Selection of dichotomy limits for multifactorial prediction of arrhythmic events and mortality in survivors of acute myocardial infarction

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Aims To evaluate the predictive value and optimum dichotomy limits for different combinations of prognostic indicators for the prediction of arrhythmic events and cardiac mortality in post-infarction patients.

Background Studies of new interventions based on risk stratification after myocardial infarction have often used a single variable as a predictor of risk. However, whether the dichotomy limits of these single variables, derived from univariate analyses, should be altered when such variables are combined for the prediction of risk after myocardial infarction has not been examined.

Methods Left ventricular ejection fraction, signal-averaged electrocardiography, heart rate variability index, mean heart rate and ventricular extrasystole frequency were recorded pre-discharge in 439 survivors of their first myocardial infarction. Arrhythmic events and cardiac mortality were recorded during 1 year (range 1–6 years) follow-up.

Results During follow-up for at least 1 year, there were 25 cardiac deaths and 23 arrhythmic events. Different optimum dichotomy limits were obtained for the prediction of cardiac mortality vs arrhythmic events, for different combinations of variables, for different selected levels of sensitivity and for different numbers of variables abnormal before identification of those at risk. The dichotomy limit of the heart rate variability index for the prediction of events appeared to be the least affected by the inclusion of other variables. For example, when predicting arrhythmic events using combinations of left ventricular ejection fraction and/or heart rate variability, the optimum dichotomy limits when each variable was used alone was 32% and 18 units respectively; 43% and 18 units when either left ventricular ejection fraction or heart rate variability are required to be abnormal, and 52% and 19 units when both are required to be abnormal before identification of those at risk of arrhythmic events.

Conclusions Dichotomy limits derived from univariate analyses do not optimally predict events when used in the multivariate setting. Risk stratification can be improved by using several variables in combination and is further improved by using dichotomy limits of these variables which are different from those used in or derived from univariate analyses.

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Key Words: Myocardial infarction, risk stratification, arrhythmic events, cardiac mortality.

Introduction

Arrhythmic events in post-infarction patients remain difficult to predict and are still based mainly on estimates of left ventricular contractility (1–3). However, with the introduction of thrombolytic therapy designed to preserve left ventricular function, and ACE inhibitor therapy to treat patients with left ventricular dysfunction after myocardial infarction, early mortality has declined and the ejection fraction may no longer be a reliable predictor of arrhythmic events. Heart rate variability and other variables have recently been shown to be better than the ejection fraction for predicting arrhythmic events after myocardial infarction (4–6); however, the predictive value of single variables is still too low for clinical use.

It has been shown that the prediction of clinical events can be improved by combining variables. For example, the positive predictive accuracy for arrhythmic events rises from 15% when heart rate variability is used
alone to 32% when heart rate variability is combined with the presence of late potentials\textsuperscript{7}. The optimum combination for predicting arrhythmic events appears to be based on using the heart rate variability index. However, it is not known whether the dichotomy limits (that is, the thresholds of normality and abnormality of the scale used to measure the variable) used in or derived from univariate analyses provide the optimum prediction of post-infarction arrhythmic and other events when these variables are combined. The influence of the combination of variables or the selection of end-point on the optimum dichotomy limits of these variables is also unclear. What is 'optimal' in one setting may not be 'optimal' in another. These issues may have important implications for the design of prospective clinical trials in the prevention of arrhythmic events post myocardial infarction. We therefore evaluated the optimum combination and dichotomy limits of the left ventricular ejection fraction, signal-averaged ECG, mean heart rate, heart rate variability and ventricular premature complex frequency for predicting arrhythmic events and cardiac mortality after a first acute myocardial infarction.

**Methods**

**Patient population**

The patient population consisted of 439 consecutive patients aged $\leq 70$ years old admitted to our hospital with their first acute myocardial infarction and who survived to hospital discharge. Only patients admitted from home and surviving the acute phase of myocardial infarction were enrolled and studied prospectively. Acute myocardial infarction was diagnosed if at least two of the following three criteria were met:

1. characteristic chest pain lasting $\geq 30$ min;
2. a sequential increase and decrease in plasma concentrations of creatine phosphokinase, aspartate transaminase or lactate dehydrogenase with a peak concentration at least twice the upper limit of normal for our laboratory; and
3. development of new pathological Q waves or ST/T changes suggestive of non-Q wave infarction.

