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Projektpartner

# A Statistical Model for Risk Stratification on the Basis of Left Ventricular Ejection Fraction and Heart-Rate Turbulence

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Running head: A new model for risk stratification

# Introduction

Recent multi-center randomized clinical trials (i.e. MADIT, AVID, MUSST) have shown that mortality can be effectively reduced in selected post-infarction patients at high risk for sudden cardiac death by implantation of a cardioverter-defibrillator[1,2,3]. As the selection of high risk patients is a crucial part of prophylaxis, risk stratification strategies are becoming increasingly important.

The sensitivity, the specificity and, in particular, the positive predictive accuracy of currently used risk stratifiers are only moderate[10,11]. We recently introduced Heart Rate Turbulence (HRT) as a new powerful risk predictor in survivors of myocardial infarction[4]. HRT is characterised by an early acceleration and a late deceleration of the sinus rhythm after a single ventricular premature complex (VPC). The acceleration starts immediately after the VPC and lasts for only a small number of RR intervals. Subsequent deceleration reaches a maximum usually around the 10th cycle following a VPC. The absence of this phenomenon indicates a significantly increased risk of subsequent mortality. HRT is independent of the presently available stratifiers. In the MPIP population, HRT and left ventricular ejection fraction (LVEF) were the only independent risk predictors[4].

The goal of this analysis was to develop a statistical model for the prediction of the survival probability of post-infarction patients with arrhythmia based on LVEF and HRT. For this purpose we used the data from the MPIP-trial.

# Methods

## Patient population

Of the 715 survivors of acute myocardial infarction enrolled in the MPIP study [4], 134 patients were excluded from our analyses because of atrial fibrillation, no VPCs during Holter monitoring, missing LVEF or because of technically insufficient or missing Holter recordings. The remaining 581 patients were used in this study. Their clinical characteristics are shown in Table 1. The patients were followed for a maximum of 2 years during which 77 of them died.

*Table 1:*     *The MPIP data set*

| Variable | | Mean (SD) Number (%) |
|---|---|---|
| **HRT** | **(1)** | 154 (26.5%) |
| | **(2)** | 73 (12.6%) |
| **LVEF** | | 46.29 (14.83) |
| **Salvos observed (Y/N)** | | 67 (11.5%) |
| **Number of extra systolic beats in the longest salvo** | | 3.21 (2.25) |
| **Couplets observed (Y/N)** | | 168 (28.9%) |
| **Mean heart rate** | | 72.02 (11.51) |
| **Heart rate variability index** | | 27.48 (13.06) |

**Assessment of the risk predictors**

Holter recordings were performed in the second or third week after the index infarction. Initially, the Holter tapes were processed at Columbia University, New York with a Laser Holter 8000 System (Marquette Medical Systems, WI, USA). After visual inspection and manual editing, computer files were generated listing RR interval duration (sampling frequency 128 Hz) and QRS morphological classifications on a beat-to-beat basis. The following Holter risk predictors were quantified:

(1) Salvos present,

(2) Number of extra systolic beats in the longest salvo,

(3) Couplets present,

(4) mean heart rate (defined as the mean of all sinus rhythm cycles in a Holter recording),

(5) HRV triangular index (using the previously published technology),

(6) HRT (using the previously published technology [4, 13]).

(7) LVEF was assessed two weeks after infarction by radionuclide ventriculography [4, 12].

Previous analyses have shown that among the parameters described, only LVEF and HRT have a statistically significant impact on survival. Therefore, all further analyses have focused on those two parameters.

**Statistical analyses**

The endpoint of the study was total mortality. The identification of important prognostic factors was performed by the proportional hazard model of Cox (Cox, 1972). Based on the results of previous analyses, we included in the model only LVEF and HRT. These two factors were the only ones statistically significant correlated with mortality (Schmidt et al., 1999). Variable HRT was categorical with three levels (0 = turbulence onset *and* turbulence slope normal, 1 = turbulence onset *or* turbulence slope normal, 2 = turbulence onset *and* turbulence slope abnormal). LVEF was used as continuous variable.

