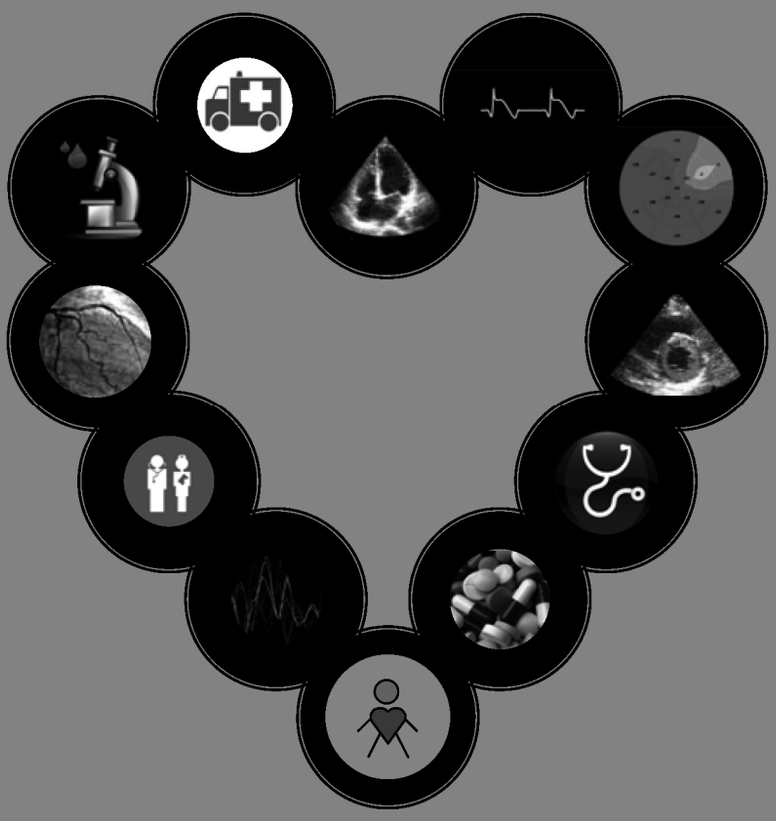
Improving risk stratification after acute myocardial infarction : focus on emerging applications of echocardiography

Antoni, M.L.



Chapter 5

Relationship between Discharge Heart Rate and Mortality in Patients after Acute Myocardial Infarction Treated with Primary Percutaneous Coronary Intervention

M. Louisa Antoni, Helèn Boden, Victoria Delgado,
Eric Boersma, Kim Fox, Martin J. Schalij, Jeroen J. Bax

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Abstract

Objectives

In patients with coronary artery disease, the prognostic value of heart rate has been mainly evaluated in patients with left ventricular dysfunction. Patients with ST-segment elevation acute myocardial infarction (STEMI) are currently treated with primary percutaneous coronary intervention (PCI) and in this contemporary population of patients, the relationship between heart rate and mortality during a follow-up >1 year has not been investigated.

Methods and results

The population comprised 1453 STEMI patients treated with primary PCI. Resting heart rate was measured before discharge and all patients were followed prospectively.

Main outcome measure: The endpoints were defined as all-cause mortality and cardiovascular mortality. The median follow-up duration was 40 months. During this period, 83 (6%) patients died of which 52 (4%) died from cardiovascular disease. After adjusting for parameters reflecting a greater infarct size and the presence of heart failure, heart rate at discharge remained a strong predictor of mortality. Patients with a heart rate of ≥70bpm had a 2 times increased risk of cardiovascular mortality at 1 year and 4 year follow-up compared to patients with a heart rate <70bpm. In addition, every increase of 5bpm in heart rate at discharge was associated with a 29% and 24% increased risk of cardiovascular mortality at 1 and 4 year follow-up, respectively.

Conclusion: In STEMI patients treated with primary PCI and optimal medical therapy, heart rate at discharge was an important predictor of mortality up to 4 year follow-up even after adjustment for parameters reflecting a greater infarct size and the presence of heart failure.

Conclusions

In STEMI patients treated with primary PCI and optimal medical therapy, heart rate at discharge was an important predictor of mortality up to 4 year follow-up even after adjustment for parameters reflecting a greater infarct size and the presence of heart failure.

