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# Risk Stratification in Post-MI Patients Based on Left Ventricular Ejection Fraction and Heart-Rate Turbulence

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## Summary

**Objectives:** Development of risk stratification criteria for predicting mortality in post-infarction patients taking into account LVEF and heart-rate turbulence (HRT).

**Methods:** Based on previous results the two parameters LVEF (continuously) and turbulence slope (TS) as an indicator of the HRT were combined for risk stratification. The method has been applied within two independent data sets (the MPIP-trial and the EMIAT-study).

**Results:** The criteria were defined in order to match the outcome of applying  $LVEF \leq 30\%$  in sensitivity. In the MPIP trial the optimal criteria selected are TS normal and  $LVEF \leq 21\%$  or TS abnormal and  $LVEF \leq 40\%$ . Within the placebo group of the EMIAT-study the corresponding criteria are: TS normal and  $LVEF \leq 23\%$  or TS abnormal and  $LVEF \leq 40\%$ . Combining both studies the following criteria could be obtained: TS normal and  $LVEF \leq 20\%$  or TS abnormal and  $LVEF \leq 40\%$ . In the MPIP study 83 out of the 581 patients (= 14.3 %) are fulfilling these criteria. Within this group 30 patients have died during the follow-up. In the EMIAT-trial 218 out of the 591 patients (= 37.9 %) are classified as high risk patients with 53 deaths. Combining both studies the high risk group contains 301 patients with 83 deaths (ppv = 27.7 %). Using the MADIT-criterion as classification rule ( $LVEF \leq 30\%$ ) a sample of 375 patients with 85 deaths (ppv = 24 %) can be selected.

**Conclusions:** The stratification rule based on LVEF and TS is able to select high risk patients suitable for implanting an ICD. The rule performs better than the classical one with LVEF alone. The high risk group applying the new criteria is smaller with about the same number of deaths and therefore with a higher positive predictive value. The classification criteria have been validated within a bootstrap study with 100 replications. In all samples the rule based on TS and LVEF (= NEW) was superior to LVEF alone, the high risk group has been smaller ( $\bar{n} \pm s$ :  $301 \pm 14.5$  (NEW) vs.  $375 \pm 14.5$  (LVEF)) and the positive predictive value was larger ( $\bar{p} \pm s$ :  $27.2 \pm 2.6\%$  (NEW) vs.  $23.3 \pm 2.2\%$  (LVEF)). The new criteria are less expensive due to a reduced number of high risk patients selected.

## Introduction

The development of the implantable cardioverter defibrillator (ICD)<sup>1</sup> changed the treatment of patients with malignant arrhythmias. Several randomized clinical trials<sup>2-8</sup> have shown that arrhythmic mortality can be effectively reduced by this therapy. However, the question arises as to which patients will truly benefit from prophylactic ICD therapy.

Risk stratification is a major topic due to the large number of potential candidates and the related costs. Therefore the development of selection criteria remains a serious problem and is the target of many investigations. Usually a combination of various tests are recommended. In a recent meta-analysis<sup>9</sup> a three step procedure was proposed based on signal averaged ECG and LVEF in the first stage followed by ambulatory ECG in the second stage and finally EPS in the third stage. The authors estimated that about 11.8 % of all post MI patients are classified as having a high risk.

Huikuri et. al.<sup>10</sup> investigated the predictive power of various parameters in the  $\beta$ -blocking era. Their conclusions was that the common markers have limited power in identifying high risk patients. In a following editorial Moss<sup>11</sup> recommended that at present it is probably the best to use LVEF as the only marker with a cut-off level of 30 % or 35 %.

The Task Force on Sudden Cardiac Death of the European Society of Cardiology recently recommended a risk stratification strategy which combines a marker of structural damage, such as depressed left ventricular ejection fraction (LVEF), with markers of autonomic imbalance<sup>12</sup>.

Heart-rate turbulence (HRT) is a powerful new risk predictor in survivors of myocardial infarction<sup>13</sup> which represents a measure of the autonomic response to postextrasystolic pauses after singular ventricular premature complexes (VPC)<sup>14-16</sup>. In a study that developed the concept of HRT<sup>13</sup>, HRT and LVEF were found to be the only independent predictors of subsequent mortality in post-infarction patients.

