Prevalence and Prognostic Significance of Ventricular Arrhythmias After Acute Myocardial Infarction in the Fibrinolytic Era

GISSI-2 Results

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**Background.** Several studies performed before the advent of thrombolysis have shown that the presence of ventricular arrhythmias is an independent risk factor for subsequent mortality in patients recovering from acute myocardial infarction. Since fibrinolysis affects the natural history of infarction and may alter the clinical relevance of different risk factors, the aim of the present study was to establish the prevalence and prognostic value of ventricular arrhythmias in post-myocardial infarction patients treated with fibrinolytic agents during the acute phase.

**Methods and Results.** Twenty-four-hour Holter recordings obtained before discharge from the hospital in 8,676 post-myocardial infarction patients of the GISSI-2 study were analyzed for the presence of ventricular arrhythmias. Patients were followed for 6 months from the acute event; total and sudden cardiovascular mortality rates were computed, and relative risks in univariate and multivariate analyses were calculated. Ventricular arrhythmias were present in 64.1% of the patients, more than 10 premature ventricular beats per hour were recorded in 19.7% of the patients, and nonsustained ventricular tachycardia was present in 6.8% of the patients. Ventricular arrhythmias were more frequent when signs or symptoms of left ventricular damage were present. During follow-up, there was a total of 256 deaths (3.0% of patients), 84 of which (32.8% of total deaths) were cardiac sudden deaths. Mortality rates were 2.0% in patients without ventricular arrhythmias, 2.7% in patients with one to 10 premature ventricular beats per hour, 5.5% in those with more than 10 premature ventricular beats per hour, and 4.8% in those with complex premature ventricular beats. Even after adjusting for several risk factors, the presence of frequent (more than 10 premature ventricular beats per hour) ventricular arrhythmias remained a significant predictor of total (RRc1, 1.62; 95% confidence interval, 1.16–2.26) and sudden mortality (RRc1, 2.24; 95% confidence interval, 1.22–4.08). On the other hand, the presence of nonsustained ventricular tachycardia was not associated with a worsening of the prognosis in the adjusted analysis (RRc1, 1.20; 95% confidence interval, 0.80–1.79).

**Conclusions.** This study shows that approximately 36% of patients recovering from acute myocardial infarction presented with less than one premature ventricular beat per hour in Holter recordings obtained before discharge from the hospital, whereas almost 20% of patients showed frequent (more than 10 premature ventricular beats per hour) ventricular arrhythmias. Due to the large size of the population of this study, these figures may be used as a reliable estimate of the prevalence of arrhythmias in postinfarction patients treated with fibrinolytic agents during the acute phase. Frequent premature ventricular beats are confirmed as independent risk factors of total and sudden death in the first 6 months following the acute event; the significance of nonsustained ventricular tachycardia in this population appears more controversial. (Circulation 1993;87:312–322)

**KEY WORDS** • arrhythmias • acute myocardial infarction • thrombolysis • risk stratification • premature ventricular beats • GISSI-2

Several studies published during the past 15 years have shown that the presence of frequent and/or complex ventricular arrhythmias is an independent risk factor for subsequent mortality in patients recovering from acute myocardial infarction.1–7

These results prompted the design of clinical trials to investigate whether suppression of ventricular arrhythmias by antiarrhythmic agents would reduce mortality. The results of the first trials with a variety of antiarrhythmic agents have been quite disappointing;6,9 more recently, the Cardiac Arrhythmia Suppression Trial (CAST) studies have demonstrated an increase rather than a decrease in total mortality associated with the use of antiarrhythmic drugs despite effective control of the arrhythmias.10,11 At the same time, a growing body of evidence has accumu-
lated on the effects of thrombolysis on the natural history of infarction\textsuperscript{12-15} and on the prevalence and clinical relevance of different risk factors known to play an important role in terms of mortality risk of post–myocardial infarction patients.\textsuperscript{16,17}

Indeed, thrombolysis was shown to be effective in reducing the incidence of life-threatening arrhythmias such as ventricular fibrillation during the in-hospital phase\textsuperscript{18} and the prevalence of late potentials at the time of discharge\textsuperscript{19} as well as in improving left ventricular function.\textsuperscript{18} Because all the studies that suggested a relation between ventricular arrhythmias and increased mortality were performed in the prefibrinolytic era, it was thought necessary to reassess the prevalence and prognostic significance of ventricular arrhythmias in patients recovering from myocardial infarction and treated with thrombolytic agents during the acute phase.