Introduction

Heart rate has demonstrated to be a risk factor of mortality and cardiovascular morbidity in various populations including patients with coronary artery disease.[1-3] In patients with coronary artery disease, the prognostic value of heart rate has been mainly evaluated in patients with left ventricular dysfunction.[4 5] In particular, subanalysis performed in patients with coronary artery disease and left ventricular dysfunction from the placebo arm of the BEAUTIFUL trial, recently demonstrated that an elevated resting heart rate of 70 bpm or higher was a strong independent predictor of long-term outcome during 2 year follow-up.[5 6] Patients with ST-segment elevation acute myocardial infarction (STEMI) are currently treated with primary percutaneous coronary intervention (PCI). The use of primary PCI has improved the outcome of STEMI patients significantly. In this contemporary population of STEMI patients, the relationship between heart rate and adverse outcome during a follow-up >1 year has not been investigated. Most studies evaluating the relation between heart rate and adverse outcome in STEMI patients have included a follow-up duration up to 6 months.[7-9] Accordingly, the aim of the current study was to investigate the clinical relevance of discharge heart rate in relationship to survival up to 4 years in patients with STEMI treated with primary PCI and optimal medical therapy.

Methods

Patient population and data collection

The patient population comprised 1453 patients from an ongoing clinical registry of patients admitted with STEMI treated with PCI. All patients were treated according to the institutional STEMI protocol (MISSION!), which is based upon the most recent American College of Cardiology/American Heart Association/European Society of Cardiology guidelines.[10-12] This protocol, designed to improve care around STEMI, includes a prehospital, inhospital and outpatient clinical framework.[13] All patients are transferred directly from the ambulance to the catherization laboratory for primary PCI. Within 48 hours of admission, 2-dimensional echocardiography is performed to quantify left ventricular ejection fraction according to the biplane Simpson's method.[14] After discharge, all patients are followed at the outpatient clinic. The aim of the current study was to assess

the relationship between discharge heart rate and all-cause mortality and cardiovascular mortality up to 4 year follow-up. For this purpose, resting heart rate was measured from 12-lead electrocardiography before discharge and patients who presented with atrial fibrillation or cardiogenic shock were not included in the present study. Patient data were prospectively collected in the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center, Leiden, the Netherlands) and retrospectively analysed.

Follow-up

Follow-up was performed by review of medical records and retrieval of survival status through the municipal civil registries, which is updated regularly and therefore very accurate in the Netherlands. The endpoints were defined as all-cause mortality and cardiovascular mortality. All medical records were reviewed independently by two observers, and the primary cause of death was recorded. All deaths were classified as cardiac unless unequivocally proven noncardiac.

Statistical analysis

Continuous data are presented as mean ± standard deviation or median and 25th and 75th percentiles as appropriate. Categorical data are presented as frequencies and percentages. Elevated heart rate at discharge was analyzed as a continuous variable, divided by the cutoff value of 70 bpm and categorized into 4 groups by quartiles (<62 bpm, 62 – 70 bpm, 70 – 78 bpm, ≥78 bpm). The cutoff value of 70 bpm was derived from the patient population as the median heart rate at discharge of the total population and is in line with previous studies assessing the risk associated with an elevated heart rate.[2 3 5 15] Differences in baseline characteristics between the different quartiles of heart rate at discharge were evaluated using the one-way analysis of variance (ANOVA) and chi-square tests, where appropriate. Beta-blocker dosage was reported for metoprolol, which is the beta-blocker of preference according to the institutional protocol (MISSION!) and was used by 93% of the patients treated with a beta-blocker at discharge.[13] Multivariable analysis was performed to assess the predictive value of heart rate at discharge for cardiovascular and all-cause mortality at 1 and 4 year follow-up. Because of the relatively small number of endpoint events, the number of covariables had to be limited. Therefore, selection of parameters to

be entered in the multivariable models was based both on clinical judgment and univariable statistical significance. Based on these considerations, the multivariable models were corrected for age, Killip class ≥2, the left anterior descending coronary artery as culprit vessel and left ventricular ejection fraction. The interaction between gender and the different quartiles of heart rate at discharge was tested for all endpoints. Event rates were plotted in Kaplan-Meier curves for all-cause mortality and cardiovascular mortality occurring after discharge and for each quartile of heart rate at discharge. All statistical tests were two-sided, and a P value <0.05 was considered to be statistically significant.

