# Improved Stratification of Autonomic Regulation for risk prediction in post-infarction patients with preserved left ventricular function (*ISAR-Risk*)

**Axel Bauer[1][†], Petra Barthel[1][†], Raphael Schneider[1], Kurt Ulm[2], Alexander Müller[1], Anke Joeinig[1], Raphael Stich[1], Antti Kiviniemi[3], Katerina Hnatkova[4], Heikki Huikuri[3], Albert Schömig[1], Marek Malik[4], and Georg Schmidt[1]***

[1]Medizinische Klinik und Deutsches Herzzentrum München der Technischen Universität München, Ismaninger Straße 22, 81675 München, Germany; [2]Institut für Medizinische Statistik und Epidemiologie der Technischen Universität München, München, Germany; [3]Department of Medicine, University of Oulu, Oulu, Finland; and [4]Division of Cardiac and Vascular Sciences, St George's, University of London, London, UK

| | |
|---|---|
| **Aims** | To investigate the combination of heart rate turbulence (HRT) and deceleration capacity (DC) as risk predictors in post-infarction patients with left ventricular ejection fraction (LVEF) > 30%. |
| **Methods and results** | We enrolled 2343 consecutive survivors of acute myocardial infarction (MI) (<76 years) in sinus rhythm. HRT and DC were obtained from 24 h Holter recordings. Patients with both abnormal HRT (slope ≤ 2.5 ms/RR and onset ≥ 0%) and abnormal DC (≤4.5 ms) were considered suffering from severe autonomic failure (SAF) and prospectively classified as high risk. Primary and secondary endpoints were all-cause, cardiac, and sudden cardiac mortality within the first 5 years of follow-up. During follow-up, 181 patients died; 39 deaths occurred in 120 patients with LVEF ≤ 30%, and 142 in 2223 patients with LVEF>30% (cumulative 5-year mortality rates of 37.9% and 7.8%, respectively). Among patients with LVEF > 30%, SAF identified another high-risk group of 117 patients with 37 deaths (cumulative 5-year mortality rates of 38.6% and 6.1%, respectively). Merging both high-risk groups (i.e. LVEF ≤ 30% and/or SAF) doubled the sensitivity of mortality prediction compared with LVEF ≤ 30% alone (21.1% vs. 42.1%, $P < 0.001$) while preserving 5-year mortality rate (38.2%). |
| **Conclusion** | In post-MI patients with LVEF>30%, SAF identifies a high-risk group equivalent in size and mortality risk to patients with LVEF ≤ 30%. |
| **Keywords** | Autonomic function • Myocardial infarction • Risk stratification • Sudden death |

## Introduction

Reduction of mortality by implantable cardioverter-defibrillators (ICDs) has been well documented by several trials in cardiac patients with compromised left ventricular function assessed, as a rule, by low left ventricular ejection fraction (LVEF).[1–5] Although the results of these studies have now been projected into standard clinical practice, a substantial problem remains because of the low sensitivity of the criterion of reduced LVEF.[6–8] Many cardiac patients who die from sudden cardiac death, likely preventable by prophylactic ICD implantation, do not have left ventricular performance particularly compromised.[6,8–10] According to current guidelines, these patients are considered as low risk patients and are not protected by intensive prophylactic treatment.[11,12] At present, methods for identification

---

of high-risk patients without compromised LVEF are lacking. Consequently, prophylactic ICD implantation (or other prophylactic therapy) has never been tested in these patients. Hence, adequately potent risk stratification methods need to be first demonstrated in patients with preserved LVEF before any risk reduction prophylaxis can be attempted.

To address this need, we have conducted a large cohort follow-up study to investigate whether the assessment of abnormalities in cardiac autonomic function makes risk stratification feasible among patients without seriously compromised ventricular performance. To characterize abnormalities in cardiac autonomic function, we defined severe autonomic failure (SAF) as a combination of severely impaired baroreflex function with abnormal autonomic tone. For this purpose, we used Heart Rate Turbulence (HRT)[13] and cardiac Deceleration Capacity (DC).[14] Although the risk prediction power of these parameters was previously documented in independent patient populations, the ways of combining them have not been studied. In particular, previous studies suggested that DC might be more useful in identification of low-risk patients while the power of HRT is mainly in the selection of high-risk cases. This study therefore investigated the definition of high risk as the combination of mildly abnormal DC[14] (to exclude low-risk patients) with highly abnormal HRT[13] (to select high-risk patients).

# Methods

## Study design, setting, and participants

Between January 1996 and March 2005, patients were enrolled into a prospective cohort study at two centres, namely the German Heart Centre and the Klinikum Rechts der Isar, both in Munich, Germany (see *Figure 1* for patient numbers). Eligible patients suffered from acute myocardial infarction (MI) no more than 4 weeks before enrolment, were not older than 75 years, presented in sinus rhythm, and did not meet the criteria for secondary therapy by implantable cardioverter-defibrillator (ICD)[11] before hospital discharge for the index MI. Of the 2343 study patients, 1455 were included in earlier investigations[7,14] and are reported here with extended follow-up (5 vs. 2 years). At the same time, the number of primary endpoints increased from 70 to 181.