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Therefore, the present study concerns the prevalence and prognostic value of ventricular arrhythmias detected in Holter recordings of 8,676 patients recovering from acute myocardial infarction who were enrolled in the Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardo (GISSI-2) study\textsuperscript{20} and had been followed for 6 months.

The size of the population of the GISSI-2 study allows a reliable evaluation of the impact on 6-month mortality of frequent and complex arrhythmias in a population highly representative of post–myocardial infarction patients in the 1990s.

Methods

Trial Design and Studied Population

The details of the design and the main results of the GISSI-2 study are provided in the original report.\textsuperscript{20}

The trial entry criteria were 1) chest pain with ST segment elevation of $\geq 1$ mm in any limb lead of the ECG and/or $\geq 2$ mm in any precordial lead, 2) admission to the cardiac care unit within 6 hours of the onset of symptoms, and 3) no clear contraindication to fibrinolytic treatment and/or to heparin. No age restriction or exclusion criteria were imposed other than those strictly related to contraindications to thrombolytic treatments. Eligible patients were randomized by telephone call to the coordinating center, which operated on a 24-hour-a-day basis. Treatment was assigned according to a computer-generated list stratified by hospital.

Twelve thousand three hundred eighty-one patients were randomized within 6 hours of the onset of symptoms: 6,199 received streptokinase (1.5 million units over 30–60 minutes) and 6,182 received tissue-type plasminogen activator (t-PA) (Actilyse, 100 mg over 3 hours).

According to the factorial design, 6,175 patients were also randomly allocated to receive subcutaneous heparin (12,500 units twice daily), and 6,206 patients were allocated to the no-heparin group.

Laboratory examinations (i.e., 24-hour ECG monitoring, two-dimensional echocardiogram, ECG stress testing) were required by the study protocol to obtain the main prognostic variables needed for risk stratification of patients at discharge.

A 24-hour ambulatory ECG monitoring was performed in 8,676 patients an average of 17 days (range, 6–36 days) after randomization following a washout of antiarrhythmic and $\beta$-blocking therapy whenever this was considered feasible by the attending physician. The Holter recordings were performed and analyzed peripherally by participating cardiac care unit personnel, and the following data were reported in the study forms: total number of premature ventricular beats (PVBs), presence of couplets, presence of nonsustained ($<30$ seconds) ventricular tachycardia (three or more consecutive PVBs at a rate of $>100$ beats per minute), and presence of sustained ventricular tachycardia.

To assess the prevalence of ventricular arrhythmias and their prognostic significance, the patients were divided according to three different criteria: 1) frequency of arrhythmias: less than one PVB per hour, one to 10 PVBs per hour, and more than 10 PVBs per hour; 2) presence or absence of complex arrhythmias, defined as more than 10 PVBs per hour and/or any number of couplets and/or runs of nonsustained ventricular tachycardia; and 3) presence or absence of runs of nonsustained ventricular tachycardia.

Central quality control of the ECG recordings was ensured by checking a randomly selected sample of 912 ECG recordings (10.5% of the 8,676 examinations) by two experienced cardiologists blinded to study treatments to verify the correct assignment of patients according to criteria 1 and 3.

Patient Follow-up

The participating cardiac care units were requested to record clinically relevant events (e.g., death, reinfarction, cerebrovascular accident) and interventions such as percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass graft surgery (CABG) occurring to their patients within the first 6 months from admission to the trial. Information on survival for patients not traced by cardiac care units was obtained centrally through inquiries to the appropriate census offices.