Results of all survival analyses are presented in form of Kaplan-Meier curves as survival curves based on the result of the Cox-model and as relative risks with corresponding 95% confidence limits. A significance level of 0.05 was used for the analyses.

# Results

The influence of LVEF on the mortality rate is shown in figure 1. The median of LVEF (46) was used to split the sample. The difference between the survival rates of the resulting groups was statistically significant. Figure 2 shows the survival rates for the patients in each of the three categories of HRT. The influence of HRT remained significant in both sub-samples divided with respect to LVEF (see figure 3). Therefore, both parameters were included in a multivariate analysis in order to get a prognostic score for identifying the high risk group.

*__Figure 1:__* *Survival curves for high and low values of LVEF (mean of 46 is used for cut point)*
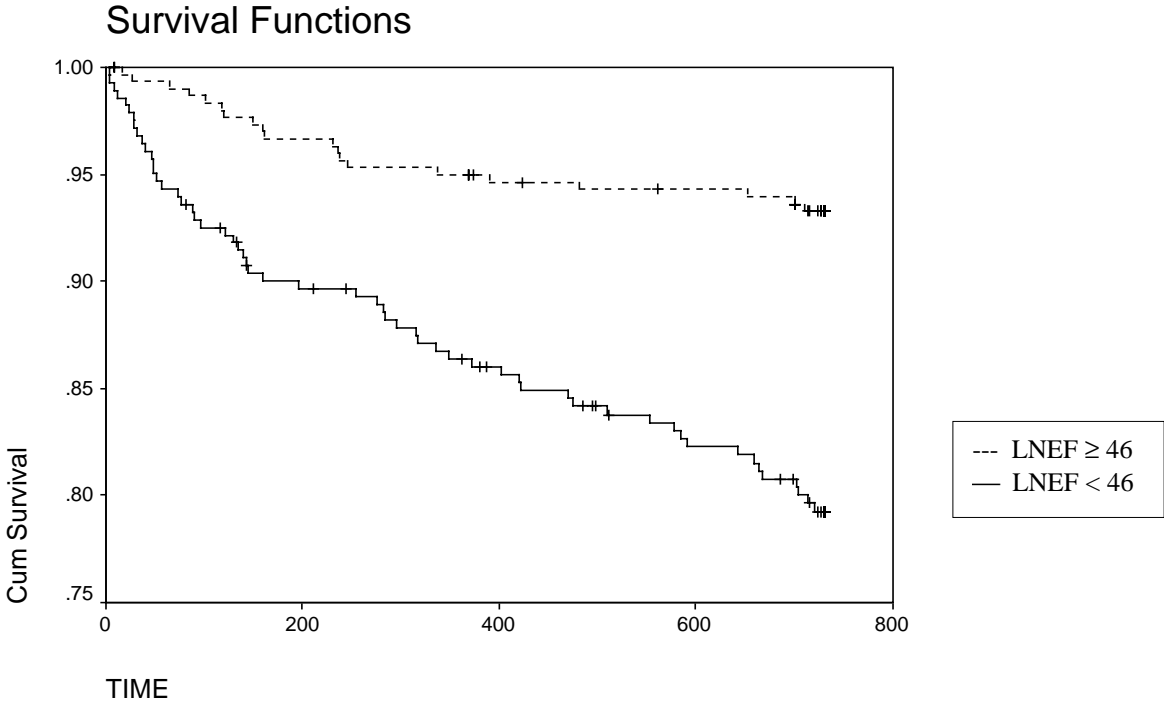