MI was diagnosed if a patient had at least two of the following findings: chest pain for $\geq 20$ min, creatine kinase-MB above the doubled upper normal limit of our laboratory, and ST-segment elevation of $\geq 0.1$ mV in two or more limb leads or $\geq 0.2$ mV in two or more contiguous precordial leads at the time of admission. Diabetes mellitus was considered present either if a patient was diagnosed and was receiving treatment (diet, tablets, or insulin) or if a blood glucose concentration of $\geq 11$ mmol/L was found in repeated samples. The patients were followed up for a median of 4.9 years (2.8–5.0 years). The local Ethics Committee approved the collection of data and analysis of Holter recordings. Since the data obtained were non-invasive and did not exceed usual clinical management of the patients, the local Ethics Committee decided that signed informed consent was not needed. However, we did obtain oral informed consent.

## Assessment of autonomic markers

Each patient of the study population ($n = 2343$) underwent 24 h Holter recording. These recordings were obtained at a median of 8 days after the index infarction (interquartile range 5–11 days). All recordings were routinely processed using standard commercial equipment (Oxford Excel Holter system, Oxford instruments; Pathfinder



**Figure 1** Flow chart of patient selection.
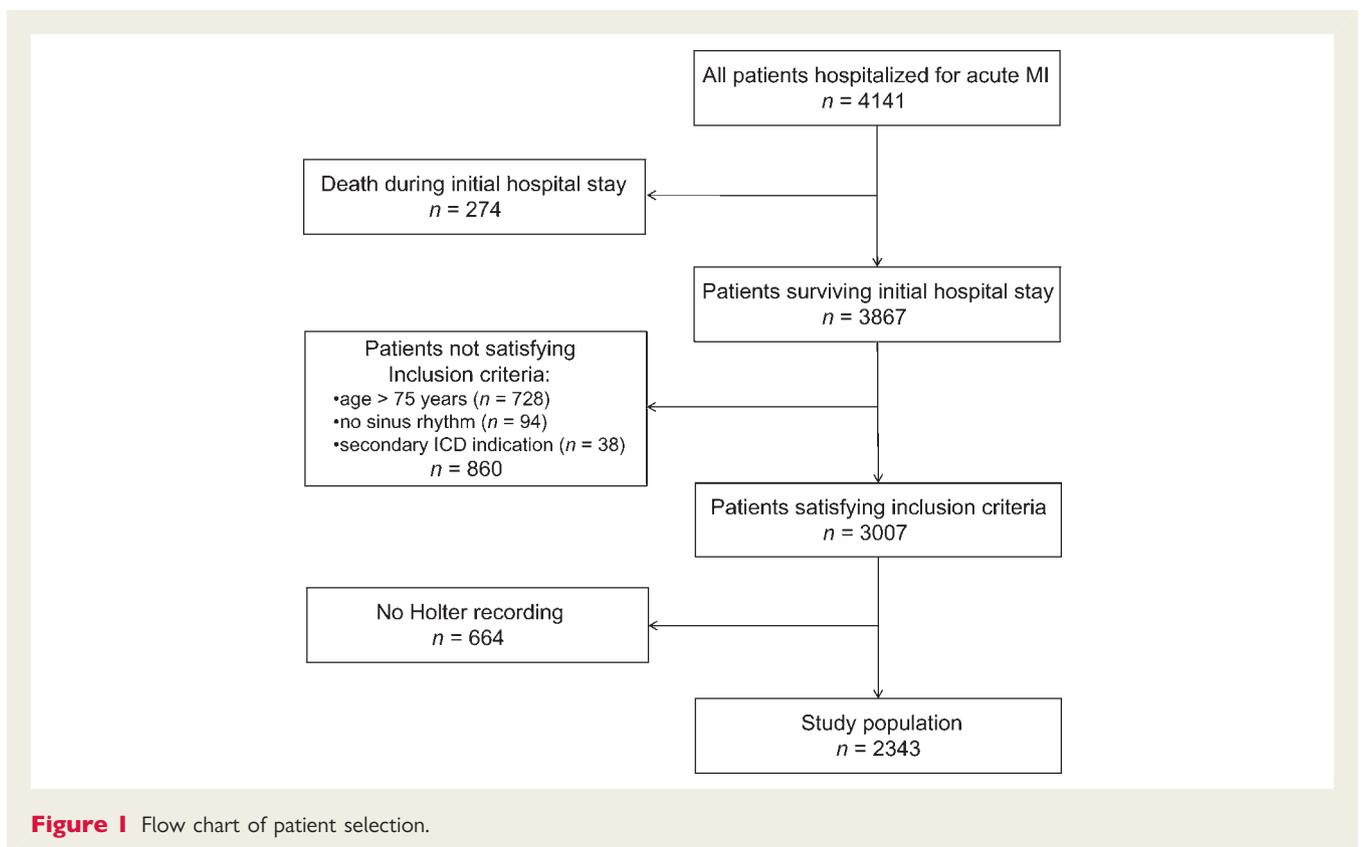
700, Reynolds Medical; and Mortara Holter system, Mortara Instrument) to obtain the sequence of individual RR intervals together with the distinction of sinus rhythm beats and ventricular premature complexes. Using these sequences, HRT and DC were calculated using previously published technologies[13–15] that are presently available as simple add-ons to standard modern Holter systems.

Briefly, HRT quantifies the physiological short-term oscillation of cardiac cycle lengths that follows spontaneous ventricular premature complexes.[16] HRT consists typically of a brief heart rate acceleration followed by a gradual heart rate deceleration. These HRT phases are quantified by two numerical descriptors, HRT onset and HRT slope. DC is an integral measure of all deceleration-related oscillation observed over 24 h. Computation of DC is based on a novel signal processing algorithm capable of extracting periodic components out of non-stationary biological signals.