Follow-up data are therefore available for the entire population from the day of the 24-hour ECG recording to 6 months after randomization.

Sudden cardiac death was defined as unexpected death occurring within 1 hour after the onset of symptoms.

Statistical Analysis

The $\chi^2$ statistics were used to test the significance of differences in the prevalence of arrhythmias among different groups of patients.

Both unadjusted and adjusted associations between ventricular arrhythmias at discharge and 6-month mortality are presented. Mantel-Haenszel-Peto odds ratios (OR\textsubscript{adj}) were used to measure univariate associations and are provided with 95% confidence intervals (CI).

The probability values refer to comparisons of the survival experience of the different groups by means of the log-rank test. To compare the cumulative survival to 6 months of follow-up, all patients surviving more than 6 months after randomization have been censored at 180 days.

The multivariate analysis was performed using the Cox proportional hazard model to assess the independent prognostic value of arrhythmias, and the results are
TABLE 1. Clinical Characteristics of the Studied Population

<table>
<thead>
<tr>
<th>Age (%)</th>
<th>Time History</th>
<th>Treatments at discharge (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤70 Years</td>
<td>80.7</td>
<td>Insulin-dependent (%)</td>
</tr>
<tr>
<td>&gt;70 Years</td>
<td>19.3</td>
<td>Absence of late (beyond day 4) clinical congestive heart failure; or extensive left ventricular damage in the absence of clinical heart failure. Clinical heart failure was defined as the presence of at least two of the following signs: presence of a third sound, rales, dyspnea, or radiological evidence of pulmonary congestion. Extensive left ventricular damage, when not clinically evident, was established in the presence of an echocardiographic left ventricular ejection fraction of ≤35% or of ≥45% injured myocardial segments (the left ventricle is evaluated by two-dimensional echocardiography and divided into 11 segments).21</td>
</tr>
</tbody>
</table>

Results

The clinical characteristics of the population are shown in Table 1. An AMI was confirmed in 8,624 of the 8,676 patients (99.4%) who underwent the 24-hour ECG recording. In the remaining 52 patients (0.6%), an acute elevation of the ST segment without cardiac enzyme elevation was observed, indicating an acute coronary syndrome without conclusive evidence of myocardial infarction. Because all of the subjects in this study underwent acute thrombolysis, this small group of patients may represent a population with "aborted" myocardial infarction due to early reperfusion.

Prevalence of Ventricular Arrhythmias

The quality control analysis showed that 98% of the patients were classified correctly.

Overall, 3,112 (35.9%) were free from ventricular arrhythmias, and 1,712 patients had more than 10 PVBs per hour (19.7%); furthermore, 2,892 patients (33.3%) presented with complex ventricular arrhythmias, and nonsustained ventricular tachycardia was observed in 586 patients (6.8% of the recordings) (Table 2).

The prevalence of ventricular arrhythmias was not modified by the type of fibrinolytic agent administered (streptokinase or t-PA) or by the addition of subcutaneous heparin. Among the 4,373 t-PA–treated patients and the 4,303 patients treated with streptokinase, 36.0% and 35.7%, respectively, were free from ventricular arrhythmias, whereas 19.7% and 19.8% presented with more than 10 PVBs per hour, 32.8% and 33.9% had complex ventricular arrhythmias, and 6.6% and 6.9% had nonsustained ventricular tachycardia, respectively. Similarly, of the 4,366 patients treated with heparin and the 4,310 patients not treated with heparin, 35.2% and 36.6%, respectively, did not show ventricular arrhythmias, whereas 20.2% and 19.3% presented with more

TABLE 2. Prevalence of Different Classes of Ventricular Arrhythmias in Predischarge 24-Hour Holter Monitoring