Survival Functions

***Figure 2:*** *Survival curves for the three levels of HRT*
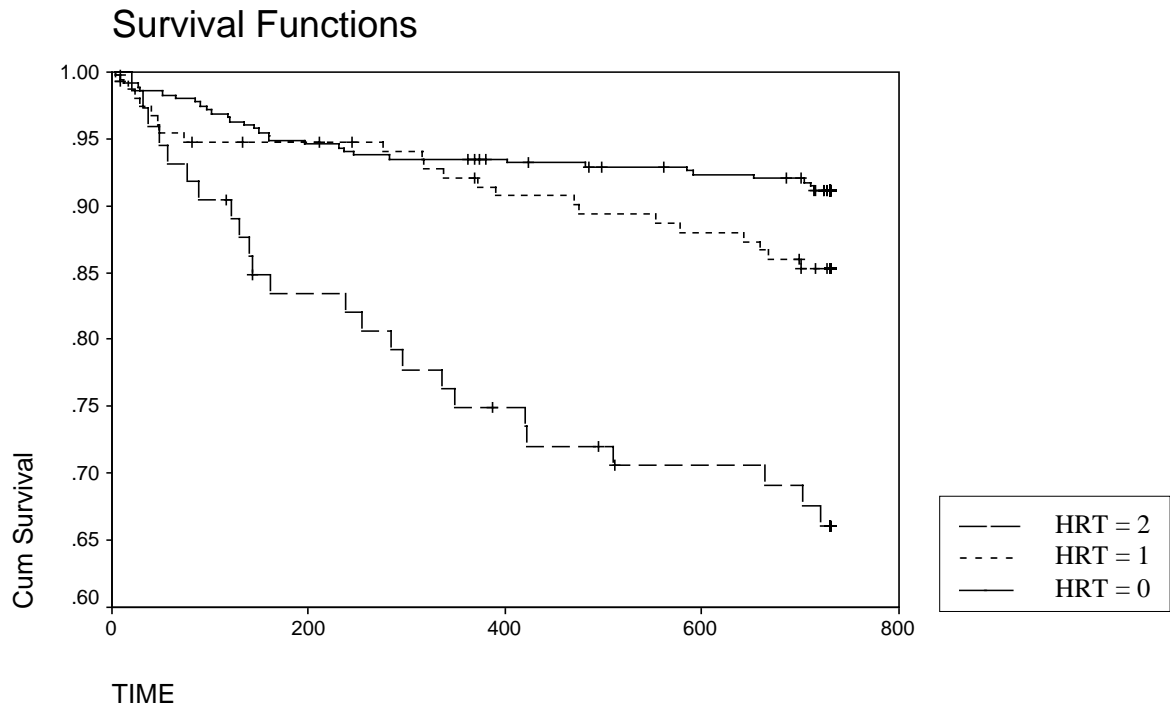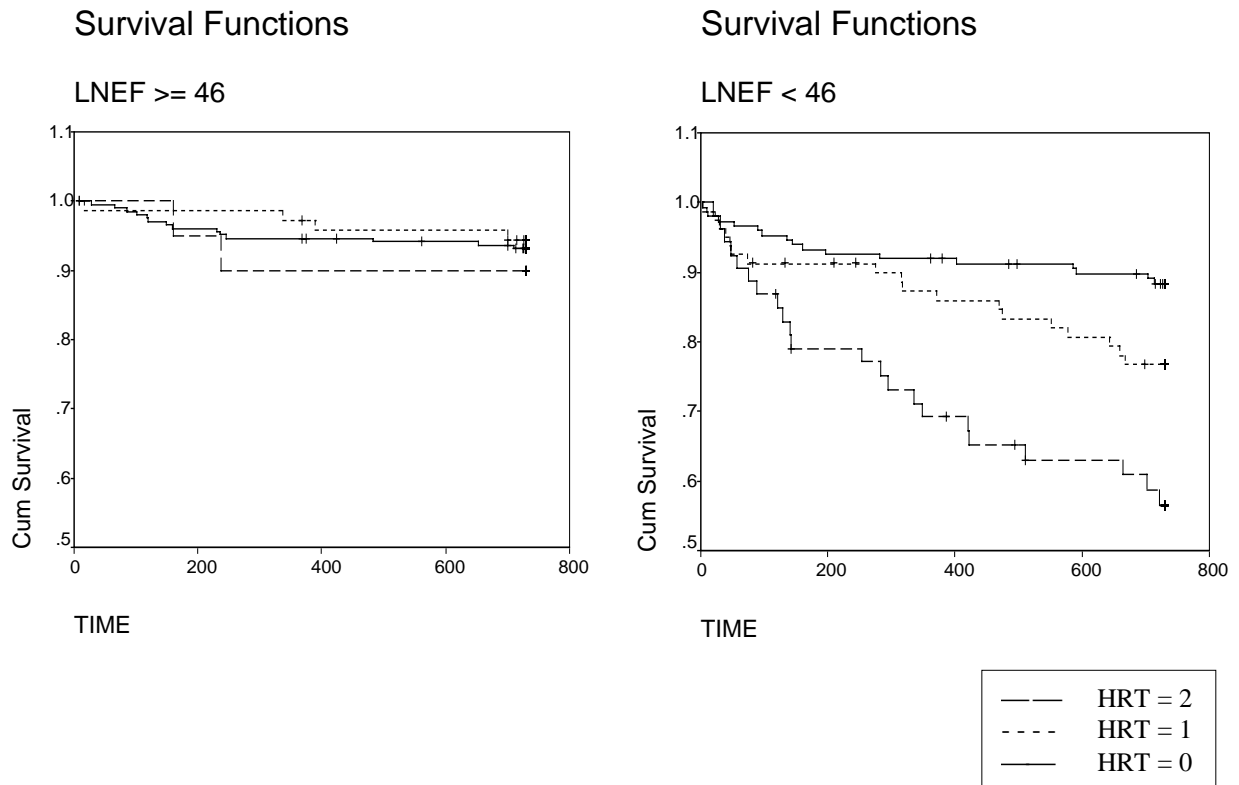


