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Identification of Responders to Amiodarone

Subgroup Analysis of the EMIAT Study

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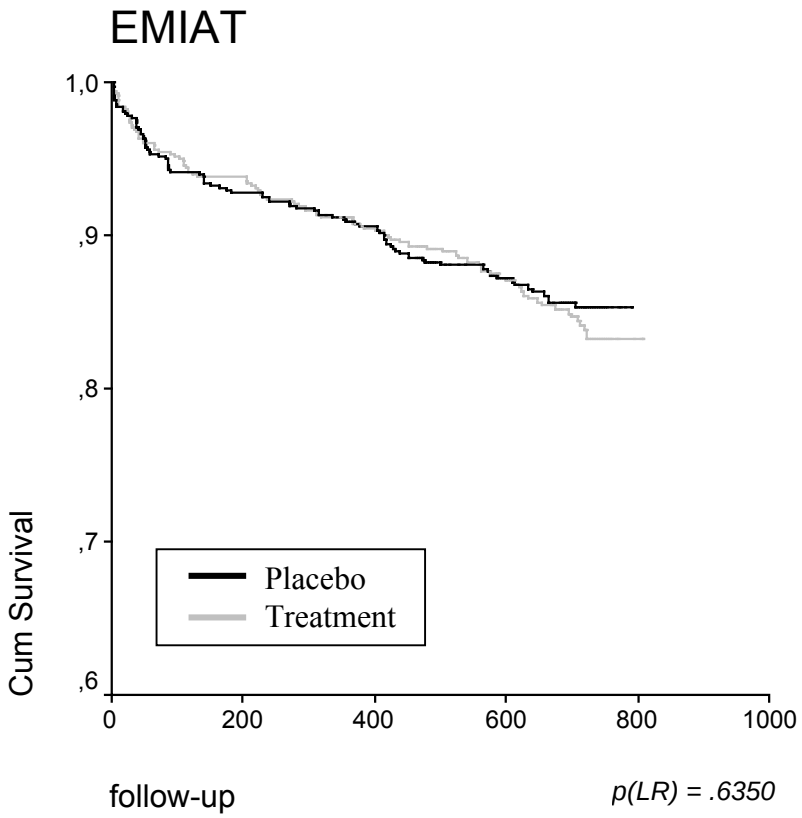
Summary

Clinical trials often judge the efficacy of a new treatment by comparing the survival patterns of patients who are randomly assigned to undergo the new or a standard/placebo treatment. Usually, the entire groups are analyzed, although certain subgroups of patients may react differently to the new treatment than others. Some patients taking the new treatment might benefit from it (the positive responders) while others may be harmed by it (the negative responders). We applied a newly developed responder identification method (Kehl & Ulm, 2003) on the doubleblinded placebo controlled European Myocardial Infarction Amiodarone Trial (EMIAT). The method, which is based on bump hunting, proceeds to find the so called predictive factors, which describe positive and negative trends in survival in special subgroups of patients, solely due to Amiodarone. Factors found to be predictive were: age, previous infarction, beta-blocker treatment, onset, NYHA classification, and sex. Negative responders to Amiodarone, i.e. patients taking Amiodarone who survived shorter than a similar group under placebo, were patients who were older than 65 years, have had a previous infarction, and were not on beta-blockers. Positive responders to Amiodarone, (longer survival time), were male patients who were not negative responders, had NYHA classification greater than or equal to two, and onset greater than one. Further studies are needed to investigate this hypothesis.

Introduction

In a randomized clinical trial where two treatments are compared, a question of particular interest is whether the overall result holds for all patients or if some subgroups respond differently to the new treatment. This question is especially important for studies in which the new treatment did not show an overall increase in survival compared to placebo (or standard treatment) as in the European Myocardial Infarction Amiodarone Trial (EMIAT). Figure 1 shows the Kaplan-Meier survival curves for the two study arms of EMIAT (Amiodarone & placebo) and the log-rank test for difference in survival (p(LR)=.6350). It is possible, however, that a certain subgroup of Amiodarone patients have higher or lower survival rates than a similar group under placebo. The identification of such subgroups was our aim in this analysis.