<table>
<thead>
<tr>
<th>PVBs per hour</th>
<th>0 (n, %)</th>
<th>1–10 (n, %)</th>
<th>&gt;10 (n, %)</th>
<th>Complex PVBs (n, %)</th>
<th>Nonsustained ventricular tachycardia (n, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population (8,676 patients)</td>
<td>3,112 (35.9)</td>
<td>3,852 (44.4)</td>
<td>1,712 (19.7)</td>
<td>2,892 (33.3)</td>
<td>586 (6.8)</td>
</tr>
<tr>
<td>CHF</td>
<td>Yes (721 patients)</td>
<td>193 (26.8)</td>
<td>327 (45.3)</td>
<td>201 (27.9)</td>
<td>318 (44.1)</td>
</tr>
<tr>
<td></td>
<td>No (7,955 patients)</td>
<td>2,919 (36.7)</td>
<td>3,525 (44.3)</td>
<td>1,511 (18.9)</td>
<td>2,574 (32.3)</td>
</tr>
<tr>
<td></td>
<td>EF ≤35% (358 patients)</td>
<td>90 (25.1)</td>
<td>154 (43.0)</td>
<td>114 (31.8)</td>
<td>153 (42.8)</td>
</tr>
<tr>
<td></td>
<td>EF &gt;35% (2,236 patients)</td>
<td>811 (36.3)</td>
<td>1,038 (46.5)</td>
<td>387 (17.3)</td>
<td>690 (30.9)</td>
</tr>
<tr>
<td>Myocardial segment injured</td>
<td>≥45% (419 patients)</td>
<td>110 (26.3)</td>
<td>190 (45.4)</td>
<td>119 (28.4)</td>
<td>185 (44.2)</td>
</tr>
<tr>
<td></td>
<td>&lt;45% (7,051 patients)</td>
<td>2,551 (36.2)</td>
<td>3,137 (44.5)</td>
<td>1,363 (19.3)</td>
<td>2,318 (32.9)</td>
</tr>
</tbody>
</table>

PVBs, premature ventricular beats; CHF, clinical heart failure; EF, ejection fraction.
than 10 PVBs per hour, 32.9% and 33.8% had complex ventricular arrhythmias, and 6.3% and 7.2% had nonsustained ventricular tachycardia, respectively.

Signs or symptoms of severe left ventricular damage were strongly associated with the occurrence and severity of ventricular arrhythmias. Of the patients without clinical symptoms of congestive heart failure, 36.7% were free of arrhythmias compared with 26.8% of those with patent clinical congestive heart failure ($p < 0.001$); similarly, 36.3% of the patients with an ejection fraction of >35% compared with 25.1% of those with an ejection fraction of ≤35% ($p < 0.002$) and 36.2% of patients with <45% injured myocardial segments compared with 26.3% of those with ≥45% injured segments ($p < 0.0001$) did not show arrhythmias before hospital discharge.

Similarly, the prevalence of frequent (more than 10 PVBs per hour) or complex PVBs and the occurrence of runs of nonsustained ventricular tachycardia were significantly higher in patients with symptoms or signs of depressed left ventricular function than in those free of these clinical signs.

Prognostic Significance of Ventricular Arrhythmias

Six-month mortality data were available for 8,552 patients (98.5% of the total). There was a total of 256 deaths (3.0%), of which 84 were defined as sudden cardiac deaths (0.98% of the total population and 32.8% of all deaths).

Figure 1 shows the 6-month survival curves of patients with no PVBs, with one to 10 PVBs per hour, and with more than 10 PVBs per hour. The mortality risk of the subgroups with more frequent arrhythmias appears significantly increased: compared with the mortality rate of patients without ventricular arrhythmias (2.0%), those with one to 10 PVBs per hour experience a mortality rate of 2.7% ($OR_{MHP}$, 1.33; 95% CI, 0.97–1.81), whereas patients with more than 10 PVBs per hour have a mortality rate of 5.5% ($OR_{MHP}$, 2.98; 95% CI, 2.13–4.17).

Similarly, the presence of complex ventricular arrhythmias (more than 10 PVBs per hour and/or any number of couplets and/or nonsustained ventricular tachycardia) was associated with a higher mortality rate (4.8% versus 2.1%; $OR_{MHP}$, 2.55; 95% CI, 1.96–3.32) (Figure 2).