The goal of this study was to develop a risk-stratification algorithm for the prediction of mortality in post-infarction patients that makes use of HRT and LVEF and which can be adapted to various

mortality rates and sensitivity requirements. Data from the MPIP-study<sup>17</sup> and the EMIAT-trial<sup>18</sup> were used to develop the algorithm for selecting high-risk patients.

## **Methods**

### **Patient population**

#### **a) MPIP-trial**

The MPIP study<sup>17</sup> enrolled survivors of acute myocardial infarction, aged  $\leq 70$  years, and followed them for a period of 2.5 years. Patients were excluded from the current analysis because of atrial fibrillation, no VPB during Holter monitoring, missing LVEFs or because of technically insufficient or missing Holter recordings. Five hundred eighty-one patients were used in the analysis. Their clinical characteristics are shown in Table 1. During the follow-up period, 19 % (77 out of 581) of the patients died.

#### **b) EMIAT-trial placebo-arm**

The primary goal of this randomized trial was to compare the effect of Amiodarane against placebo on total mortality<sup>18</sup>. Altogether 1168 patients have been enrolled in that study. The main inclusion criterion had been a LVEF  $\leq 40$  %. For the purpose of developing a classification rule all patients from the EMIAT-trial randomized into the placebo-arm were used (n = 591 patients with 82 deaths). The patients were followed up for about 2 years. The basic data of this sample are also shown in table 1.

Table 1: Basis data of both studies

	STUDY		Total
	EMIAT	MPIP	
Status censored	509	504	1013
dead	82	77	159
Total	591	581	1172

	EMIAT			MPIP		
	n	Median	(5% – 95%)	n	Median	(5% – 95%)
LVEF	591	31	(16 – 40)	581	46	( 24 – 72 )
TS	591	4,4	( ,7 – 17,7 )	581	5,9	( ,6 – 25,1 )

	STUDY		Total
	EMIAT	MPIP	
TS normal	419	446	865
abnormal	172	135	307
Total	591	581	1172

### 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 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.

Both parameters of HRT, Turbulence Onset (TO) and Turbulence Slope (TS) were assessed using previously published methods<sup>13</sup>. LVEF was quantified by radionuclide ventriculography.

## Statistics

A Cox-Model<sup>19</sup> was used for the analysis. Based on the results of previous analyses only LVEF (continuously) and the turbulence slope (TS) as a measure of the heart rate turbulence (HRT) have been included in the model. In order to determine the appropriate relationship between LVEF and total mortality smoothing splines and fractional polynomials<sup>20-22</sup> have been applied.

The identification of high risk patients can be based on several criteria. One way could be to use the standard procedure ( $LVEF \leq 30\%$ ) and to select those patients with the same risk or a greater one. Another approach could be to assess optimal cutpoints in applying the CART procedure<sup>23</sup>.

For any risk stratification procedure certain parameters can be calculated in order to describe the outcome of a particular. The high risk group can be described by the sample size, the average mortality rate at a certain time  $t$  and the range ( $t = 2$  years have been used), the sensitivity (= percentage of deaths in that risk group divided by the total number of deaths), the positive predictive value (= percentage of deaths in that particular sample). This value is approximately the same as the average 2-years mortality rate due the small number of censored individuals within the two years follow-up.

Each decision rule has to be validated. The best way would be either to split the data available in a trainings- and a validation sample or to use new data. The disadvantage with the two studies available is the reduced number of events and the missing of new data. In the situation where no validation sample is available a technique called bootstrap can be used<sup>24, 25</sup>. The idea is simple. Based on the data available new samples of the same size are generated by random selection with replacement. This means some of the patients are more than one times in a bootstrap-sample whereas others are missing. This procedure can be repeated as often as desired. The application of a decision rule on the bootstrap samples can be used to describe the performance in new patients in form of mean and standard deviations or range. In order to obtain these values 100 bootstrap samples have been generated.