Figure 1: *Kaplan-Meier survival curve estimates for the placebo and Amiodarone treatment arms of EMIAT, p-value of the log-rank statistic for difference in survival is 0.6350.*



The fact that the survival time of a patient taking the new treatment is greater than that of a similar patient under placebo can either be due to (i) chance, (ii) better initial prognosis, or (iii) the new therapy. Factors responsible for initial prognosis classification are called **prognostic**. Factors describing solely treatment effect are called **predictive**. Note, that predictive factors can be successfully determined only after (all) prognostic factors have been adjusted for. We also define **positive responders** to be patients who benefit from the new treatment. Their benefit is expressed in a longer survival time than that of patients with the same predictive factors, randomized in the placebo/standard treatment group. We define **negative responders** to be patients who are harmed by the new treatment. Their survival time is shorter than that of a similar group of patients under the classical treatment, described by some predictive factors. A third group of patients are neither positive nor negative responders. Their survival time does not differ from similar patients under placebo.

Responder identification can be easily done for subgroups defined by one factor. The subgroup analysis becomes more complicated when interactions between several factors and the treatment define a subgroup. Janse et al (1998), for example, did subgroup analysis of the EMIAT data in order to find patients, who may benefit from treatment with Amiodarone – they were looking for positive responders. The strategy performed in this substudy of EMIAT was to choose four important, readily available baseline characteristics and consider all groups resulting from their combinations. Only interactions of up to third order were considered. No adjustment for prognostic factors was done. As a result of their analysis, Janse et al reported that *benefit of prophylactic Amiodarone treatment was seen for patients with left-ventricular ejection fraction less than 30%, with arrhythmia on Holter, taking beta-blockers, and with low baseline heart rate. A slight trend towards benefit was seen for patients with ejection fraction between 30% and 40%, without arrhythmia on Holter, off beta-blockers, and with low baseline heart rate.*

Malik et al (2000) performed subgroup analysis of the EMIAT data set with final aim to test the hypothesis that EMIAT patients with depressed heart rate variability (HRV) benefit from the Amiodarone treatment (i.e. are positive responders). They performed this analysis by developing a Cox-PH model on the entire data set, including treatment and seven prognostic factors. The authors fitted models on various subgroups of data and concluded, that *patients with left-ventricular ejection fraction less than 40% and depressed HRV do benefit from prophylactic treatment with Amiodarone*. For further details, please refer to the original publications.

Using the Cox-PH model with treatment interactions for responder identification purposes becomes cumbersome very quickly as the level of interaction grows. Our research aimed at developing an algorithm which overcomes the hurdle of high power interaction terms. With the help of the bump hunting procedure (Friedman & Fisher, 1999), we developed a method which is able to identify positive and negative responders in clinical studies. Note, that this is a post-hoc analysis, therefore, the resulting models cannot be characterized with a goodness of fit criterion. Additional studies are necessary for testing the hypothesis developed in responder analysis.

This paper presents the results of an application of our method on the EMIAT data set, in which the new treatment showed no significant overall effect. Due to the large costs, no additional studies have been performed up to now.