As expected, mortality rates were consistently higher among patients with clinical signs of congestive heart failure or echocardiographic evidence of extensive left ventricular damage. However, in each subgroup of patients, the presence of more than 10 PVBs per hour or of complex ventricular arrhythmias was significantly associated with a higher mortality risk regardless of the presence of left ventricular dysfunction (Table 3 and Figures 3 and 4).

Given the low incidence of sudden death (0.98%), the impact of arrhythmias on the risk of sudden death was investigated regardless of left ventricular function.

Seventeen sudden cardiac deaths (0.6%) were observed among patients without ventricular arrhythmias; 32 (0.8%) occurred among those with one to 10 PVBs per hour ($OR_{MHP}$, 1.50; 95% CI, 0.85–2.64), and 35 (2.1%) occurred among those with more than 10 PVBs per hour. The presence of more than 10 PVBs per hour was significantly associated with a higher incidence of sudden death ($OR_{MHP}$, 4.07; 95% CI, 2.30–7.20), whereas the presence of complex ventricular arrhythmias was associated with an $OR_{MHP}$ of 3.29 (95% CI, 2.08–5.19) of sudden cardiac death (mortality rates were 1.7% and 0.6%, respectively, in the presence and absence of complex ventricular arrhythmias).

Similar results are obtained in the multivariate analysis; the adjusted RR confirm that the presence of frequent or complex ventricular arrhythmias is an im-
portant predictor of total mortality ($RR_{\text{CI}}$, 1.62; 95% CI, 1.16–2.26 for more than 10 PVBs per hour; and $RR_{\text{CI}}$, 1.64; 95% CI, 1.27–2.12 for complex ventricular arrhythmias) and of sudden mortality ($RR_{\text{CI}}$, 2.24; 95% CI, 1.22–4.08 for more than 10 PVBs per hour; and $RR_{\text{CI}}$, 2.11; 95% CI, 1.34–3.17 for complex ventricular arrhythmias).

Prognostic Significance of Nonsustained Ventricular Tachycardia

Nonsustained ventricular tachycardia showed an univariate association with the risk of death; the increase in risk also was statistically significant for sudden mortality (Table 4).

Once the relevant epidemiological and clinical variables were adjusted for, however, nonsustained ventricular tachycardia was no longer a significant predictor of mortality ($RR_{\text{CI}}$, 1.20; 95% CI, 0.80–1.79 for total mortality; and $RR_{\text{CI}}$, 1.42; 95% CI, 0.74–2.74 for sudden mortality).

Similar results are obtained using a more restrictive definition of nonsustained ventricular tachycardia, i.e., episodes with a ventricular rate of >120 beats per minute ($RR_{\text{CI}}$, 1.54; 95% CI, 0.71–3.11 for total mortality).

Sustained Ventricular Tachycardia

Sustained ventricular tachycardia was identified on the 24-hour ECG monitoring at predisharge in only 12 patients (0.1% of the total population). At 6 months, two of the 12 patients had died (16.7%), whereas the mortality rate in patients without sustained ventricular tachycardia was 3.0% (254 of 8,540). However, the small size of the subgroup presenting with sustained ventricular tachycardia and the obvious fact that they also underwent several specific and more aggressive treatments clearly contraindicate formal statistical comparisons.

Antiarrhythmic and $\beta$-Blocking Therapy After Discharge

Predisharge 24-hour ECG monitoring was performed after a washout of $\beta$-blocker and antiarrhythmic agents; therefore, the prevalence of ventricular arrhythmias is unlikely to be affected by these treatments.

After discharge, 25.6% of the patients were treated with $\beta$-blockers, and 11.2% were treated with antiarrhythmic drugs. Because these treatments were not randomized, clinical characteristics, severity of the underlying cardiac disease, and hence prognosis in patients receiving or not receiving these drugs may be highly different. Six-month mortality data were also adjusted for postdischarge treatment with antiarrhythmics and $\beta$-blockers, and therefore the prognostic value of the various subtypes of arrhythmias presented must be considered independent of the use of these treatments at discharge.