Consistent with previous reports, HRT onset was considered abnormal if $\geq 0\%$,[13] HRT slope if $\leq 2.5$ ms per RR interval,[13] and DC if $\leq 4.5$ ms.[14]

Patients who exhibited these pathologies in both components of HRT as well as in DC were considered to suffer from seriously abnormal cardiac autonomic modulations. The term SAF was used to describe this abnormality.

## Left ventricular performance

In each patient, LVEF was assessed by left ventricular angiography ($n = 1686$) or biplane echocardiography ($n = 657$) during the second week after the index infarction. In agreement with previous reports on the utilization of prophylactic ICDs in patients with compromised left ventricular performance,[3,11] reduced LVEF was defined if $\leq 30\%$.

## Endpoints of the study

Last planned follow-up assessment was 1/2007. In cases of death, the reason for death was verified from hospital and autopsy records, and from either the primary physician or those witnessing the death. An independent endpoint committee determined the mode of death. Deaths were categorized as cardiac and non-cardiac. Cardiac deaths were further categorized as sudden and non-sudden. Cardiac death was defined as sudden if it was[1] a witnessed death occurring within 60 min of the onset of new symptoms, unless there was an obvious non-cardiac cause,[2] an unwitnessed death within 24 h in the absence of pre-existing progressive circulatory failure or other causes of death, or[3] death during attempted resuscitation. The primary endpoint of the study was all-cause mortality within the first 5 years of follow-up; secondary endpoints were cardiac and sudden cardiac death also at 5 years of follow-up. The cut-off of 5 years was derived from the expected ICD longevity.

## High-risk groups

Some patients who suffered from SAF also had LVEF $\leq 30\%$ which made them eligible for prophylactic ICD implantation based on the presently available criteria. Thus, to investigate what risk stratification by SAF offers in addition to reduced LVEF, we considered and compared two distinct high-risk groups, that is (i) patients with LVEF $\leq 30\%$ and (ii) patients with LVEF $>30\%$ and SAF. We also considered the group of all patients with SAF, and a combination of these high-risk groups, that is patients with either LVEF $\leq 30\%$ or LVEF $>30\%$ and SAF.

## Statistics

Continuous variables are presented as median and inter-quartile range; qualitative data are expressed as absolute numbers and percentages. Comparison of variables between high-risk groups (LVEF $\leq 30\%$ or

SAF and LVEF $> 30\%$) was performed with either a linear or logistic model in order to adjust for differences in age and sex. Survival curves for total mortality were estimated by the Kaplan–Meier method[17] and compared using the two-sided log-rank test.[18] The influence of SAF on total mortality was estimated with the Cox proportional-hazards model adjusted for established risk factors, including age $\geq 65$ years, presence of diabetes mellitus, history of previous MI, arrhythmia signs on Holter ($\geq 10$ VPCs/h and/or non-sustained ventricular tachycardia on Holter) and sex. Mortality rates of both high risks groups (LVEF $\leq 30\%$ and SAF and LVEF $> 30\%$) were also compared by the Cox-model adjusted for age and sex. The proportional hazard assumption of the various parameters was investigated by using Schoenfeld residuals. Hazard ratios together with 95% confidence limits were calculated. Secondary endpoints (cardiac death and sudden death) were analysed with competing risk models[19] and compared with the procedure proposed by Gray.[20] Differences were considered statistically significant, if $P < 0.05$. Sensitivity and specificity were calculated for the prediction of all-cause, cardiac, and sudden cardiac death in (i) patients with LVEF $\leq 30\%$, (ii) patients with SAF, (iii) patients with SAF and LVEF $>30\%$, and (iv) patients with either LVEF $\leq 30\%$ or $>30\%$ and SAF (i.e. LVEF $\leq 30\%$ and/or SAF).[21]

## Statement of responsibility

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

# Results

The clinical characteristics of recruited patients are shown in *Table 1*. Eighteen patients (i.e. 0.8% of the total population) were lost to follow-up. They were censored at the date of latest contact.

**Table 1** Characteristics of the study population ($n = 2343$)

| Characteristic | |
|---|---|
| Age (years) (median, IQR) | 59 (51–67) |
| Female sex [n (%)] | 456 (20) |
| Diabetes mellitus [n (%)] | 412 (18) |
| History of previous MI [n (%)] | 261 (11) |
| CK$_{max}$ (U/L) (median, IQR) | 1189 (598–2460) |
| Creatinine (μmol/L) (median, IQR) | 1.1 (1.0–1.3) |
| LVEF (%) | 55 (45–62) |
| VPC (count/h) (median, IQR) | 0.5 (0.1–3.5) |
| Nonsustained VT [n (%)] | 156 (7) |
| PCI [n (%)] | 2159 (92) |
| Thrombolysis [n (%)] | 62 (3) |
| CABG [n (%)] | 39 (2) |
| Aspirin [n (%)] | 2298 (98) |
| β-Blocker [n (%)] | 2210 (94) |
| ACE inhibitors [n (%)] | 2132 (91) |
| Statins [n (%)] | 2057 (88) |
| Diuretics [n (%)] | 926 (40) |

ACE, angiotensin-converting enzyme; CABG, coronary artery bypass graft; CK, creatine kinase; IQR, inter-quartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; VPC, ventricular premature complex; VT, ventricular tachycardia.

During the first 5 years of follow-up, 181 patients died (Table 2). Only 39 (22%) of these deaths occurred in patients with LVEF $\leq 30\%$ ($n = 120$; 5.1% of the total population) whereas 142 (78%) occurred in patients with LVEF $> 30\%$ ($n = 2223$; 94.9% of the total population). Cumulative mortality curves of patients stratified by LVEF $\leq 30\%$ are shown in the left panels of Figure 2. After 5 years, cumulative mortality rates of patients with LVEF $\leq 30\%$ and $> 30\%$ were 37.9% and 7.8%, respectively ($\chi^2 = 110.1$, $P < 0.001$).