Survival Functions

***Figure 3:*** *Survival curves for HRT within the two groups divided by LVEF*



Survival Functions

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LVEF is measured on a continuous scale. First we investigated the appropriate form of the influence of LVEF on mortality. The usual assumption is a linear effect and there are several ways to check it. Following a proposal of Royston (2000), the first step is to use smoothing splines[7, 8].

**_Figure 4:_** **_Influence of LVEF on the relative risk analyzed by smoothing splines, fractional polynomials, and under the linear assumption._**
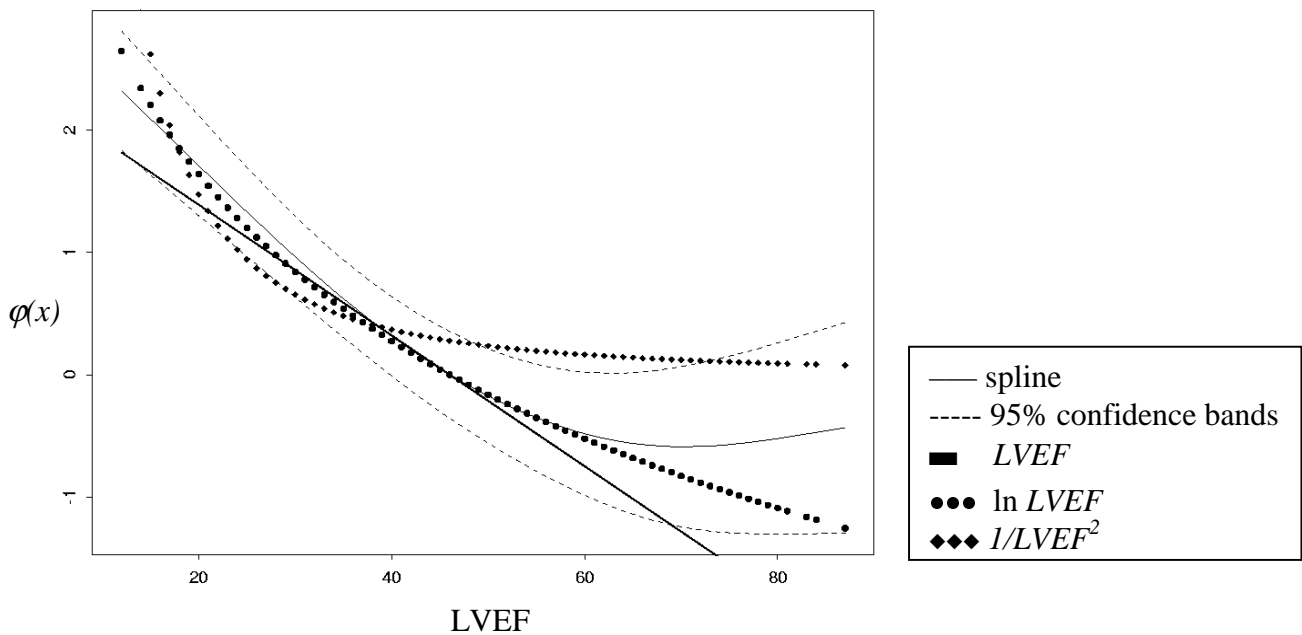