Discussion

The analysis of the prevalence and prognostic significance of ventricular arrhythmias resulting from a large population of patients with AMI undergoing early thrombolysis allows a reappraisal of their impact on mortality.

Prevalence of Ventricular Arrhythmias

The study provides new baseline data on post-AMI ventricular arrhythmias: as expected, the prevalence of ventricular arrhythmias was lower than that reported from the studies performed before the advent of thrombolysis. Arrhythmias were present in 64% of the patients compared with 86% of patients in the Multicenter Postinfarction Research Group (MPIP) study$^2$ and 84% of patients in the placebo group of the BHAT study.$^7$ Furthermore, the prevalence of nonsustained ventricu-
TABLE 3. Six-Month Mortality Risk According to PVB Class and Complex Ventricular Arrhythmias

<table>
<thead>
<tr>
<th>PVBs class</th>
<th>Deaths (%)</th>
<th>OR\textsubscript{MHP} (95% CI)</th>
<th>Deaths (%)</th>
<th>OR\textsubscript{MHP} (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients with CHF</td>
<td></td>
<td>Patients without CHF</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>11/189 (5.8)</td>
<td>1</td>
<td>51/2,874 (1.8)</td>
<td></td>
</tr>
<tr>
<td>1-10</td>
<td>32/324 (9.9)</td>
<td>1.69 (0.89–3.23)</td>
<td>70/3,478 (2.0)</td>
<td></td>
</tr>
<tr>
<td>&gt;10</td>
<td>28/194 (14.4)</td>
<td>2.56 (1.32–4.96)</td>
<td>64/1,493 (4.3)</td>
<td></td>
</tr>
<tr>
<td>Complex PVBs</td>
<td>No</td>
<td>26/398 (6.5)</td>
<td>1</td>
<td>93/5,304 (1.7)</td>
</tr>
<tr>
<td></td>
<td>45/309 (14.6)</td>
<td>2.43 (1.48–3.98)</td>
<td>92/2,541 (3.6)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>71/707 (10.0)</td>
<td>2.56 (1.80–3.94)</td>
<td>185/7,845 (2.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patients with EF ≤35%</td>
<td></td>
<td>Patients with EF &gt;35%</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>9/89 (10.1)</td>
<td>1</td>
<td>9/804 (1.1)</td>
<td></td>
</tr>
<tr>
<td>1-10</td>
<td>12/150 (8.0)</td>
<td>0.77 (0.31–1.94)</td>
<td>14/1,030 (1.3)</td>
<td></td>
</tr>
<tr>
<td>&gt;10</td>
<td>23/111 (20.7)</td>
<td>2.19 (1.03–4.68)</td>
<td>16/382 (4.2)</td>
<td></td>
</tr>
<tr>
<td>Complex PVBs</td>
<td>No</td>
<td>14/201 (7.0)</td>
<td>1</td>
<td>18/1,533 (1.2)</td>
</tr>
<tr>
<td></td>
<td>30/149 (20.1)</td>
<td>3.30 (1.74–6.25)</td>
<td>21/683 (3.1)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>44/350 (12.6)</td>
<td>2.26 (1.89–10.31)</td>
<td>39/2,216 (1.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patients with ≥45% injured myocardial segments</td>
<td></td>
<td>Patients with &lt;45% injured myocardial segments</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>10/108 (9.3)</td>
<td>1</td>
<td>48/2,515 (1.9)</td>
<td></td>
</tr>
<tr>
<td>1-10</td>
<td>17/184 (9.2)</td>
<td>1.00 (0.44–2.26)</td>
<td>69/3,107 (2.2)</td>
<td></td>
</tr>
<tr>
<td>&gt;10</td>
<td>23/118 (19.5)</td>
<td>2.26 (1.08–4.73)</td>
<td>58/1,341 (4.3)</td>
<td></td>
</tr>
<tr>
<td>Complex PVBs</td>
<td>No</td>
<td>20/227 (8.8)</td>
<td>1</td>
<td>88/4,676 (1.9)</td>
</tr>
<tr>
<td></td>
<td>30/183 (16.4)</td>
<td>2.03 (1.12–3.67)</td>
<td>87/2,287 (3.8)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>50/410 (12.2)</td>
<td>2.19 (1.59–3.02)</td>
<td>175/6,963 (2.5)</td>
<td></td>
</tr>
</tbody>
</table>

PVBs, premature ventricular beats; OR\textsubscript{MHP}, Mantel-Haenszel-Peto odds ratio; CI, confidence intervals; CHF, clinical heart failure; EF, ejection fraction.