Among patients with LVEF $> 30\%$, SAF identified 117 cases (i.e. 5.0% of the total population) as high-risk patients, out of whom 37 died during the first 5 years of follow-up. Cumulative mortality curves of these patients are shown in the right panels of Figure 2. After 5 years of follow-up, cumulative mortality rates of patients with and without SAF were 38.6% and 6.1%, respectively ($\chi^2 = 134$, $P < 0.001$). If one of the SAF components, i.e. either DC or HRT, was abnormal, the corresponding cumulative mortality rate was 9.5%; if neither component was abnormal, the cumulative mortality rate was 4.0%. On multivariable analysis (adjusted for age, presence of diabetes mellitus, history of previous MI, arrhythmia on Holter and sex), SAF yielded a hazard ratio of 4.6 [95% confidence interval (CI) 3.1–7.0] ($P < 0.001$).

There was no significant difference between the mortality rates of both high-risk groups adjusted for age and sex (SAF and LVEF $> 30\%$ vs. LVEF $\leq 30\%$; hazard ratio of 0.83 (95% CI 0.52–1.32). Similar figures were observed for cardiac death (relative risk = 0.88, 95% CI 0.51–1.52) and sudden cardiac death (relative risk = 0.93, 95% CI 0.42–2.08). Merging of the two high-risk groups, i.e. considering patients with either LVEF $\leq 30\%$ or LVEF $> 30\%$ and SAF, led to an increase in sensitivity (Table 3), while maintaining a high 5-year mortality rate at 38.2%.

Compared to patients with LVEF $\leq 30\%$, patients with SAF and LVEF $> 30\%$ were older (68 vs. 62 years) and more often of female sex (32% vs. 12%) (Table 4). After adjustment for age and sex statistically significant differences between both high-risk groups were observed for prescription of diuretics (61% vs. 83%) and creatine kinase (1.257 vs. 2.269 U/L).

# Discussion

In this population, SAF identifies high-risk post-MI patients among those with LVEF $> 30\%$. The size and risk-profile of the group of patients with LVEF $> 30\%$ and SAF are practically identical to those of the high-risk group defined by reduced LVEF. This is not only true for total mortality but also for cardiac and sudden cardiac mortality.

Although risk stratification based purely on LVEF identified only approximately one-quarter of the patients who died during follow-up, combination of LVEF $\leq 30\%$ with LVEF $> 30\%$ and SAF identified approximately one-half of them. At the same time, specificity was unaffected. It is thus likely that prophylactic ICD treatment in patients with LVEF $> 30\%$ and SAF would be no less efficacious than in patients with LVEF $\leq 30\%$. ICD therapy might actually be even more effective in patients with LVEF $> 30\%$ and SAF since these patients are less prone to deaths from pump failure which restricts the benefit offered by ICD.[22,23]

There are good reasons to combine DC with HRT when defining SAF. Although both these parameters reflect cardiac autonomic modulations, HRT expresses reflex reaction to the cardiac rhythm to distinct disturbance by isolated ventricular premature beat.[13,24,25] On the contrary, DC integrates all the regulatory processes that slow heart rate on a beat-to-beat basis thus expressing an overall status of the autonomic, predominantly vagal balance.[14,15] Both these facets of autonomic assessment are reasonably independent each of the other which facilitates making their combination such a strong risk predictor. (Note the difference between cumulative mortality rates of 38.6% and 9.5% when both HRT and DC were abnormal, and when only one factor was abnormal, respectively.).

A number of other risk factors have been reported to differentiate between high- and low-risk survivors of MI independently of LVEF (e.g. heart-rate profile of post-exercise recovery,[26,27] non-linear dynamics, detrended fluctuation analysis,[28] T wave alternans,[29–32] electrophysiological testing,[33,34] etc.). With some of these factors, however, the reported sensitivities and specificities among patients with preserved LVEF are rather low. Other reported risk factors appear more viable. For instance, similar data to our findings were reported with T wave alternans (although with a smaller population and fewer events).[35] Possibly, combinations of T wave alternans with HRT and DC would improve risk prediction in this population even further.[36]

Moreover, in contrast to the other techniques,[37] SAF assessment requires only a Holter recording to be obtained in post-infarction patients and is thus not limited only to patients who tolerate a specific provocative investigation (e.g. patients who can exercise for the assessment of T wave alternans and/or post-exercise heart rate recovery).

**Table 2** Endpoints at 5 years

| Group | Total | All-cause deaths | Cardiac deaths | Sudden cardiac deaths | Death not specified |
|---|---|---|---|---|---|
| LVEF $\leq 30\%$ | 120 | 39 | 29 | 12 | 3 |
| SAF | 152 | 52 | 40 | 16 | 3 |
| LVEF $> 30\%$ and SAF | 117 | 37 | 27 | 14 | 3 |
| Others (=LVEF $> 30\%$ and no SAF) | 2106 | 105 | 48 | 29 | 8 |
| Total | 2343 | 181 | 104 | 55 | 14 |