## Results

The optimal form to model the influence of LVEF on total mortality was obtained by using a logarithmic transformation. Fig. 1 shows the influence of LVEF and TS on the 2-years mortality rate varying between 5 % and 65 % in both samples. The effect of TS on mortality can also be seen from fig. 1. Using the recent MADIT II criterion<sup>8</sup> (LVEF  $\leq$  30 %), the 2-years mortality rate is 24 % or higher in the MPIP study and  $\geq$  21 % in the EMIAT-trial.

Identifying the patients with similar 2-years mortality rates using LVEF and TS the following criteria can be obtained.

	<b>MPIP</b>	<b>EMIAT</b>	<b>total</b>
TS normal:	LVEF $\leq$ 21 %	LVEF $\leq$ 23 %	LVEF $\leq$ 20 %
TS abnormal:	LVEF $\leq$ 40 %	LVEF $\leq$ 40 %	LVEF $\leq$ 40 %

Applying these criteria obtained for both samples altogether 301 patients are classified as high risk patients with 83 deaths (ppv = 27,6 %). Using the MADIT II criteria (LVEF  $\leq$  30 %) the high risk group contains 375 patients with 85 deaths (ppv = 22.7 %) (s. Table 2).

The selection rule based on LVEF and TS is able to identify a smaller number of high risk patients by nearly identical number of deaths.



Figure. 1: Influence of LVEF alone and in combination with turbulence slope (= TS) on the 2-years all cause mortality rate for both studies considered.