Patients were excluded if they had important non-cardiac disease, a history of previous cardiac surgery or pacemaker implantation or were unable to be followed-up. Patients with atrial fibrillation, left bundle branch block, ventricular pre-excitation and those in whom ambulatory monitoring, signal-averaged ECG or assessment of left ventricular ejection fraction could not be made were also excluded.

Patients were followed-up for at least 1 year (range 1–6 years). Sudden death and ventricular tachycardia were classified by a group of physicians without knowledge of risk stratification results. Based on the Cardiac Arrhythmia Pilot Study\textsuperscript{8}, sudden death was defined as death within 1 h of last being seen alive. Arrhythmic events were defined as sudden death and/or symptomatic, sustained ($\geq 30$ s) ventricular tachycardia documented electrocardiographically.

**Left ventricular function**

Before hospital discharge, all patients performed a symptom-limited treadmill exercise test using a Bruce or modified-Bruce protocol. An abnormal test was defined as significant ST segment depression ($\geq 1.5$ mm in at least two leads), an exercise duration of less than 3 min, an increase in blood pressure of less than 30 mmHg or exercise-induced angina. Patients with an abnormal test had pre-discharge selective coronary arteriography and left ventricular angiography. In these patients, left ventricular ejection fraction was calculated from the right anterior oblique view using a Mac angiocomputer package based on the formula of Sandler and Dodge\textsuperscript{9}. All other patients underwent radionuclide angiography in the supine position with the left ventricular ejection fraction calculated by the multiple-gated method. A previous pilot study in our department has shown that ejection fraction calculated by these two methods correspond well to each other\textsuperscript{7}.

**Signal-averaged electrocardiogram**

In each patient, a high gain signal averaged electrocardiogram was obtained before hospital discharge at a median of day 7 (range 5–10 days) using a commercially available system from Arrhythmia Research Technology (model 1200 EPX). The method used has been described elsewhere\textsuperscript{10}. In brief, the system utilizes Frank orthogonal leads, a sampling rate of 1 KHz and low and high pass filters of 250 and 40 Hz, respectively. In each patient, 200 to 500 ventricular complexes were averaged; the achieved noise level was $\leq 0.5 \mu V$ in 96% of recordings. Recordings were made when the patients were not taking any anti-arrhythmic medication. The duration of the signal-averaged QRS complex ($t_{QRS}$) was used for the detection of late potentials because this is better for predicting arrhythmic events than either the root mean square voltage of the terminal 40 ms or the duration of low amplitude signals $<40 \mu V$\textsuperscript{11}. Furthermore, a univariate result of the signal-averaged ECG was more suitable for combination with other univariate risk factors.

**Ambulatory 24 h monitoring**

Ambulatory 24 h electrocardiograms were recorded at a median of 7 days (range 5 to 11 days) after admission using Marquette or Reynolds 2 channel recorders (leads II and CM\textsubscript{3}). None of the patients was receiving specific anti-arrhythmic medication during the recording period.
Beta-blockers were stopped at least two half-lives before the recording. The heart rate variability index was calculated for each patient as previously described. In brief, each beat is classified as normal or abnormal using the matching-pairs principle. A frequency distribution of normal-to-normal RR intervals is constructed and the area of the histogram (that is, the total number of normal-to-normal intervals) is divided by its height. The result is expressed in technical units. The average number of ventricular premature complexes per hour and the average normal-to-normal RR interval (mean NN) were also calculated.

**Statistical analysis**

Comparisons of risk factors between those who did and did not suffer events were compared using the non-parametric Wilcoxon test. Values are expressed as mean ± standard deviation.

Sensitivity was defined as the percentage of patients with a positive test result from all patients with an end-point; specificity as the percentage of patients with a negative test result from all patients with an end-point; and positive predictive accuracy as the percentage of patients with an end-point from all patients with a positive test result.