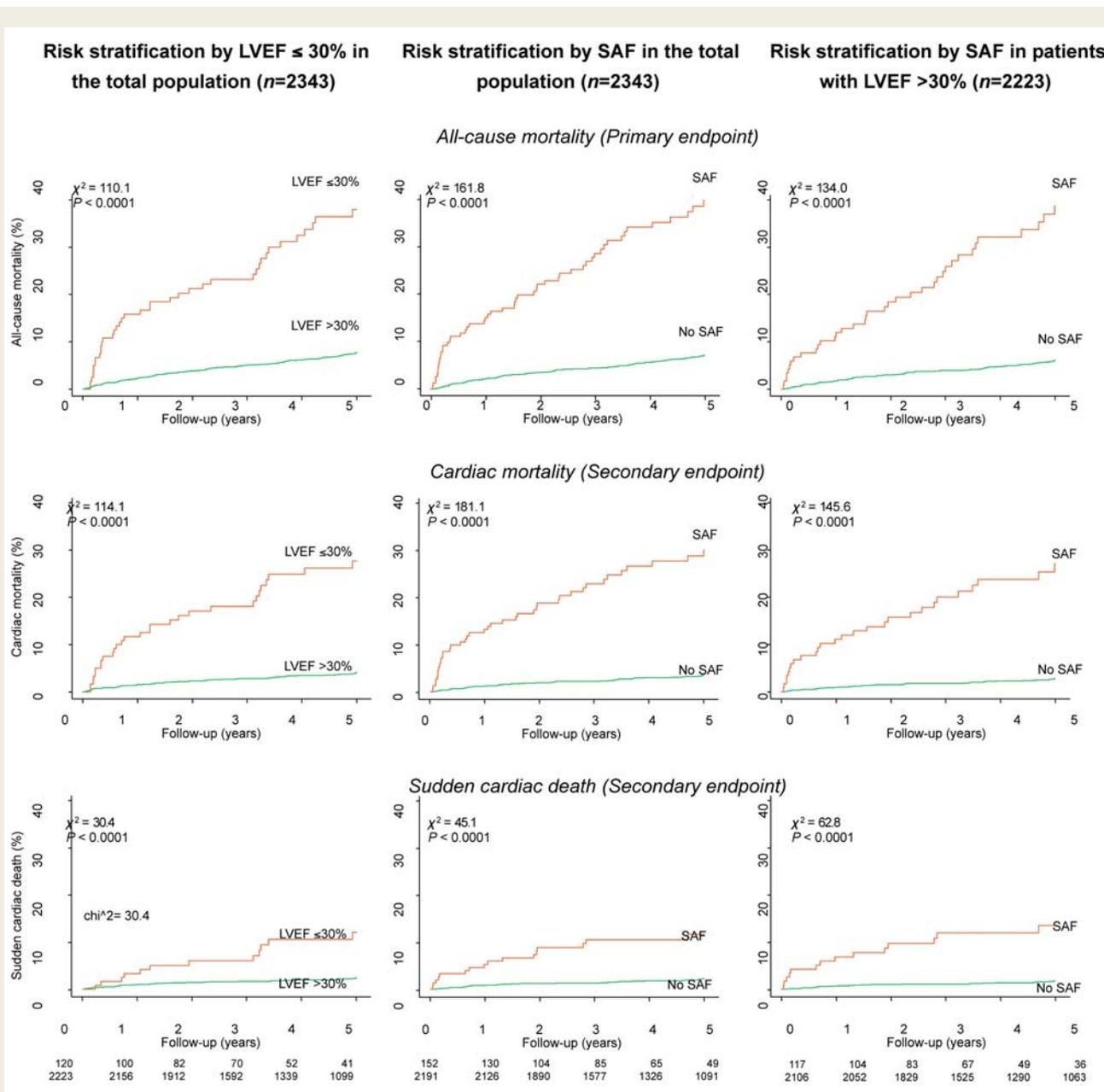LVEF left ventricular ejection fraction; SAF severe autonomic failure.

**Figure 2** Kaplan–Meier curves of all-cause mortality, cardiac mortality and sudden cardiac death for all patients ($n = 2343$) stratified by left ventricular ejection fraction (LVEF; left panels), for all patients ($n = 2343$) stratified by presence of severe autonomic failure (SAF; middle panels) and for patients with LVEF >30% ($n = 2223$) also stratified by presence of SAF (right panels). The number of patients of the individual groups involved in the analyses at 0, 1, 2, 3, 4, and 5 years are shown under the graphs (the same numbers apply to all three end-points). The top and the bottom row corresponds to the upper and bottom Kaplan–Meier curve respectively.

The clinical efficacy of ICD implantation in patients with LVEF > 30% and SAF needs to be prospectively tested. Since the incidence and mortality rates are equal to those in patients with LVEF ≤ 30% in whom successful ICD trials exist,[1−3] such prospective studies appear fully viable.

The cumulative mortality of patients with SAF and LVEF > 30% constantly increased over the observation period and did not saturate. In other words, patients with LVEF > 30% and SAF continue to be at increased risk even if surviving the first years after MI.

Thus, these patients would probably benefit from ICD prophylaxis even late after MI.