From figure 4 it can be seen, that the effect of LVEF is not linear. In order to describe the influence of LVEF in a functional form, we applied a technique called fractional polynomials[9]. Within that approach the set of possible functions is restricted to

$$\varphi(x) = \sum_{i=1}^{m} \beta_i x^{P_i} \qquad (m \le 2)$$

with $\beta_i$ the unknown coefficients and the exponents $p_i$ are selected among a given set of values (*{-2, - 1.5, - 1, - 0.5, 0.5, 1, 1.5, 2, 2.5, 3,* ln *x}*). A great variety of associations can be modeled with this set of functions.

It turned out that the relationship in the whole sample can be described adequately using one of the following functions:

$$\varphi(x) = \frac{\beta}{LVEF^2} \qquad (m=1, p_1 = -2)$$
$$\varphi(x) = \beta \cdot \ln LVEF$$

Both functions are presented in fig. 4 together with the usual linear form. The goodness of fit using either function is much larger compared with the linear function (R = 59.655 for $1 / LVEF^2$, R = 48.114 for ln$LVEF$ and R = 39.554 for $LVEF$). However, the transformation ln$LVEF$ performed a better fit in the subgroups with higher risk (HRT $\geq$ 1) and was, therefore, used in the further analysis together with HRT as categorical variable. In the multivariate analysis both variables turned out to be statistically significant (Table 2). The goodness of fit statistics increased to R = 71.887.

*Table 2:*      ***Results of the Cox-model (n = 581 patients, 77 deaths)***

| variable | $\beta$ | *p*-value | RR = $e^\beta$ (95 % CI) |
|---|---|---|---|
| **ln LVEF** | -1.57 | < 0.0001 | —* |
| **HRT = 1** | 0.373 | 0.186 | 1.45 (0.84 – 2.52) |
| **HRT = 2** | 0.891 | 0.003 | 2.44 (1.34 – 4.43) |

*     *There is no relative risk given for LVEF. The risk depends on the values of LVEF. E. g. the relative risk for a patients with LVEF = 20 compared to those with LVEF = 30 is 1.89. LVEF = 30 compared with LVEF = 40 gives a relative risk of 1.57.*

The following prognostic score (PS) can be obtained based on the result of the Cox-model:

$$PS = \begin{cases} -1.57 \cdot \ln LVEF & HRT = 0 \\ -1.57 \cdot \ln LVEF + 0.373 & HRT = 1 \\ -1.57 \cdot \ln LVEF + 0.891 & HRT = 2 \end{cases}$$
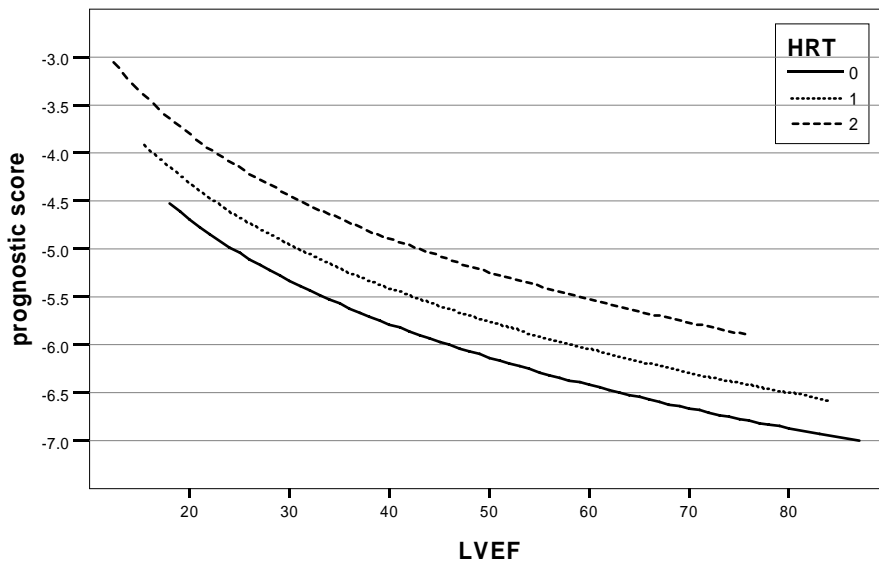
Figure 5 shows the relationship between the prognostic score PS, LVEF and HRT. Higher score is associated with a higher mortality rate. A prognostic score of about -4.5 can be obtained for the following values:

*LVEF = 17 for HRT = 0,*

*LVEF = 22 for HRT = 1 and*

*LVEF = 31 for HRT = 2.*

***Figure 5:*** **Comparison of the prognostic score PS with LVEF and HRT.**



For certain values for the prognostic score the corresponding survival rates are given in figure 6. E. g. a prognostic score of -4.5 is associated with a mortality rate of 32 % after 2 years of follow-up.

***Figure 6:*** **Survival curves for some values of the prognostic score**
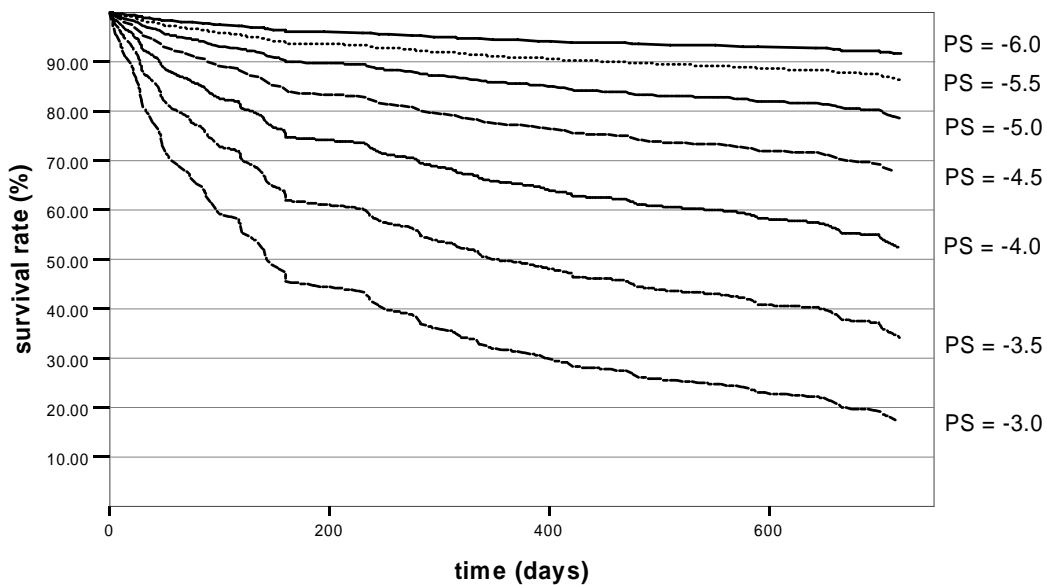
Discrimination between high and low risk

The discrimination between high and low risk patients can be based on several factors, e. g. the prognostic score, the mortality rate at 2 years, or the percentage of patients in the high risk group with their average risk at 2 years.

Figure 7 shows all three of the above criteria. Using the value of -4.5 for the prognostic score for dividing the patients into low and high risk, about 7% of the sample belong to the high risk group (score > -4.5) and their average 2 year mortality rate is about 47%. The additional line (P(2)) gives the lower boundary of the 2 years mortality rate in the high risk group (32% for a score of  -4.5). The appropriate cutpoint can be defined in using one of these criteria.