Lar tachycardia was 6.8%, lower value than that observed by Cats et al\textsuperscript{22} (19.5%), Bigger et al\textsuperscript{13} (8.6–11.6% according to different criteria), and in the MPIP study\textsuperscript{3} (11.3%). On the other hand, the prevalence of frequent PVBs (i.e., more than 10 PVBs per hour) was well within the range of values reported by other studies (21.2% for MPIP,\textsuperscript{5} 14.6% for MILIS,\textsuperscript{6} and 12.9% for BHAT\textsuperscript{7}). Differences in the size of the populations...
studied, in the selection of the patients (patients with severe heart failure were excluded from the BHAT study\(^7\)), in the definition of nonsustained ventricular tachycardia, and in the timing of Holter recordings may account for some of these discrepancies. However, the data suggest that the improved management of the patients with AMI may have not only affected inhospital mortality but also reduced cardiac electrical instability following the acute event, leading to a higher proportion of patients free from arrhythmias among those recovering from the infarction. Other studies have shown that thrombolysis may decrease the incidence of life-threatening arrhythmias (e.g., in-hospital ventricular fibrillation)\(^18\) and the prevalence of other markers of electrical instability of the infarcted heart (e.g., late potentials).\(^19\)

Furthermore, the improved profile of thrombolysed patients in terms of left ventricular function\(^16\) may indirectly account for a reduction in the prevalence of ventricular arrhythmias, the latter being strongly related to cardiac function.

Given the unusually large size of this study population (fivefold to 20-fold greater than that of other published series) and the epidemiological representativeness of the sample (reflecting the practice of the majority of Italian cardiac care units), the prevalence estimates may confidently be assumed to be the baseline clinical reality of thrombolysed patients in the 1990s.

**Prognostic Significance of Ventricular Arrhythmias**

During the 6 months of follow-up, a 3% mortality rate was observed in the population of patients in which 24-hour ECG recording was performed, about one third of which was due to sudden cardiac death. Despite the mortality rate reduction achieved in thrombolysed patients,\(^12-15\) ventricular arrhythmias retain a relevant prognostic value. Frequent or complex ventricular arrhythmias are associated with a twofold to threefold increase in total and sudden mortality risks, irrespective of the presence of signs of cardiac damage, and stratification for several relevant clinical variables does not appear to influence the association. Although other studies of a smaller population of thrombolysed patients showed that ventricular ectopic frequency was not an independent predictor of mortality,\(^17\) in the present study the presence of frequent or complex ventricular arrhythmias exerted an important effect on the mortality risk of patients recovering from AMI after treatment with fibrinolytic agents.

In our study, nonsustained ventricular tachycardia was associated with a higher mortality risk in the univariate analysis but did not retain its prognostic significance after adjustment for other prognostic variables, even when the lower limit of the ventricular rate of the runs was set at 120 beats per minute rather than at 100 beats per minute. A possible explanation might
be related to the exposure of the entire population to thrombolytic agents, which could influence the prognostic relevance of this ventricular arrhythmia by modifying the myocardial substrate. Alternatively, this discrepancy with the results of previous studies could be a function of the extreme variability of nonsustained ventricular tachycardia in 24-hour ECG recordings in post-AMI patients, recently highlighted by the analysis of the data from the Cardiac Arrhythmia Pilot Study (CAPS). The wide temporal variability observed might account for the different prevalence rates and prognostic value estimates of this repetitive arrhythmia. In any case, the results of this study appear to challenge the importance generally attributed to nonsustained ventricular tachycardia in predicting mortality in post-AMI patients, particularly compared with the stability of the risk estimates associated with other arrhythmic indicators.