Intentionally, we did not compare primarily patients with LVEF ≤ 30% with all patients with SAF. Those patients who have both compromised LVEF and SAF are eligible for prophylactic ICD implantation according to present guidelines and we are not suggesting that SAF should compete with these guidelines. (In our population, we have not found any practically viable criterion that would allow excluding patients with LVEF≤30% from ICD

**Table 3** Positive and negative predictive accuracies, sensitivities and specificities for prediction of all-cause mortality, cardiac mortality, and sudden cardiac death by high-risk groups

|  | LVEF ≤ 30% | SAF | SAF (in LVEF > 30%) | LVEF ≤ 30% or LVEF > 30% and SAF |
|---|---|---|---|---|
| Total count | 120 | 152 | 117 | 237 |
| Prediction of all-cause mortality at 5 years |  |  |  |  |
|     All-cause deaths | 39 | 52 | 37 | 76 |
|     Positive predictive accuracy (%) | 37.9 | 39.9 | 38.6 | 38.2 |
|     Negative predictive accuracy (%) | 92.2 | 92.8 | 93.9 | 93.9 |
|     Sensitivity (%) | 21.1 | 28.2 | 26.0 | 42.1 |
|     Specificity (%) | 96.5 | 95.7 | 96.5 | 93.1 |
| Prediction of cardiac mortality at 5 years |  |  |  |  |
|     Cardiac deaths | 29 | 40 | 27 | 56 |
|     Positive predictive accuracy (%) | 27.6 | 29.9 | 27.1 | 27.3 |
|     Negative predictive accuracy (%) | 95.9 | 96.4 | 97.2 | 97.2 |
|     Sensitivity (%) | 27.1 | 37.2 | 34.8 | 52.9 |
|     Specificity (%) | 96.1 | 95.2 | 96.0 | 92.2 |
| Prediction of sudden cardiac death at 5 years |  |  |  |  |
|     Sudden cardiac deaths | 12 | 16 | 14 | 26 |
|     Positive predictive accuracy (%) | 12.0 | 11.6 | 13.4 | 12.8 |
|     Negative predictive accuracy (%) | 97.7 | 97.8 | 98.3 | 98.3 |
|     Sensitivity (%) | 22.1 | 27.1 | 30.7 | 46.6 |
|     Specificity (%) | 95.4 | 94.1 | 95.3 | 90.9 |

LVEF, left ventricular ejection fraction; SAF, severe autonomic failure.

prophylaxis—data not presented here.) Rather, we show that SAF identifies a group with considerable high risk among those patients who are not covered by present guidelines on primary ICD prophylaxis.

The strong predictive power of SAF was confirmed by further analyses the details of which are beyond the scope of this text. Among others, while a number of conventional measures of heart-rate variability (HRV) were significant predictors of mortality, SAF yielded the strongest relative risk both uni- and multivariably independent of the cut-off values of conventional HRV measures. Also, the SAF components, i.e. HRT and DC were significant and independent multivariable predictors.

Several limitations of our study need to be recognized. We enrolled patients younger than 76 years. Therefore, our findings cannot be extrapolated to older post-infarction patients. Moreover, SAF assessment is restricted to patients presenting in sinus rhythm and thus not applicable for instance to patients with atrial fibrillation which is known to be associated with increased mortality risk including risk of sudden death.[38] Holter recordings were obtained at median of 8 days after index infarction which might trigger a question of reproducibility. Nevertheless, previous publications on HRT[13,39,40] and DC[14] showed that the power of SAF components was maintained also in populations that collected post-infarction Holter recordings at different times. Our enrolment spanned almost 10 years during which some advances in acute treatment have been made. More detailed analysis of our data (not presented here) does not show any differences in these findings between earlier and later parts of the population. Since it is difficult to distinguish between life saving ICD therapy and other ICD interventions, we did not include ICD therapy into study endpoints. As seen in *Table 4*, the numbers of patients with effective ICD therapy were small (only 4% of patients with LVEF ≤30% experienced ICD therapy while surviving the follow-up) and including the ICD interventions into endpoints (analysis not presented here) did not change the principal results. The threshold of LVEF ≤ 30% and >30% was prospectively selected when designing this study. However, the results are not dependent on this selection. When re-analysing the data for high-risk groups of LVEF ≤35% vs. >35% and SAF, the results were practically identical. A fraction of the data in our study was included in earlier investigations.[7,14] However, the present study is based on much larger data collection with substantially increased follow-up period in which the number of endpoints was more than doubled. To test the consistency of our data, we analysed the previously used and the new data separately and confirmed that the results are fully independent of the original publications (analysis not presented here). Finally, although cohort studies of this kind characterize risk groups, they cannot replace intervention trials.

In spite of these limitations, the results of our cohort study are sufficiently robust to indicate that the autonomic markers should be strongly considered in future cardiac prophylaxis. Assessment of SAF after acute MI is presently readily available.

**Table 4** Comparison of high-risk groups

| Characteristic | LVEF ≤ 30% | SAF and LVEF > 30% | P-value |
|---|---|---|---|
| *n* | 120 | 117 | |
| LVEF (%) (median, IQR) | 25 (21−28) | 46 (39−56) | <0.0001 |
| Age (years) (median, IQR) | 62 (55−68) | 68 (60−72) | <0.0001 |
| Female sex [*n* (%)] | 14 (12) | 37 (32) | <0.0001 |
| *P-values adjusted for age and sex* | | | |
| Diabetes mellitus [*n* (%)] | 26 (22) | 37 (32) | 0.349 |
| History of previous MI [*n* (%)] | 34 (28) | 20 (17) | 0.029 |
| $CK_{max}$ (U/L) (median, IQR) | 2269 (952−5139) | 1257 (510−2455) | <0.0001 |
| Creatinine (mg/dL) (median, IQR) | 1.3 (1.1−1.5) | 1.2 (1.0−1.4) | 0.316 |
| VPC (count/h) (median, IQR) | 5 (1−27) | 7 (2−40) | 0.700 |
| Non-sustained VT [*n* (%)] | 22 (18) | 18 (15) | 0.748 |
| Mean HR (bpm) (median, IQR) | 73 (66−82) | 74 (68−81) | 0.140 |
| SDNN (ms) (median, IQR) | 66 (53−85) | 68 (55−89) | 0.606 |
| PCI [*n* (%)] | 110 (92) | 103 (88) | 0.523 |
| Thrombolysis [*n* (%)] | 1 (1) | 2 (2) | 0.685 |
| CABG [*n* (%)] | 5 (4) | 3 (3) | 0.445 |
| Aspirin [*n* (%)] | 113 (94) | 113 (97) | 0.503 |
| β-Blocker [*n* (%)] | 109 (91) | 102 (87) | 0.475 |
| ACE inhibitors [*n* (%)] | 109 (91) | 108 (92) | 0.694 |
| Statins [*n* (%)] | 93 (76) | 91 (78) | 0.751 |
| Diuretics [*n* (%)] | 100 (83) | 71 (61) | <0.0001 |
| ICD implantation [*n* (%)] | 20 (17) | 6 (5) | 0.013 |
| ICD therapy in patients who survived follow-up [*n* (%)] | 5 (4) | 1(1) | 0.166 |