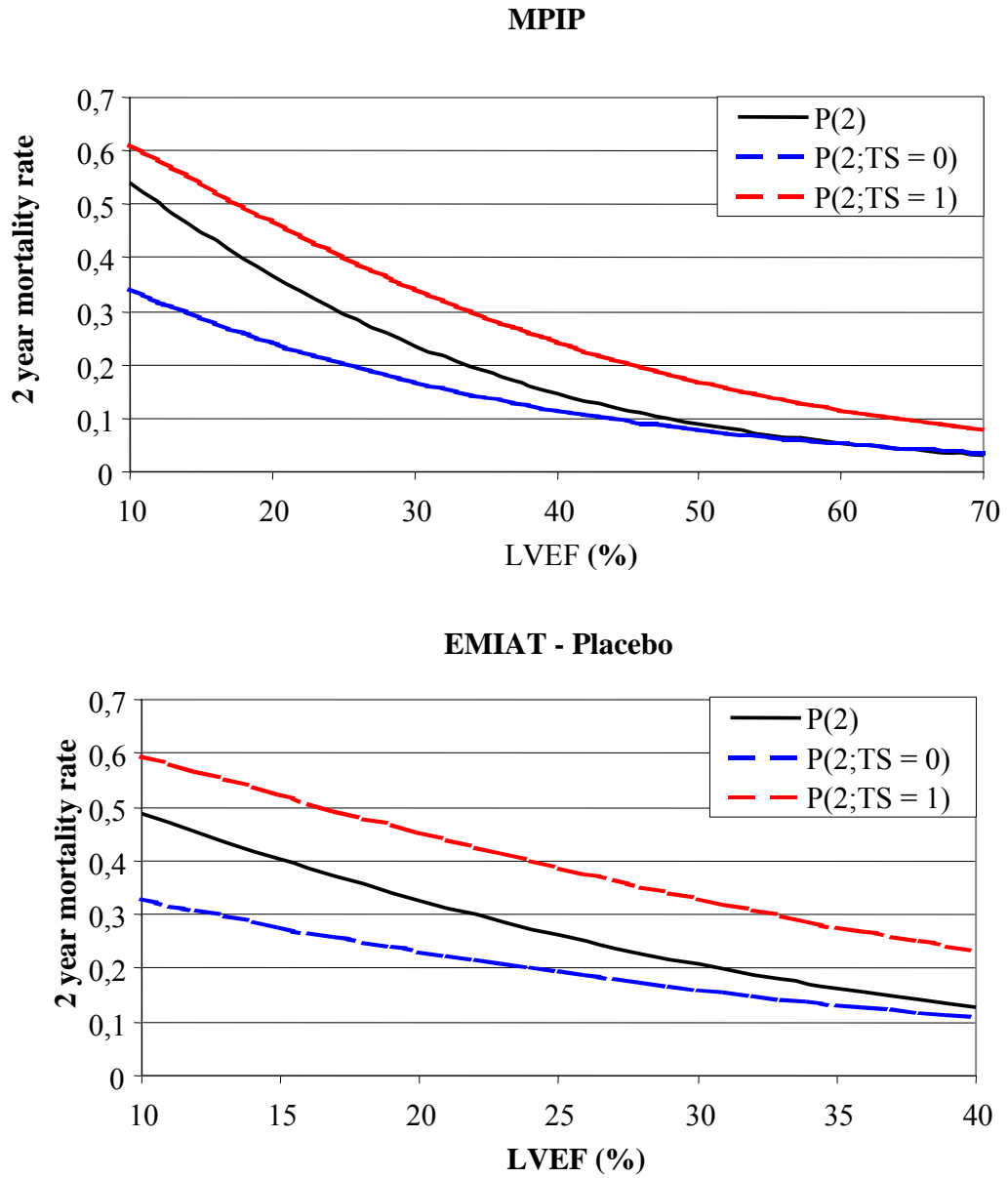


Table 2: Patients in the high-risk group

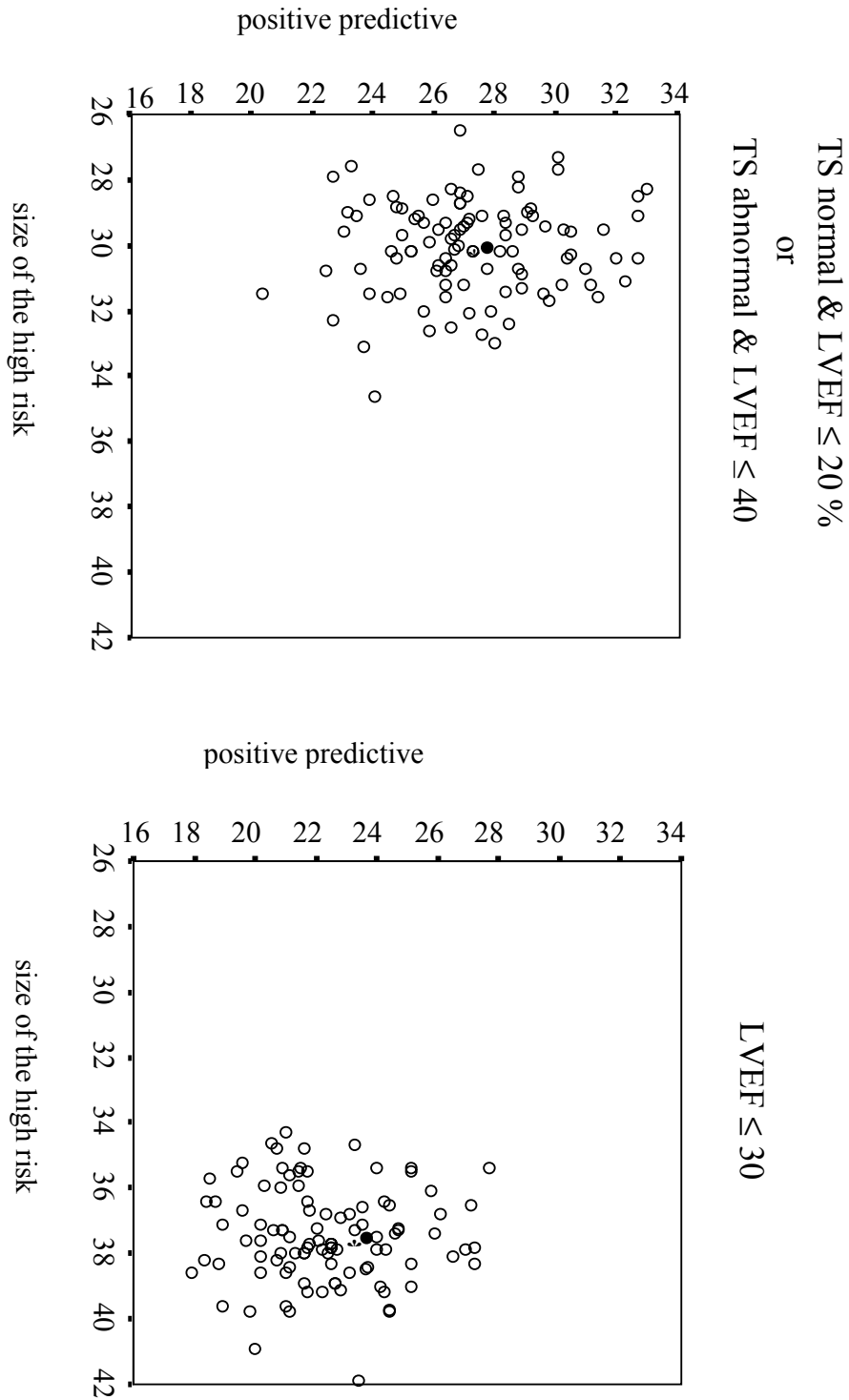
	EMIAT			MPIP			total		
	n	dead	%	n	dead	%	n	dead	%
total	591	82	13,9	581	77	13,3	1172	159	13,6
LVEF $\leq$ 30%	278	53	19,1	97	32	33,0	375	85	22,7
TS=0, LVEF $\leq$ 20%	46	11	23,9	3	1	33,3	49	12	24,5
TS=1, LVEF $\leq$ 40%	172	42	24,4	80	29	36,3	252	71	28,2
together	218	53	24,3	83	30	36,1	301	83	27,6