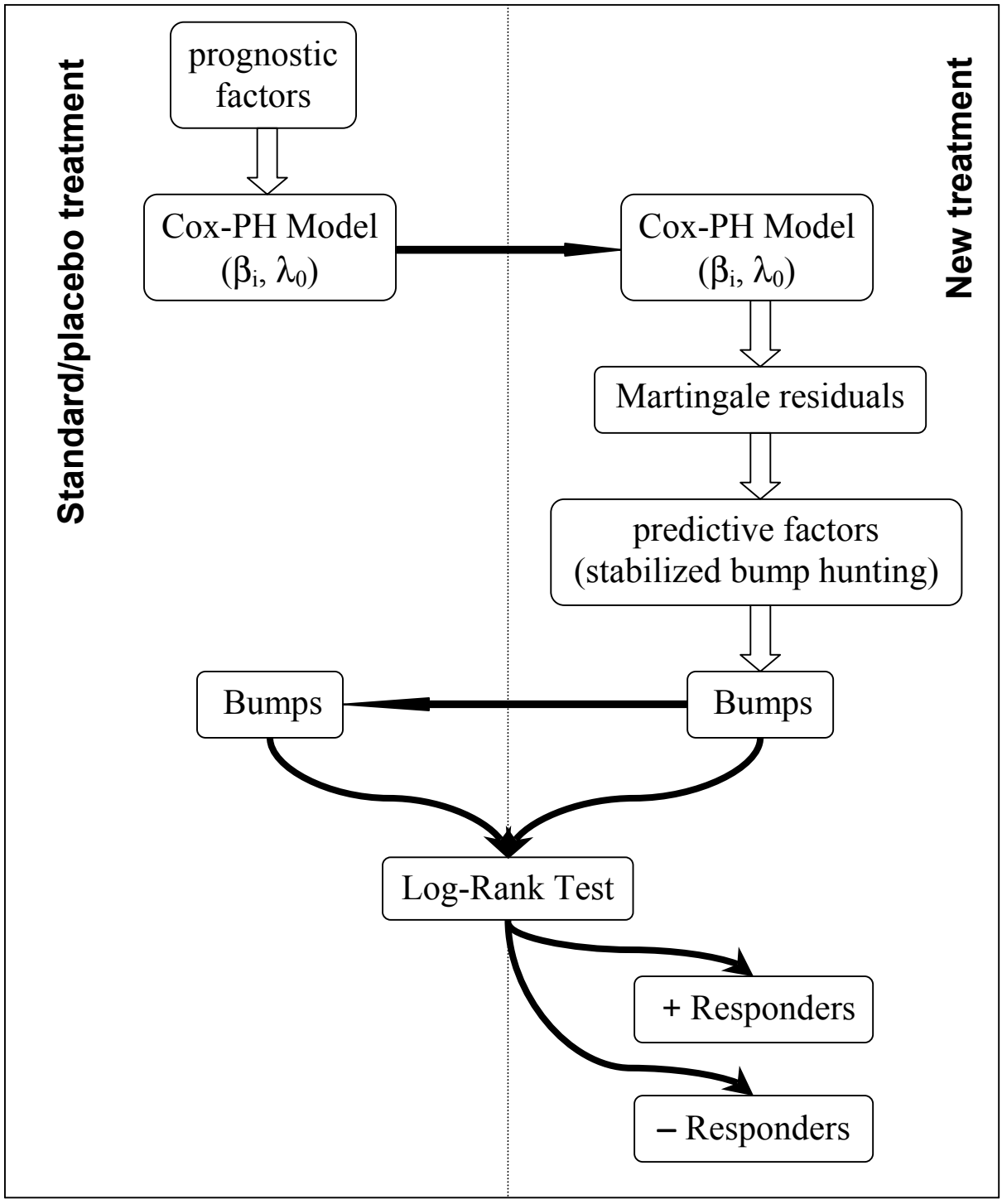
Methods

Responder identification was performed using the responder identification method described in Kehl & Ulm (2003).

In the first step of the suggested method, a prognostic model (we used a Cox-PH model) is developed on the standard treatment group (in the case of EMIAT – on placebo) in order to adjust for prognostic factors. The model is then applied on the new treatment group using the parameters estimated in the standard treatment group. Martingale residuals, which can be thought of as measuring the difference between observed and predicted number of deaths, are calculated in the new treatment group and used as a target variable in the stabilized bump hunting analysis. Note that residual values close to zero signify good fit of the prognostic model to the new treatment data, whereas patients with large residual values have large discrepancies between observed and predicted with the prognostic model cumulative hazard.

In order to identify common factors among patients with large martingale residuals, a procedure called bump hunting (Friedman & Fisher, 1999) was applied. Bump hunting creates a system of rules involving predictive factors, which identify bumps (i.e. groups) of patients with large negative and large positive residuals. Provided that each bump contains patients with different survival rates in the placebo and treatment groups (comparison performed with the log-rank test or, when needed with an exact version of it), the bump found in the new treatment arm would identify patients who are positive or negative responders. The method is summarized in the flow diagram of figure 2. For more details, including performance evaluation, please, refer to the methodological paper (Kehl & Ulm, 2003).