ACE, angiotensin-converting enzyme; CABG, coronary artery bypass graft; CK, creatine kinase; HR, heart rate; IQR, inter-quartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; VPC, ventricular premature complex; VT, ventricular tachycardia.

# Supplementary material

Supplementary material is available at *European Heart Journal* online.

# Acknowledgement

# Funding

# References

1. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, Levine JH, Saksena S, Waldo AL, Wilber D, Brown MW, Heo M. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. *N Engl J Med* 1996;**335**:1933−1940.
2. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. *N Engl J Med* 1999;**341**:1882−1890.
3. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;**346**:877−883.
4. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;**350**:2140−2150.
5. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;**352**:225−237.

6. Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. *N Engl J Med* 2001;**345**:1473–1482.

7. Barthel P, Schneider R, Bauer A, Ulm K, Schmitt C, Schomig A, Schmidt G. Risk stratification after acute myocardial infarction by heart rate turbulence. *Circulation* 2003;**108**:1221–1226.

8. Buxton AE. Risk stratification for sudden death: do we need anything more than ejection fraction? *Card Electrophysiol Rev* 2003;**7**:434–437.

9. Myerburg RJ, Interian A Jr, Mitrani RM, Kessler KM, Castellanos A. Frequency of sudden cardiac death and profiles of risk. *Am J Cardiol* 1997;**80**:10F–19F.

10. Myerburg RJ, Mitrani R, Interian A Jr, Castellanos A. Interpretation of outcomes of antiarrhythmic clinical trials: design features and population impact. *Circulation* 1998;**97**:1514–1521.

11. Gregoratos G, Abrams J, Epstein AE, Freedman RA, Hayes DL, Hlatky MA, Kerber RE, Naccarelli GV, Schoenfeld MH, Silka MJ, Winters SL, Gibbons RJ, Antman EM, Alpert JS, Gregoratos G, Hiratzka LF, Faxon DP, Jacobs AK, Fuster V, Smith SC Jr. ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/NASPE Committee to Update the 1998 Pacemaker Guidelines). *Circulation* 2002;**106**:2145–2161.

12. Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, Gregoratos G, Klein G, Moss AJ, Myerburg RJ, Priori SG, Quinones MA, Roden DM, Silka MJ, Tracy C, Smith SC Jr, Jacobs AK, Adams CD, Antman EM, Anderson JL, Hunt SA, Halperin JL, Nishimura R, Ornato JP, Page RL, Riegel B, Blanc JJ, Budaj A, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo JL, Zamorano JL. ACC/AHA/ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (writing committee to develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation* 2006;**114**:e385–e484.

13. Schmidt G, Malik M, Barthel P, Schneider R, Ulm K, Rolnitzky L, Camm AJ, Bigger JT Jr, Schomig A. Heart-rate turbulence after ventricular premature beats as a predictor of mortality after acute myocardial infarction. *Lancet* 1999;**353**:1390–1396.

14. Bauer A, Kantelhardt JW, Barthel P, Schneider R, Makikallio T, Ulm K, Hnatkova K, Schomig A, Huikuri H, Bunde A, Malik M, Schmidt G. Deceleration capacity of heart rate as a predictor of mortality after myocardial infarction: cohort study. *Lancet* 2006;**367**:1674–1681.

15. Bauer A, Kantelhardt JW, Bunde A, Malik M, Schneider R, Schmidt G. Phase-rectified signal averaging detects quasi-periodicities in non-stationary data. *Physica A* 2006;**364**:423–434.

16. Bauer A, Malik M, Schmidt G, Barthel P, Bonnemeier H, Cygankiewicz I, Guzik P, Lombardi F, Müller A, Oto A, Schneider R, Watanabe M, Wichterle D, Zareba W. Heart rate turbulence: standards of measurement, physiological interpretation, and clinical use (ISHNE Consensus). *J Am Coll Cardiol* 2008;**52**:1353–1365.

17. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Ass* 1958;**53**:457–481.

18. Peto R, Peto J. Asymptotically efficient rank invariant test procedures. *J R Stat Soc* 1972;**A135**:185–198.

19. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Stat Med* 1999;**18**:695–706.

20. Gray RJ. A class of k-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat* 1988;**16**:1141–1154.

21. Heagerty P, Lumley T, Pepe M. Time-dependent ROC curves for censored survival data and a diagnostic marker. *Biometrics* 2000;**56**:337–344.

22. Hohnloser SH, Kuck KH, Dorian P, Roberts RS, Hampton JR, Hatala R, Fain E, Gent M, Connolly SJ. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. *N Engl J Med* 2004;**351**:2481–2488.