### Validation

In order to validate these criteria 100 bootstrap samples all of size  $n = 1172$  have been generated. Using  $LVEF \leq 30\%$  for identifying high risk patients the size of that group was between 343 and 419 patients ( $\bar{n} \pm s: 375 \pm 14.5$ ). Applying the new criteria the size of the high risk group varied between 265 and 346 patients ( $\bar{n} \pm s: 301 \pm 14.5$ ). In all samples the high risk group based on the new criteria was smaller than using LVEF alone. The positive predictive values varied between 18 % and 28 % for LVEF alone ( $\bar{x} \pm s: 22.3 \pm 2.2\%$ ) and between 20 % and 33 % ( $\bar{x} \pm s: 27.2 \pm 2.6\%$ ) for the new criteria. Again in each bootstrap sample the ppv for the new criteria was larger than for LVEF alone (s. fig. 2).

In summary: the new criteria perform better than LVEF alone in identifying high risk patients. The number of deaths recognized by both methods are nearly identical. However the sample of high risk patients is much smaller using the new criteria with a reduction of 19.7 % and a range between 4 % and 29 %.

Figure 2: The result within 100 bootstrap samples comparing the size of the high risk group and the corresponding positive predictive value (ppv) for the two decision rules considered ( $LVEF \leq 30\%$  and the new one). The result obtained in the original data are marked (x).



## Cost effectiveness

A major concern for identifying patients suitable for implanting an ICD are the costs<sup>26,27</sup>.

The estimation of the total costs is based on the following assumption that the implantation of an ICD is about € 30,000.- and € 150.- are required for performing a Holter-ECG.

Using only LVEF for the decision no Holter-ECG has to be performed. In applying LVEF in combination with TS an additional Holter-EGG is necessary if LVEF is between 21 % and 40 %. If LVEF is above 40 % the patients belongs to the low-risk group and with a LVEF  $\leq$  20 % this is a high risk patient independent of the TS-status.

Considering both studies 705 out of the 1172 patients had a LVEF between 21 % and 40 %.

The average costs for both criterias are as follows.

a) LVEF  $\leq$  30 %: 375 ICD \* € 30,000.- = Mio. € 11.25

b) new criteria: 301 ICD \* € 30,000.- + 705 Holter \* € 150.- = Mio. € 9.14

Applying the new criteria the high risk group can be reduced and therefore also in the costs of about 19 %.

## Discussion

In the original study<sup>13</sup>, LVEF was dichotomized at  $\leq 30\%$  vs.  $> 30\%$ , and it was determined that LVEF and TS were the only significant and independent predictors of mortality. In the current analyses, we evaluated the association between LVEF and mortality and chose to use LVEF, logarithmically transformed, as a continuous variable in all analyses.