Figure 2: *Flow-diagram of the responder identification method.*



Results

Data

The European Myocardial Infarction Amiodarone Trial (EMIAT) was designed to compare the drug Amiodarone to placebo with respect to all cause mortality in a double blind setting (Julian et al, 1997). It included a total of 1486 survivors of acute myocardial infarction who had left ventricular ejection fraction (LVEF) of 40% or less, randomised into two groups of 743 patients each. There were 103 deaths in the Amiodarone arm and 102 deaths in the placebo arm of the study. A total of 1168 patients had Holter recordings available with sinus rhythm and at least one ventricular premature beat (VPB), which are necessary for calculation of the parameters Onset and Slope – the two components of Heart Rate Turbulence (HRT) (Schmidt et al, 1999). This subset of EMIAT had 576 patients in the Amiodarone arm, 86 of which died during the two years of follow-up (85% censoring), 592 patients were in the placebo group, 82 of which died (86% censoring). Baseline patient characteristics as well as categorization schemes can be found in table 1.

Table 1: *Baseline characteristics of EMIAT for patients with Holter recordings.*

			Placebo (n = 592)		Treatment (n = 576)	
Variable	**Code Name**	**Dichotomization**	**Mean (SD)**	**Number (%)**	**Mean (SD)**	**Number (%)**
Follow-up (days)	**FOLLOWUP**		604.78 (191.94)		605.7 (191.14)	
Censoring	**DEATH**	1 if event		82 (14%)		86 (15%)
Left-ventricular ejection fraction	**LVEF**	1 if LVEF ≤ 30	29.92 (7.52)	278 (47%)	30.22 (6.99)	274 (48%)
Age	**AGE**	1 if AGE > 65	60.62 (9.33)	240 (41%)	60.20 (9.67)	219 (38%)
Heart rate at initial visit	**HR**	1 if HR > 80	74.69 (14.39)	179 (30%)	74.26 (14.25)	170 (30%)
Heart rate variability index	**HRVI**	1 if HRVI ≤ 20	26.08 (10.38)	185 (31%)	26.35 (10.42)	175 (30%)
Onset	**ONSET**	1 if ONSET > 1	0.99 (0.023)	158 (27%)	0.99 (0.026)	148 (26%)
Slope	**SLOPE**	1 if SLOPE ≤ 2.5	6.60 (8.08)	172 (29%)	6.44 (8.39)	189 (33%)
Sex	**SEX**	1 = male		506 (86%)		486 (84%)
More than one infarct	**INFARCT**	1 = Yes		157 (27%)		188 (33%)
New York Heart Association Classification	**NYHA**	2 3 1		251 (42%) 44 (7%) rest		264 (46%) 45 (8%) rest
Diabetes	**DIABETES**	1 = Yes		95 (16%)		98 (17%)
β - blocker	**BETABLO**	1 = Yes		262 (44%)		255 (44%)
Arrythmia on Holter	**ARRHYTHM**	1 = Yes		208 (35%)		211 (37%)
Heart Rate Turbulence	**HRT**	1 if ONSET = 1 or SLOPE = 1 2 if ONSET = 1 & SLOPE = 1 0 if ONSET = 0 & SLOPE = 0		174 (29%) 78 (13%) rest		181 (31%) 78 (14%) rest

Prognostic Model

The Cox-PH model summarized in table 2 was developed on the placebo arm of EMIAT using stepwise selection methods and was validated internally. The prognostic model we found contains the continuous factors left-ventricular ejection fraction (LVEF) and baseline heart rate (HR), and the categorical factors "previous infarction" (INFARCT) and Heart Rate Turbulence (HRT).