The relationships between positive predictive accuracy and sensitivity were calculated for individual variables and various combinations of these variables for predicting events at one-year using a previously described algorithm. In brief, positive predictive curves which associate the positive predictive accuracy with values of sensitivity were computed for the univariate and multivariate prediction of arrhythmic events and mortality. For the computation of these curves, the dichotomy points of individual variables were varied in order to achieve all different values of sensitivity, and for each value of sensitivity, the maximum positive predictive accuracy was computed. These calculations were repeated for each individual variable and for each combination of variables for the prediction of both arrhythmic events and mortality.

Optimum dichotomy limits (that is, the cut-off points which achieve the highest statistical significance associating the variable with outcome) were calculated for individual variables and their combination using Fisher’s exact test; multivariate analysis using logistic regression was not used as this does not allow dichotomy limits to be varied easily.

**Results**

**Clinical characteristics**

During a follow-up period of ≥1 year (median 2.7 years, range 1–6 years), there were 25 cardiac deaths, 13 of which were sudden. There were 23 arrhythmic events, defined as sudden death (13 patients) and/or symptomatic, sustained (>30 s) ventricular tachycardia documented electrocardiographically (15 patients). The clinical characteristics of the total patient population, together with a comparison of those patients who developed arrhythmic events with those who died from cardiac causes is given in Table 1. Between these two groups of patients there were no significant differences in age, mean left ventricular ejection fraction, the proportion with a left ventricular ejection fraction <40% and the proportion who received thrombolysis. In the total population, 177 (40%) received beta-blockers, however a smaller proportion of those who had events were receiving beta-blockers.

The values of left ventricular ejection fraction ranged from 9 to 85%, total QRS duration from 56 to 187 ms, mean NN from 418.0 to 1485.1 ms, heart rate variability index from 3.57 to 64.40, and ventricular premature complexes frequency from 0 to 670.1 per hour. Table 2 compares the mean values (+ SD) of these variables in patients who did and did not suffer from arrhythmic events and/or cardiac death. There was a significant difference in left ventricular ejection fraction, mean NN, heart rate variability index and ventricular premature complex frequency between those who did and those who did not die from cardiac causes and between those who did and those who did not have arrhythmic events. However, a significant difference in tQRS duration was found only between patients who did and those who did not have arrhythmic events.
Table 2: Mean values ± standard deviations of the individual variables. The column n shows the number of patients in each group.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>LVEF</th>
<th>tQRS</th>
<th>Mean NN</th>
<th>HRV index</th>
<th>VPC</th>
</tr>
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<tbody>
<tr>
<td>Cardiac mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>414</td>
<td>46.9 ± 14.2</td>
<td>94.7 ± 17.2</td>
<td>867.4 ± 168.2</td>
<td>27.4 ± 10.4</td>
<td>14.7 ± 63.9</td>
</tr>
<tr>
<td>Yes</td>
<td>25</td>
<td>33.6 ± 12.4</td>
<td>99.6 ± 20.1</td>
<td>710.7 ± 120.8</td>
<td>18.0 ± 9.0</td>
<td>78.4 ± 163.2</td>
</tr>
<tr>
<td>P value*</td>
<td></td>
<td>0.0001</td>
<td>0.1782</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0027</td>
</tr>
<tr>
<td>Arrhythmic events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>416</td>
<td>46.7 ± 14.3</td>
<td>94.5 ± 17.1</td>
<td>865.6 ± 168.6</td>
<td>27.2 ± 10.2</td>
<td>13.4 ± 55.4</td>
</tr>
<tr>
<td>Yes</td>
<td>23</td>
<td>36.4 ± 12.8</td>
<td>104.1 ± 20.4</td>
<td>729.5 ± 137.7</td>
<td>19.6 ± 13.4</td>
<td>107.8 ± 208.1</td>
</tr>
<tr>
<td>P value*</td>
<td></td>
<td>0.0007</td>
<td>0.0082</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0014</td>
</tr>
</tbody>
</table>

*Wilcoxon two-sample test/Kruskal-Wallis test.
LVEF = left ventricular ejection fraction; tQRS = total QRS duration; Mean NN = mean normal-to-normal RR interval; HRV = heart rate variability; VPC = ventricular premature beat frequency.