We proceeded to develop a risk stratification algorithm which utilized both risk predictors, LVEF alone and in combination with TS. The model makes use of different LVEF cut-off points in the patient subgroups with normal and abnormal TS achieving desired levels of sensitivity and positive predictive accuracy.

The optimal separation of low- and high-risk groups remains a different task. With decreasing number of patients in the high risk group the mortality rate increases. The cost-effectiveness therefore is also increasing. However one has to take into account that the so-called low-risk groups contains more and more deaths. But in any case the definition of the criteria for being a high-risk patients remains a problem. One can use the 2 year mortality rate as criterion. In this situation one gets different cutpoints for LVEF depending on turbulence slope. In order to compare the effect of the new procedure with the established one ( $\text{LVEF} \leq 30\%$ ), the following cutpoints have been derived using the data of both studies together (MPIP and EMIAT).

TS normal:  $\text{LVEF} \leq 20\%$

TS abnormal:  $\text{LVEF} \leq 40\%$

Using these criteria a Holter-ECG has to be performed for patients with a LVEF between 21 and 40 %. Based on these definitions of high-risk 301 patients are fulfilling these criteria with 83 deaths. On the other hand 375 patients have a  $\text{LVEF} \leq 30\%$  with 85 deaths. This means applying the new criteria the high-risk group can be reduced by about 19 % with nearly equal number of deaths or similar sensitivity.

Several authors have addressed the problems associated with risk stratification. In post-MI patients there may be a variety of causes of death. All the markers available may be correlated with cardiac death, which accounts for about 60 % of all deaths. The markers may be inadequate for

other causes. But it seems that the process of identifying high risk patients is still an important task and the problem can be solved step by step. In this way the combination of LVEF and turbulence slope is one step to reduce the number of high risk patients. The next step will be investigate whether the patients identified as having a high risk truly benefit from an ICD. There is still room for developing new and more specific markers.

## References

1. Mirowski M, Mower MM, Staewen WS, Tabatznik B, Mendeloff AI: Standby automatic defibrillator. An approach to prevention of sudden coronary death. *Arch Intern Med.* 1970 Jul; 126 (1): 158-61.
2. Moss AJ, Hall WJ, Cannom DS, et al. 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: 1933-40.
3. The Antiarrhythmics versus Implantable Defibrillator (AVID) Investigators. A comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med* 1997; 337 (22): 1576-83.
4. Buxton A, Lee KL, DiCarlo L, et al.: A Randomized Study of the Prevention of Sudden Death in Patients with Coronary Disease. *N Engl J Med* 1999; 342 (25): 1882-1890.
5. Connolly SJ, Gent M, Roberts RS, et. al.: Canadian Implantable Defibrillator Study (DIDS) - A Randomized Trial of the Implantable Cardioverter Defibrillator Against Amiodarone. *Circulation* 2000; 101: 1297-1302.
6. Kuck KH, Cappato R, Siebels J, et. al.: Randomized Comparison of Antiarrhythmic Drug Therapy with Implantable Defibrillators in Patients Resuscitated form Cardiac Arrest - The Cardiac Arrest Study Hamburg (CASH). *Circulation* 2000; 102: 748-54.
7. Domanski MJ, Sakseena S, Epstein AE, et. al.: Relative Effectiveness of the Implantable Cardioverter-Defibrillator and Antiarrhythmic Drugs in Patients with Varying Degrees of Left Ventricular Dysfunction Who Have Survived Malignant Ventricular Arrhythmias. *Am College of Cardiology* 1999; 34 (4): 1090-5.
8. Moss AJ, Zareba W, Hall WJ, et al.: Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002; 346: 877-83
9. Bailey JJ, Berson AS, Handelsman H, Hodges M: Utility of Current Risk Stratification Tests for Predicting Major Arrhythmic Events After Myocardial Infarction. *Journal of the American College of Cardiology* 2001; 38 (7): 1902-11.
10. Huikuri HV, Tapanainen JM, Lindgren K, Raatikainen P, Mäkikallio TH, Airaksinen KEJ, Myerburg RJ: Prediction of Sudden Cardiac Death After Myocardial Infarction in the Beta-Blocking Era. *Journal of the American College of Cardiology* 2003; 42 (4): 652-8.
11. Moss AJ: Dead Is Dead, but Can We Identify Patients at Increased Risk for Sudden Cardiac Death? *Journal of the American College of Cardiology* 2003; 42 (4): 659-60.