***Figure 7:***     ***Comparison of the percentage of patients with prognostic score greater than or equal to the value given on the x-axis and corresponding mortality rate at two years together with the average risk in the group.***
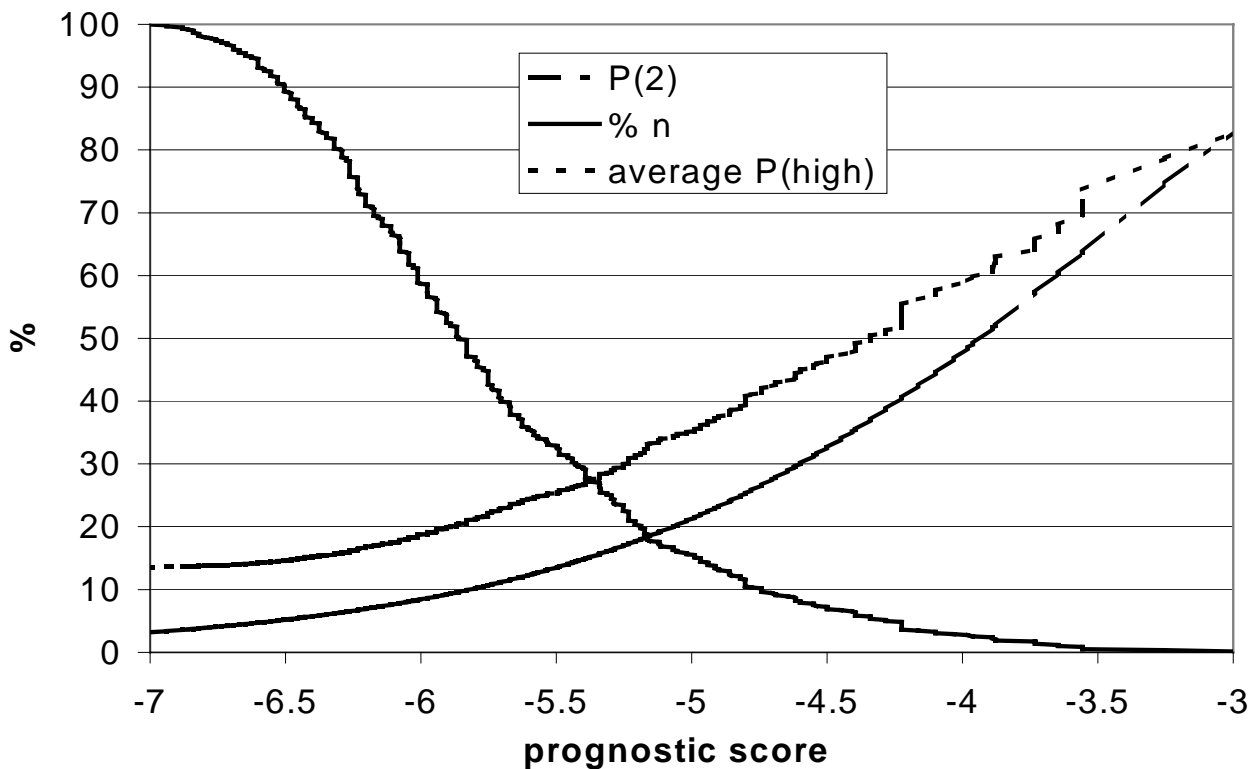
Comparison of LVEF and the pair LVEF and HRT.

In order to show the advantage of using LVEF together with HRT instead of LVEF alone we used the percentage of patients in the high risk group for comparison. Table 3 gives the corresponding cut-points for LVEF together with the number of deaths in the high risk group.

***Table 3:*** ***Comparison of the prognostic scores based on LVEF alone or LVEF in combination with HRT***

| percentage of patients in the high risk group | LVEF alone | | | | LVEF + HRT | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 2 years mortality-rate (%) | | | | 2 years mortality-rate (%) | |
| | LVEF | deaths/n | min | average | prognostic score | deaths/n | min | average |
| 5 % | 24 | 14/33 | 21.9 | 37.8 | -4.34 | 17/33 | 37.0 | 49.6 |
| 10 % | 27 | 24/63 | 18.1 | 28.8 | -4.80 | 25/60 | 25.8 | 41.0 |
| 15 % | 29 | 29/88 | 16.4 | 25.4 | -4.97 | 33/87 | 21.9 | 35.7 |
| 20 % | 32 | 35/117 | 14.6 | 22.9 | -5.19 | 37/117 | 18.0 | 31.5 |
| 25 % | 35 | 39/145 | 13.4 | 21.1 | -5.30 | 42/145 | 16.3 | 28.7 |

It can be seen that the combination of LVEF and HRT is able to identify more deaths among the same number of patients than LVEF alone and the mortality rates are always higher. The lower the number of patients in the high risk group, the grater the difference in the mortality rates.