Figure 1: Selection of optimum dichotomy limits for left ventricular ejection fraction (a) and heart rate variability index (b). These graphs compare the probability (Y axis) that a selected dichotomy limit (X axis) is associated with outcome (cardiac mortality ———— or arrhythmic events —— ——). For left ventricular ejection fraction, optimum dichotomy limits for prediction of cardiac mortality and arrhythmic events are 45% and 32%, respectively. For heart rate variability index, corresponding dichotomy limits are 18 units for cardiac mortality or arrhythmic events.

Selection of optimum dichotomy limits

When the variables were combined, the optimum dichotomy limits for each of the variables varied depending on the combination of variables used, the event predicted, the selected level of sensitivity and the number of variables defined as abnormal on each analysis of those at risk. For example, using left ventricular ejection fraction alone, the optimum dichotomy limits for the prediction of cardiac mortality and arrhythmic events are 45% and 32%, respectively (Fig. 1(a)). Using the heart rate variability index alone, the optimum dichotomy limit for predicting either event is 18 units (Fig. 1(b)).

For predicting arrhythmic events when both left ventricular ejection fraction and heart rate variability index are used and are required to be abnormal (Fig. 3(a)), the respective optimum dichotomy limits for predicting events are 49% and 19 units. When either left ventricular ejection fraction or heart rate variability index are required to be abnormal, the respective optimum dichotomy limits changed to 32% and 18 units (Fig. 3(b)).

In other words, the dichotomy limits of the heart rate variability index for predicting arrhythmic events or cardiac mortality are largely unaffected by including left ventricular ejection fraction in the analysis; however, the dichotomy limit for left ventricular ejection fraction varied, in this example, from 32% to 52%.

Sensitivity and positive predictive accuracy

The optimum prediction of cardiac mortality and arrhythmic events at sensitivity levels of 40% and 60% are shown in Tables 3 and 4, respectively. At a sensitivity of 40% for arrhythmic events, individual variables provide a predictive value of about 20%. The optimum combination for predicting arrhythmic events is based on using four of the five variables, that is, requiring that...
These graphs show the combinations of left ventricular ejection fraction and/or heart rate variability index. The probability (Y axis) that a selected dichotomy limit is associated with events is plotted against the heart rate variability index (X axis) for different selected levels of left ventricular ejection fraction (Z axis), starting at 10% in increments of 3%: (a) The optimum combination of predicting arrhythmic events when both left ventricular ejection fraction and heart rate variability are required to be abnormal are dichotomy limits of 52% and 18 units, respectively, (b) The optimum combination for predicting arrhythmic events when either left ventricular ejection fraction or heart rate variability are required to be abnormal are dichotomy limits of 43% and 18 units, respectively.

Four or more of the five variables are abnormal, based on dichotomy limits tailored to achieve 40% sensitivity, before selecting a patient at risk. For predicting cardiac mortality, the highest positive predictive accuracy of 62.5% is derived from using all five variables.

The positive predictive accuracy of individual variables and their combinations for predicting arrhythmic events and cardiac mortality at different levels of sensitivity are represented in Figs 4 and 5, respectively.

Discussion

Reduced heart rate variability and abnormalities on the signal-averaged ECG are the most promising of the variables recently put forward for improving risk stratification after myocardial infarction. Previous studies have shown that combinations of these variables perform better than single variables for predicting arrhythmic events. The present study extends previous
Figure 3  These graphs show the combinations of left ventricular ejection fraction and/or heart rate variability index. The probability (Y axis) that a selected dichotomy limit is associated with events is plotted against heart rate variability index (X axis) for different selected levels of left ventricular ejection fraction (Z axis), starting at 10% in increments of 3%; (a) The optimum combination for predicting cardiac mortality when both left ventricular ejection fraction and heart rate variability are required to be abnormal are dichotomy limits of 49% and 19 units, respectively, (b) The optimum combination for predicting cardiac mortality when either left ventricular ejection fraction or heart rate variability are required to be abnormal are dichotomy limits of 32% and 18 units, respectively.