Table 2: *Results of the multivariate Cox model on the placebo group of EMIAT.*

Variable	β	p(Wald)	Exp(B)	95% CI for Exp(B)	
				Lower	Upper
LVEF	-0.035	.013	0.966	0.939	0.993
HR	0.024	.001	1.024	1.009	1.039
INFARCT	0.603	.008	1.827	1.171	2.850
HRT		.000			
HRT1	0.599	.030	1.820	1.059	3.128
HRT2	1.181	.000	3.257	1.818	5.835

score statistic = 69.83
p(score) = 1.14×10 $^{-13}$

Predictive Model

The prognostic model was applied on the Amiodarone arm of EMIAT using the baseline hazard function and factor coefficients as estimated in the placebo group. The martingale residuals to the prognostic model in the Amiodarone arm were used as a response variable in the search for predictive factors. We used a stabilized version of the bump hunting algorithm, which used bootstrapping (n = 100) at each border selection step. For details on the original and stabilized bump hunting, please refer to Friedman & Fisher (1999) and Kehl & Ulm (2003) respectively. The size of the EMIAT data set and most of all its high percent censoring do not allow for internal validation, so in order to develop a more stable predictive model, one can use pre-defined cut points, i.e. categorize all continuous variables before developing a predictive model. For that reason all continuous variables were categorized for use in the stabilized bump hunting algorithm (see table 1). The following predictive bump model was found on the Amiodarone arm of EMIAT:

Negative responders bump	Positive responders bump
	All not in neg. resp. bump x:
AGE > 65	ONSET > 1
with previous INFARCT	NYHA ≥ 2
off BETA-BLOCKER	SEX = male

The negative responder bump consists of a box with three borders, which describe patients taking Amiodarone who lived shorter than expected by the prognostic model. The positive responder bump also consists of a single box with three borders. Patients in that bump lived longer than expected. Table 3 represents the growth of the bump model. The rows represent model building steps, i.e. change in the model after each "border" addition, starting with the entire Amiodarone arm of EMIAT. The p-values of the log-rank test statistic comparing the restricted groups in the Amiodarone and placebo arms of EMIAT are also given at each step. The "flower" plot of figure 3 represents schematically the structure of the positive and negative responder groups. Both bumps define groups of patients who have significantly (at the .05 level) different survival estimates under Amiodarone and under placebo (see the Kaplan-Meier curves in figure 4). Table 4 gives a cross-tab of censoring and responder group, including the number of patients and their mean follow-up time in each subgroup. 56 Amiodarone patients were placed in the positive responder group by our model. Their actual survival time of 632 days (overall mean of 606 days in the Amiodarone arm) was longer than that of the corresponding group of 55 placebo patients (506 days), which may be accounted to the effect of Amiodarone. From the patients placed in the positive responder group, 2 died in the Amiodarone and 16 in the placebo group with verage survival time of 150 and 156 days respectively. 57 Amiodarone patients were placed in the negative responder group. Their estimated survival time of 494 days was shorter than the average 606 days. 25 of them died and their average follow-up time was 277 days. The corresponding group of patients under placebo consisted of 58 individuals, 14 of whom died with average survival time of 265 days. This, according to our predictive model, could be traced back to the effect of Amiodarone.

Table 3: *Growth of the bump model in the Amiodarone arm of EMIAT. P-values of the log-rank statistic for survival difference between the two treatment arms are given at each restriction. Star (*) denotes exact tests.*

Restricted set	Bump support: events/patients		Log-rank test (p-value)
	Amiodarone	Placebo	
ALL	86 / 576	82 / 592	.6350
Negative responders			
AGE > 65	52 / 219	43 / 240	.1766
AGE > 65 **&** **INFARCT = 1**	31 / 89	18 / 80	.0858
AGE > 65 **&** *INFARCT = 1* **&** **BETABLO = 0**	25 / 57	14 / 58	.0240
Positive responders			
not negative responder **&** **ONSET > 1**	19 / 127	34 / 139	.0478
not negative responder **&** *ONSET > 1* **&** **NYHA ≥ 2**	9 / 81	20 / 73	.0089*
not negative responder **&** *ONSET > 1* **&** *NYHA ≥ 2* **&** **SEX = male**	2 / 56	16 / 55	.0002*