23. Goldenberg I, Moss AJ, Hall WJ, McNitt S, Zareba W, Andrews ML, Cannom DS. Causes and consequences of heart failure after prophylactic implantation of a defibrillator in the multicenter automatic defibrillator implantation trial II. *Circulation* 2006;**113**:2810–2817.

24. Wichterle D, Melenovsky V, Simek J, Malik J, Malik M. Hemodynamics and autonomic control of heart rate turbulence. *J Cardiovasc Electrophysiol* 2006;**17**:286–291.

25. Bauer A, Schmidt G. Last piece of the heart rate turbulence puzzle? *Heart Rhythm* 2007;**4**:290–291.

26. Cole CR, Blackstone EH, Pashkow FJ, Snader CE, Lauer MS. Heart-rate recovery immediately after exercise as a predictor of mortality. *N Engl J Med* 1999;**341**:1351–1357.

27. Smith LL, Kukielka M, Billman GE. Heart rate recovery after exercise: a predictor of ventricular fibrillation susceptibility after myocardial infarction. *Am J Physiol Heart Circ Physiol* 2005;**288**:H1763–H1769.

28. Huikuri HV, Makikallio TH, Peng CK, Goldberger AL, Hintze U, Moller M. Fractal correlation properties of R-R interval dynamics and mortality in patients with depressed left ventricular function after an acute myocardial infarction. *Circulation* 2000;**101**:47–53.

29. Hohnloser SH, Ikeda T, Bloomfield DM, Dabbous OH, Cohen RJ. T-wave alternans negative coronary patients with low ejection and benefit from defibrillator implantation. *Lancet* 2003;**362**:125–126.

30. Bloomfield DM, Steinman RC, Namerow PB, Parides M, Davidenko J, Kaufman ES, Shinn T, Curtis A, Fontaine J, Holmes D, Russo A, Tang C, Bigger JT Jr. Microvolt T-wave alternans distinguishes between patients likely and patients not likely to benefit from implanted cardiac defibrillator therapy: a solution to the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II conundrum. *Circulation* 2004;**110**:1885–1889.

31. Bloomfield DM, Bigger JT, Steinman RC, Namerow PB, Parides MK, Curtis AB, Kaufman ES, Davidenko JM, Shinn TS, Fontaine JM. Microvolt T-wave alternans and the risk of death or sustained ventricular arrhythmias in patients with left ventricular dysfunction. *J Am Coll Cardiol* 2006;**47**:456–463.

32. Chow T, Kereiakes DJ, Bartone C, Booth T, Schloss EJ, Waller T, Chung ES, Menon S, Nallamothu BK, Chan PS. Prognostic utility of microvolt T-wave alternans in risk stratification of patients with ischemic cardiomyopathy. *J Am Coll Cardiol* 2006;**47**:1820–1827.

33. Schmitt C, Barthel P, Ndrepepa G, Schreieck J, Plewan A, Schomig A, Schmidt G. Value of programmed ventricular stimulation for prophylactic internal cardioverter-defibrillator implantation in postinfarction patients preselected by noninvasive risk stratifiers. *J Am Coll Cardiol* 2001;**37**:1901–1907.

34. Buxton AE, Lee KL, DiCarlo L, Gold MR, Greer GS, Prystowsky EN, O'Toole MF, Tang A, Fisher JD, Coromilas J, Talajic M, Hafley G. Electrophysiologic testing to identify patients with coronary artery disease who are at risk for sudden death. Multicenter Unsustained Tachycardia Trial Investigators. *N Engl J Med* 2000;**342**:1937–1945.

35. Ikeda T, Yoshino H, Sugi K, Tanno K, Shimizu H, Watanabe J, Kasamaki Y, Yoshida A, Kato T. Predictive value of microvolt T-wave alternans for sudden cardiac death in patients with preserved cardiac function after acute myocardial infarction: results of a collaborative cohort study. *J Am Coll Cardiol* 2006;**48**:2268–2274.

36. Exner DV, Kavanagh KM, Slawnych MP, Mitchell LB, Ramadan D, Aggarwal SG, Noullett C, Van Schaik A, Mitchell RT, Shibata MA, Gulamhussein S, McMeekin J, Tymchak W, Schnell G, Gillis AM, Sheldon RS, Fick GH, Duff HJ. Noninvasive risk assessment early after a myocardial infarction the REFINE study. *J Am Coll Cardiol* 2007;**50**:2275–2284.

37. La Rovere MT, Bigger JT Jr, Marcus FI, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. *Lancet* 1998;**351**:478–484.

38. Pedersen OD, Abildstrom SZ, Ottesen MM, Rask-Madsen C, Bagger H, Kober L, Torp-Pedersen C. Increased risk of sudden and non-sudden cardiovascular death in patients with atrial fibrillation/flutter following acute myocardial infarction. *Eur Heart J* 2006;**27**:290–295.

39. Sade E, Aytemir K, Oto A, Nazli N, Ozmen F, Ozkutlu H, Tokgozoglu L, Aksoyek S, Ovunc K, Kabakci G, Ozer N, Kes S. Assessment of heart rate turbulence in the acute phase of myocardial infarction for long-term prognosis. *Pacing Clin Electrophysiol* 2003;**26**:544–550.

40. Jokinen V, Tapanainen JM, Seppanen T, Huikuri HV. Temporal changes and prognostic significance of measures of heart rate dynamics after acute myocardial infarction in the beta-blocking era. *Am J Cardiol* 2003;**92**:907–912.