observations by showing that the dichotomy limits derived from univariate analyses do not optimally predict events when multiple variables are used. The optimum dichotomy limits varied not only with the number of variables used but also with the number of those variables that must be positive for the selection of those at risk. Furthermore, different dichotomy limits are obtained when risk stratifying for arrhythmic events compared to cardiac mortality, and at different levels of sensitivity. Combining any two of the investigations provided a positive predictive accuracy of about 21% with a sensitivity of 40% for predicting arrhythmic events and cardiac mortality in the first year. Combinations of all investigations provided a predictive value approaching 70% at the same level of sensitivity. The heart rate variability index was a component of all of the
Table 3 Optimum prediction of cardiac mortality and arrhythmic events using 1, 2, 3, 4, or 5 variables at a sensitivity of 40%

<table>
<thead>
<tr>
<th></th>
<th>Specificity</th>
<th>PPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Cardiac mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Variable: LVEF</td>
<td>90.0</td>
<td>21.2</td>
</tr>
<tr>
<td>2 Variables: Both* of Mean NN, VPC</td>
<td>96.4</td>
<td>40.0</td>
</tr>
<tr>
<td>3 Variables: All of tQRS, HRV, VPC</td>
<td>97.6</td>
<td>50.0</td>
</tr>
<tr>
<td>4 Variables: All of tQRS, Mean NN, HRV, VPC</td>
<td>98.3</td>
<td>58.8</td>
</tr>
<tr>
<td>5 Variables: All combined</td>
<td>97.1</td>
<td>62.5</td>
</tr>
<tr>
<td>(b) Arrhythmic events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Variable: HRV index</td>
<td>92.8</td>
<td>23.1</td>
</tr>
<tr>
<td>2 Variables: 1 of HRV, VPC</td>
<td>96.9</td>
<td>40.9</td>
</tr>
<tr>
<td>3 Variables: 2 of Mean NN, HRV, VPC</td>
<td>98.6</td>
<td>60.0</td>
</tr>
<tr>
<td>4 Variables: 3 of LVEF, Mean NN, HRV, VPC</td>
<td>97.6</td>
<td>64.8</td>
</tr>
<tr>
<td>5 Variables: 2 or 4 of all</td>
<td>97.8</td>
<td>69.2</td>
</tr>
</tbody>
</table>

*Indicates the number of selected variables that must be abnormal before identification of a patient as at risk of an event.

For abbreviations, see Table 2.

Table 4 Optimum prediction of cardiac mortality and arrhythmic events using 1, 2, 3, 4, or 5 variables at a sensitivity of 60%

<table>
<thead>
<tr>
<th></th>
<th>Specificity</th>
<th>PPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Cardiac mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Variable: HRV index</td>
<td>84.8</td>
<td>19.8</td>
</tr>
<tr>
<td>2 Variables: Both of Mean NN, VPC</td>
<td>91.1</td>
<td>28.8</td>
</tr>
<tr>
<td>3 Variables: 2 of LVEF, Mean NN, VPC</td>
<td>91.8</td>
<td>34.9</td>
</tr>
<tr>
<td>4 Variables: 3 of LVEF, mean NN, HRV, VPC</td>
<td>92.3</td>
<td>36.6</td>
</tr>
<tr>
<td>5 Variables: 4 of all</td>
<td>92.8</td>
<td>38.5</td>
</tr>
<tr>
<td>(b) Arrhythmic events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Variable: HRV index</td>
<td>84.9</td>
<td>18.5</td>
</tr>
<tr>
<td>2 Variables: Both of tQRS, HRV</td>
<td>89.7</td>
<td>24.6</td>
</tr>
<tr>
<td>3 Variables: 1 of LVEF, HRV, VPC</td>
<td>91.6</td>
<td>28.6</td>
</tr>
<tr>
<td>4 Variables: 2 of tQRS, Mean NN, HRV, VPC</td>
<td>94.2</td>
<td>36.8</td>
</tr>
<tr>
<td>5 Variables: 3 of all</td>
<td>93.8</td>
<td>40.0</td>
</tr>
</tbody>
</table>

For abbreviations, see Table 2.

most successful combinations of variables for the prediction of events and was the least affected by its combination with other variables.