Table 4: *Mean follow-up in cross-tab of censoring and responder groups for the two EMIAT arms.*

count / *mean follow-up*		**censored**	**events**	**total**
Amiodarone	**+ responders**	**54 / *650***	2 / *150*	56 / *632*
	− responders	32 / *664*	**25 / *277***	57 / *494*
	non-responders	404 / *662*	59 / *303*	463 / *616*
	total	490 / *661*	86 / *292*	576 / *606*
Placebo	**+ responders**	**39 / *650***	16 / *156*	55 / *506*
	− responders	44 / *681*	**14 / *265***	58 / *580*
	non-responders	427 / *662*	52 / *268*	479 / *619*
	total	510 / *663*	82 / *246*	592 / *605*

Figure 3: *Flower plot of the bump model in the Amiodarone arm of EMIAT. Petals represent borders; their intersection – bumps.*

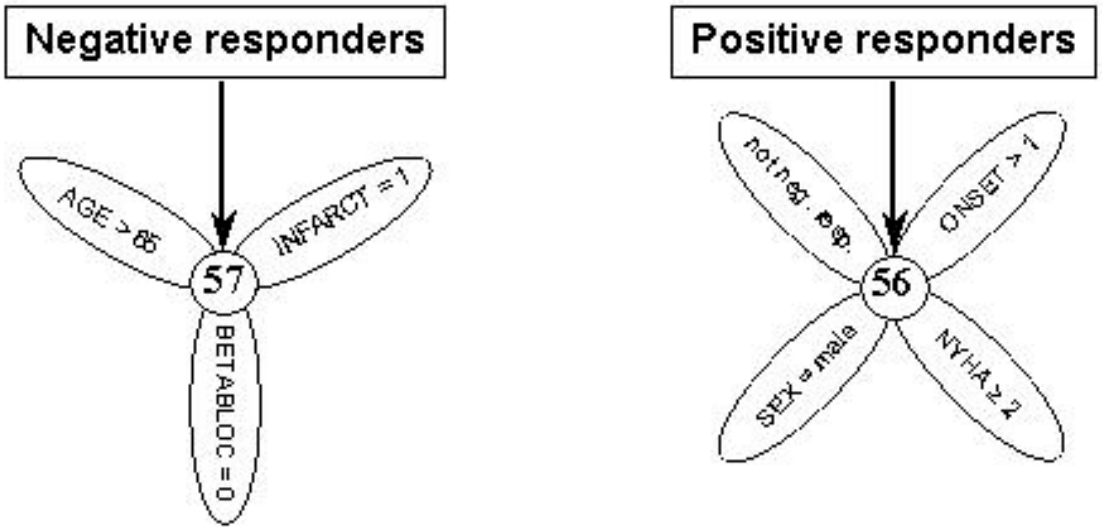
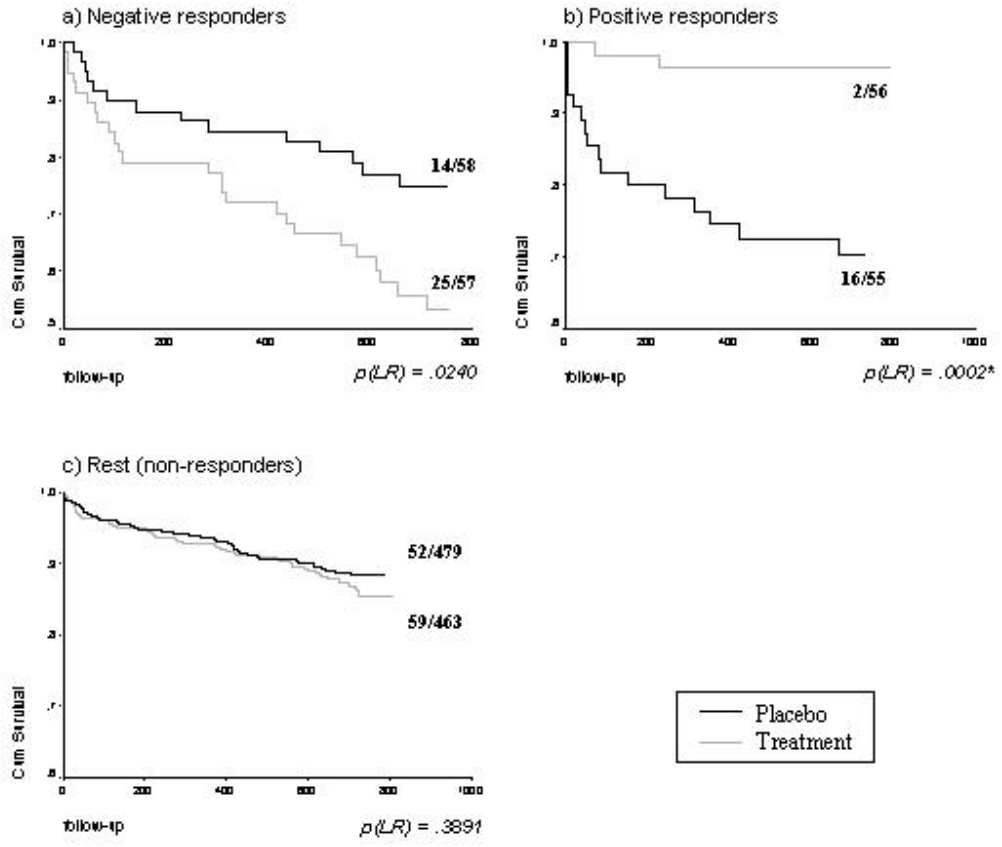


