificity of NSVT episodes (ln transformed) in predicting sudden death (denoted by solid line) and all-cause mortality (denoted by dashed line). Dotted line at unity is provided for reference.
By guest on November 10, 2017

Figure 3. ROC curves of multivariate logistic regression models. In A, all of the patients from this study (n=1080) are included, whereas B includes only patients randomized to placebo (n=525). Multivariate model including only clinical variables (age, NYHA class, ejection fraction, systolic blood pressure, cause of heart failure, and treatment group) is denoted by solid line, whereas model including number of episodes of NSVT in addition to clinical variables is denoted by dashed line. Note that there is no significant difference between models with and without variable of NSVT episodes, which demonstrates that this variable does not add further significant prognostic information to the clinical variables. Dotted line at unity is provided for reference.

Although the findings of the present study are compelling, there are several limitations. First, the possible confounding variables did not significantly improve the sensitivity or specificity of the model for sudden death, which suggests that it had limited additional prognostic information.

The CHF-STAT study enrolled 674 patients with symptoms of CHF, cardiac enlargement, ≥10 PVCs per hour, and ejection fraction ≤40% in a trial of amiodarone versus placebo. These patients were selected for an increased baseline arrhythmia and had a mean PVC frequency of >250 per hour. In this selected group, there was an 80% incidence of NSVT, the presence of which was a univariate predictor of sudden death. However, in multivariate models, only ejection fraction was a significant predictor of sudden death. Thus, these findings lead to a similar conclusion that NSVT does not predict a higher risk of sudden death.

The results of the present study suggest that AECG monitoring does not select patients at high risk for sudden death, but they neither contradict nor confirm the findings of the recent MADIT trial (Multicenter Automatic Defibrillator Implantation Trial). MADIT suggested that a highly selected group of patients (previous myocardial infarction, left ventricular ejection fraction ≤35%, documented asymptomatic NSVT, and inducible, nonsuppressible ventricular tachycardia on electrophysiological study) treated with ICDs have improved survival.

Three points seem to be most relevant to placing these trials in perspective. First, the role of the AECG is different in the 2 trials. In MADIT, the AECG results were the starting point for additional evaluation and selection of patients (eg, electrophysiological study), whereas our analysis only interprets the direct relationship of AECG variables to sudden death. It may be that electrophysiological study results would provide a more specific indicator of sudden death, although this hypothesis was not tested in either trial. Unfortunately, the MADIT investigators report that there was no information on the number of patients screened for enrollment in the trials and no follow-up of the excluded patients. Second, MADIT was not designed to investigate the prognostic value of the screening algorithm that was used, but rather addressed the question of whether automated ICD therapy would be beneficial in a highly selected group of patients. There was no attempt by the study design to determine that the screening algorithm selected the group of patients who would receive the greatest benefit or that other groups who did not meet the inclusion criteria would also benefit. All we can conclude is that AECG is not a very efficient approach to screening for sudden death candidates in the PROMISE population. Third, the patient populations are quite different. All of the MADIT patients had coronary artery disease (versus 54% of the PROMISE patients), which made this group more likely to have inducible ventricular tachycardia on electrophysiological study, and relatively few had CHF of the severity required in PROMISE (65% of the patients were NYHA class II/III in MADIT compared with 58% and 42% with NYHA class III or IV, respectively, in PROMISE). Thus, regardless of whether one accepts the MADIT results, based on the results of the present study, AECGs alone provided no specific prognostic information in the patients studied in PROMISE.

Although the findings of the present study are compelling, there are several limitations. First, the possible confounding
influence of the inclusion of patients randomized to milrinone treatment must be considered. To address this issue, multivariate statistical models designed to control for the effect of milrinone were selected. Furthermore, separate analyses with the smaller placebo group confirmed the findings of the combined group, although with reduced power. Second, this study was limited only to AECG variables and did not include QT dispersion, heart rate variability or late potentials. Although each of these may hold some promise, they have yet to be shown to add predictive information beyond that of AECG and clinical variables. Third, other mechanisms for sudden death, such as bradycardia and electromechanical dissociation, may dilute the ability of ventricular arrhythmia variables to predict sudden death in this population. However, there are few data to suggest that the AECG would provide useful predictive information for these forms of sudden death either. Fourth, caution must be exercised in the application of these findings. The patients in PROMISE (NYHA class III/IV with left ventricular ejection fraction ≤35%) were a selected sample of the overall CHF population, and these results may not be generalizable. It is possible that ventricular arrhythmias may be more specific predictors in patients with less severe CHF, although this was not the case in CHF-STAT, in which >50% were NYHA II. Finaly, the classification of death in CHF trials is always difficult because of individual variation in interpretation and multiple possible mechanisms. The PROMISE trial had a central mortality committee, which provided internally consistent, although still potentially inaccurate, classification.

The results of the present study provide important answers to the questions confronting practicing clinicians. The presence or nature of baseline ventricular arrhythmias in patients with moderate-to-severe CHF does not specifically define a group at high risk for sudden death and does not provide additional prognostic information beyond readily available clinical variables. Therefore, the clinician should avoid the understandable temptation to perform AECG in CHF patients without symptoms of arrhythmia, even in those known to have frequent ectopy. Until the results of other trials that refute these findings are available, the presence of asymptomatic NSVT should not guide therapeutic interventions, such as the institution of antiarrhythmic therapy or implantation of antifibrillatory devices.

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References
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