**Study Implications**

The results of the present study show that despite a decrease in mortality after infarction in patients treated with thrombolytic agents, ventricular arrhythmias remain a marker of electrical instability that may effectively contribute to identify subjects at increased risk of death within the first 6 months after the acute event. It is noteworthy that in the absence of complex ventricular arrhythmias and left ventricular dysfunction, mortality rate at 6 months is 1.7%. The opportunity of undertaking aggressive strategies, either diagnostic (e.g., coronary arteriography) or therapeutic (e.g., PTCA, CABG), requires cautious evaluation in these patients (representing 62% of the population discharged alive after AMI treated acutely with thrombolytic agents) in terms of benefits versus risks and versus cost expectations.

A reduction in the mortality risk by any potential specific antiarrhythmic interventions could be sought in patients with frequent or complex ventricular arrhythmias but without impaired ventricular function (approximately 30% of the entire population), although the feasibility of this approach in terms of population size needs careful evaluation given the relatively low baseline mortality (3.6% at 6-month follow-up).

The higher prevalence of ventricular arrhythmias in patients with signs or symptoms of left ventricular damage indicates a wide overlap between the population subgroups affected by these independent, negative post-AMI prognostic factors. Therapeutic strategies oriented to prevent or treat left ventricular dysfunction might represent the most important tools with which to obtain further relevant improvements in survival of post-AMI patients.
Table 4. Nonsustained Ventricular Tachycardia and 6-Month Mortality

<table>
<thead>
<tr>
<th></th>
<th>Nonsustained ventricular tachycardia</th>
<th></th>
<th></th>
<th>OR_{MHP}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (%) (n)</td>
<td>No (%) (n)</td>
<td>Total (%) (n)</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>Overall mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total population</td>
<td>4.9 (28/576)</td>
<td>2.9 (228/7,976)</td>
<td>3.0 (256/8,552)</td>
<td>1.99 (1.21-3.27)</td>
</tr>
<tr>
<td>CHF</td>
<td>15.1 (11/73)</td>
<td>9.5 (60/634)</td>
<td>10.0 (71/707)</td>
<td>1.86 (0.83-4.16)</td>
</tr>
<tr>
<td>No CHF</td>
<td>3.4 (17/503)</td>
<td>2.3 (168/7,342)</td>
<td>2.4 (185/7,845)</td>
<td>1.61 (0.89-2.91)</td>
</tr>
<tr>
<td>EF ≤35%</td>
<td>14.0 (6/43)</td>
<td>12.4 (38/307)</td>
<td>12.6 (44/350)</td>
<td>1.15 (0.44-3.02)</td>
</tr>
<tr>
<td>EF &gt;35%</td>
<td>5.1 (7/137)</td>
<td>1.5 (32/2,079)</td>
<td>1.8 (39/2,216)</td>
<td>7.88 (2.12-29.3)</td>
</tr>
<tr>
<td>Myocardial segments</td>
<td>9.3 (5/54)</td>
<td>12.6 (45/356)</td>
<td>12.2 (50/410)</td>
<td>0.73 (0.30-1.75)</td>
</tr>
<tr>
<td>injured ≥45%</td>
<td>4.6 (21/459)</td>
<td>2.4 (154/6,504)</td>
<td>2.5 (175/6,963)</td>
<td>2.46 (1.34-4.51)</td>
</tr>
<tr>
<td>Myocardial segments</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>injured &lt;45%</td>
<td>1.9 (11/576)</td>
<td>0.9 (73/7,976)</td>
<td>0.98 (84/8,552)</td>
<td>2.78 (1.18-6.55)</td>
</tr>
</tbody>
</table>

OR_{MHP}, Mantel-Haenszel-Peto odds ratio; CI, confidence intervals; CHF, clinical heart failure; EF, ejection fraction.

Appendix

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