Figure 4: *Kaplan-Meier survival curve estimates for the a) negative and b) positive responder groups of the bump model, compared in the Amiodarone and placebo groups of EMIAT. The p-value of the log-rank statistic is .0002* and .0240 respectively, where * denotes the result of an exact log-rank test. c) shows the rest of the patients.*



As a rule, among patients with ejection fraction less than 35 (EMIAT population), older patients (>65 years) who have had a previous infarction and are not taking beta-blockers seem to react particularly negative to Amiodarone, while patients who do not belong to this group, i.e. patients who are either taking beta-blockers or have just experienced their first myocardial infarction or are younger than 65 years, and **in addition** are men, have high onset (> 1), and pathological NYHA (≥ 2) seem to benefit from Amiodarone treatment.

Discussion

Applying the method which we have developed, we could identify negative as well as positive responders to Amiodaron in the EMIAT study. The comparison between both treatment arms leads to significant differences in the survival curves in those subgroups. The negative responders to Amiodarone, defined by AGE > 65 years, previous infarction, and no beta-blockers are at high risk. The 2 years mortality rate after myocardial infarction in the placebo subgroup defined by the above parameters was about 25% compared to 47% in the negative Amiodarone responder group. The positive responders to Amiodarone identified by: not negative responders, onset > 1, NYHA ≥ 2, and male are at low risk. The mortality rate in this group under Amiodarone was 4% compared to 30% under placebo.

In this analysis we distinguish between prognostic and predictive factors. The well established prognostic factors such as left-ventricular ejection fraction, heart rate measurements, as well as heart rate turbulence showed to be powerful in this data set as well. The factors and interactions which may have predictive power in the EMIAT data set were discovered with the help of the newly developed responder identification method. Those factor interactions need further investigation in a setting similar to that of the EMIAT study.

A major weakness of the bump hunting model in the responder identification method is the fact that up to now it has no goodness of fit criteria. Sometimes it is possible to perform internal or external validation, but in most cases, just as in EMIAT, the size of the data does not allow splitting and no suitable data sets are available for external validation. Stabilized bump hunting, however, performs very well even on data with few events (see simulation study in Kehl & Ulm). Its power for negative responders is 99% and for positive responders 90%. That means, that out of 100 models, the procedure recognizes correctly at least 90. In

our opinion, the power of the procedure compensates somewhat the lack of goodness of fit criteria.

The interpretability of the resulting models is another positive feature, which makes the responder identification method attractive in the area of clinical trials.

The method can also be applied to studies in which there is an overall difference in survival between the two treatment groups. For further details, please refer to the methodological paper (Kehl & Ulm, 2003).

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