# Discussion

Previous analyses have shown that among all prognostic factors measured in the MPIP patients, LVEF and HRT were the only significant and independent risk predictors. The goal of this study was to develop a statistical model which combines the information of both risk predictors.

The statistical model presented in this paper is based on the proportional hazard model of Cox[6]. HRT was used as a categorical variable with three outcomes, LVEF was used as a continuous variable. The model results in a risk score, which can be converted into an estimate of the probability of death within a predefined follow-up period and/or a corresponding survival curve. The estimates provided by the model fitted well to the actual mortality figures.

The great advantage of the new model is the exact estimation of the *individual* mortality risk. In other models, where risk predictors are used either alone or in combination, the average risk of patient *groups* is estimated. In case of the risk score presented here, a cut-off point of -4.4 would optimally separate a low risk subgroup (estimated average two-year mortality 11.2%) from a high risk subgroup (estimated average two-year mortality 48.1%) (Figure 8).

*<u>Figure 8:</u>* *Estimated two-year mortality risk presented as continuous variable and dichotomized variable.*
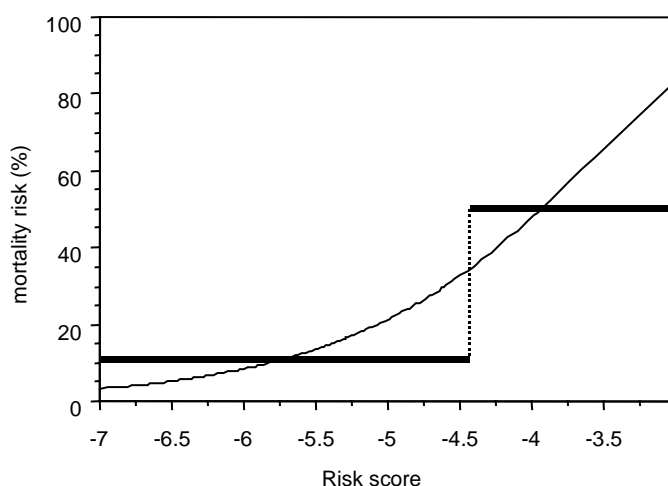


Within the low risk group, the individual two-year mortality risk may be as low as 3.2% and as high as 35.2%. Within the high risk group, e.g., the individual two-year mortality risk varies between 35.3% and 82.6%. Moreover, patients with only slightly different risk scores

around the cut-off point (e.g. -4.3 and -4.5) would be assigned to different risk groups. Due to these problems, the risk of individual patients may be over- or underestimated. A higher number of subgroups, e.g. three ore more, would alleviate these errors, but not eliminate.

The new risk score is a sharper tool than the presently available models. This should facilitate the decision whether or not an individual patient needs further diagnostic and therapeutic procedures, be it an electrophysiological study or the implantation of a cardioverter defibrillator. Another advantage of the statistical model presented is that other independent risk predictors can easily added to the model. In the case, that new methods, such as baroreflex sensitivity, T-wave alternans (or others) will proof to be independent risk predictors in a multivariate Cox analysis, the model will be re-adjusted in consideration of the β coefficients of the new risk predictors.

Limitations: None of the MPIP patients was treated by thrombolysis during the acute phase of infarction. Only a minority received betablockers, ACE inhibitors, lipid lowering drugs or ASS during follow-up. The baseline hazard $\Lambda_0(t)$ probably has to be adjusted when the model is used in post-MI patients treated by thrombolysis or PTCA/Stenting during the acute phase and with the above mentioned drugs during the chronic phase of the infarction.

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