12. Priori SG, Aliot E, Blomstrom-Lundqvist C, Bossaert L, Breithardt G, Brugada P, Camm AJ, Cappato R, Cobbe SM, Di Mario C, Maron BJ, McKenna WJ, Pedersen AK, Ravens U, Schwartz PJ, Trusz-Gluza M, Vardas P, Wellens HJ, Zipes DP: Task Force on Sudden Cardiac Death of the European Society of Cardiology. *Eur Heart J* 2001; 16: 1374-450.
13. Schmidt G, Malik M, Barthel P, et al.: Heart-rate turbulence after ventricular premature beats as a predictor of mortality after acute myocardial infarction. *Lancet* 1999, 353: 1390-6.
14. Mrowka R, Persson PB, Theres H, Patzak A: Blunted arterial baroreflex causes "pathological" heart rate turbulence. *Am J Physiol Regul Integr Comp Physiol* 2000; 279: 1171-5.
15. Davies LC, Francis DP, Ponikowski P, Piepoli MF, Coats AJ: Relation of heart rate and blood pressure turbulence following premature ventricular complexes to baroreflex sensitivity in chronic congestive heart failure. *Am J Cardiol* 2001; 87: 737-42.
16. Ghuran A, Reid F, La Rovere MT, Schmidt G, Bigger JT, Camm AJ, Schwartz PJ, Malik M: Heart rate turbulence-based predictors of fatal and nonfatal cardiac arrest. *Am J Cardiol* 2002; 89 (2) 1: 184-90.
17. Bigger JJ, Fleiss JL, Kleiger R, Miller JP, Rolnitzky LM. The relationships among ventricular arrhythmias, left ventricular dysfunction, and mortality in the 2 years after myocardial infarction. *Circulation* 1984; 69: 250-58
18. Julian DG, Gamm AJ, Frangin G, et. al. Randomised trial of effect of amiodarone on mortality in patients with left-ventricular dysfunction after recent myocardial infarction: EMIAT. *Lancet* 1997; 349: 667-74
19. Cox DR. Regression models and life-tables. *J R Stat Soc* 1972; 34: 187-220.
20. Hastie TJ and Tibshirani RJ: Generalized additive models for medical research. *Stat Methods Med Res* 1995;4:187-96
21. Harrell FE, Lee KL, Mark DB: Tutorial in Biostatistics. Multivariable prognostic models: issues in developing models, evaluation assumptions and adequacy, and measuring and reducing errors. *Statistics in Medicine* 1996; 15: 361-87.
22. Royston, P. and Altman, D. G.: Regression Using Fractional Polynomials of Continuous Covariates: Parsimonious Parametric Modeling. *Applied Statistics* 1994; 43: 429-67.
23. Breimann L, et al.: Classification and regression trees. Belmont, California: Wadsworth, 1984.
24. Efron B, Tibshirani RJ: An Introduction to the Bootstrap. Series: *Monographs on Statistics and Applied Probability* 57. Boca Raton, London, New York: Chapman & Hall/CRC, 1998.
25. Steyerberg EW, Bleeker SA, Moll HA, Grobbee DE, Moons KGM. Internal and external validation of predictive models: A simulation study of bias and precision in small samples. *Journal of Clinical Epidemiology* 2003; 56: 441-447



26. Essebag V, Eisenberg MJ. Expanding Indications for Defibrillators after Myocardial Infarction: Risk Stratification and Cost Effectiveness. *Cardiac Electrophysiology Review* 2003; 7: 43-48
27. Eisenberg, MJ. Risk Stratification for Arrhythmic Events: Are the Bangs Worth the Bucks? *Journal of the American College of Cardiology* 2001; 83: (7) 1912-5.