Clinical implications

This study shows that our approach can significantly reduce the number of false-positive results and could thus provide a basis for a prospective study of a new, relatively high risk, or expensive intervention in the prevention of arrhythmic deaths.

The biological basis of our findings is not clear. It appears, however, that depressed heart rate variability at the dichotomy levels chosen is a consistent correlate of an increased risk of death or arrhythmic events in particular, and the finding that the dichotomy value of heart rate variability appears to be largely unaffected by the inclusion of other variables emphasizes the relative independence of this parameter. The relationship between autonomic dysfunction and whether depressed heart rate variability is also an indirect marker for other prognostic factors, such as age, infarct artery patency or asymptomatic left ventricular dysfunction is not important to the study. However, further studies are needed to examine the basis for the predictive value of heart rate variability and whether changes in heart rate variability, by altering reversible factors or changing heart rate variability itself pharmacologically, will make a significant impact on events.[10] The variation in the dichotomy limits of the other variables is more difficult to explain. The risk factors used in this study are not entirely independent of each other and it may well be that the frequency of ventricular extrasystoles needed to provoke arrhythmias (if this is indeed the case) is lower when heart rate variability or the left ventricular ejection fraction are low than if these are normal. Alternatively, a low heart rate variability and frequency extrasystoles may each indirectly represent the severity of myocardial dysfunction.

Limitations of this study

The results of this study are based on a retrospective analysis of a post-infarction population aged ≤ 70 years old and surviving to hospital discharge. Over the period of recruitment and follow-up, there have been important changes in the management of patients, for example the introduction of thrombolysis, improvements in education and modification of risk factors. We cannot be certain that the same observations would be applicable to different populations, and the findings of this study need to be tested in other populations, or the analysis repeated in a larger sample.

The relationship between all the combinations of the variables and the end-points is assumed to be the same throughout the period of follow-up. There are groups of patients in whom this approach may be more effective and others in whom variables which were not examined, such as the potency of the infarct-related artery and haemostatic factors, may be more important predictors of arrhythmic events and overall cardiac mortality.

The advantages of our study are the relatively large number of patients, the duration of follow-up and
Figure 4 Positive predictive curves for individual variables and their combination for the prediction of arrhythmic events: (a) Based on left ventricular ejection fraction. (b) Based on combinations of left ventricular ejection fraction, tQRS, Mean NN and ventricular premature complexes frequency (excluding heart rate variability). —— = one of four; •••• = two of four; —— = three of four; —— = four of four. (c) Based on combinations of all five variables. —— = one of five; •••• = two of five; —— = three of five; —— = four of five; ••••• = five of five.
Figure 5 Positive predictive curves for individual variables and their combination for the prediction of cardiac mortality: (a) Based on left ventricular ejection fraction. (b) Based on combinations of left ventricular ejection fraction, tQRS, Mean NN and ventricular premature complexes frequency (excluding heart rate variability). — one of four; • • • = two of four; • • = three of four; — — = four of four. (c) Based on combinations of all five variables. — — — = one of five; • • • = two of five; — — • = three of five; — — — = four of five; • • • = five of five.
the potential relevance of our patients and results to the current management of patients admitted directly to hospital with an acute myocardial infarction. Other variables which were not examined but may have refined our results include age, the site of infarction and infarct artery patency.

Conclusions

Multiple variables perform better than single variables for predicting mortality and arrhythmic events after myocardial infarction. However, conventional dichotomy limits derived from or used in univariate analyses do not provide the best prediction of events when several predictors are combined. The optimum prediction of clinical events is obtained by changing these dichotomy limits when variables are combined. The optimum dichotomy limit is also influenced by the combination of variables used and by the clinical event selected. However, the heart rate variability index is an important component of the most successful combination of variables and its dichotomy point is relatively unaffected by the selected end-point or by the inclusion of other variables. The assessment of heart rate variability and its combination with other non-invasive variables provides a firm basis for planning prospective studies in the prevention of arrhythmic events and mortality following myocardial infarction.

References