Results

Patient characteristics

A total of 1492 patients admitted with STEMI and treated with primary PCI were evaluated. Thirty-nine (3%) patients died during the index hospitalization and were excluded from further analysis. The final patient population therefore comprised 1453 patients. Baseline characteristics of the total patient population are shown in Table 1. Mean age was 61 ± 12 years and most patients were men (1107 patients, 76%). Mean heart rate at admission was 74 ± 18 bpm and decreased during hospitalization to 70 ± 12 bpm (P <0.001). According to the quartiles of heart rate at discharge, patients were divided in 4 groups: patients with a heart rate lower than 62 bpm, 62 – 70 bpm, 70 – 78 bpm and patients with a heart rate of 78 bpm or higher (Table 1). Patients with a higher heart rate at discharge were more likely to have had a larger infarct size reflected by a higher frequency of Killip class ≥2, diabetes and higher glucose levels. In addition, the infarct characteristics demonstrated that patients with a higher heart rate at discharge were more likely to have the left anterior descending coronary artery as a culprit vessel, longer symptoms to balloon times, higher peak creatine phosphokinase and cardiac troponin T levels and lower left ventricular ejection fraction at the echocardiogram performed during admission. In line, the dosage of beta-blockers was higher for every increasing quartile of heart rate at discharge (64 ± 34 mg for patients with a heart rate <62 bpm, 69 ± 34 mg in the group with a heart rate of 62 – 70 bpm, 77 ± 37 mg for patients with a heart rate of 70 – 78 bpm and 90 ± 45 mg for patients with a heart rate of 78 bpm or higher, ANOVA p <0.001).

Table 1. Patient characteristics

	Heart rate at discharge				
	<62bpm (N = 347)	***62–70 bpm (N = 371)***	***70–78 bpm (N = 349)***	***≥78bpm (N = 386)***	***P***
Admission					
Age(years)	60 ± 12	61 ± 12	61 ± 12	61 ± 13	0.76
Male gender	289 (83%)	293 (79%)	255 (73%)	270 (70%)	<0.001
Killip class≥2	6 (2%)	7 (2%)	13 (4%)	22 (6%)	0.007
Current smoking	163 (47%)	181 (49%)	168 (48%)	184 (48%)	0.97
Diabetes	29 (8%)	38 (10%)	39 (11%)	66 (17%)	0.002
Family history of CAD	160 (46%)	157 (42%)	140 (40%)	147 (38%)	0.15
Hyperlipidemia	76 (22%)	74 (20%)	66 (19%)	73 (19%)	0.72
Hypertension	112 (32%)	122 (33%)	126 (36%)	145 (38%)	0.37
Prior myocardial infarction	35 (10%)	30 (8%)	26 (7%)	35 (9%)	0.60
Glucose level(mmol/l)	8.0 ± 2.3	8.2 ± 2.6	8.6 ± 2.8	9.0 ± 3.5	<0.001
eGFR(ml/min/1,73m^2)	96 ± 30	97 ± 33	100 ± 35	98 ± 37	0.49
Infarct					
LAD culprit vessel	135 (39%)	169 (46%)	150 (43%)	204 (53%)	0.002
Number of diseased vessels	179/112/56	175/127/69	156/119/74	173/137/76	0.49
Symptoms to balloon time (min)	160 (115, 251)	162 (122, 250)	176 (128, 275)	192 (137, 281)	0.008
Peak CPK level (U/l)	1109 (458, 2097)	1310 (555, 2396)	1651 (803, 3250)	2021 (952, 4100)	<0.001
Peak cTnT level (µg/l)	2.7 (1.0, 5.9)	3.2 (1.2, 6.7)	4.2 (1.6, 8.5)	5.0 (2.2, 10.7)	<0.001
TIMI 2–3 flow	343 (99%)	368 (99%)	341 (98%)	384 (100%)	0.13
LV ejection fraction(%)	48 ± 8	46 ± 8	45 ± 8	44 ± 9	<0.001
Discharge					
Heart rate(bpm)	56 ± 5	65 ± 2	73 ± 2	86 ± 8	
Systolic blood pressure(mmHg)	115 ± 16	115 ± 15	115 ± 15	114 ± 18	0.45
Diastolic blood pressure(mmHg)	68 ± 11	70 ± 11	70 ± 10	70 ± 11	0.14
ACE inhibitor/ARB	339 (98%)	366 (99%)	338 (97%)	374 (97%)	0.35
Antiplatelets	347 (100%)	371 (100%)	349 (100%)	386 (100%)	1.00
Beta-blockers	319 (92%)	355 (96%)	336 (96%)	366 (95%)	0.05
Beta-blockers dosage(mg)	64 ± 34	69 ± 34	77 ± 37	90 ± 45	<0.001
Statins	345 (99%)	366 (99%)	349 (100%)	380 (98%)	0.10

*P values are given for the comparison of between the different quartiles of heart rate at discharge.

ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; CAD: coronary artery

disease; CPK: creatine phosphokinase; cTnT: cardiac troponin T; eGFR: glomerular filtration rate estimated with the Cockcroft-Gault formula; LAD: left anterior descending coronary artery.
Beta-blocker dosage was reported for metoprolol, which is the beta-blocker of preference according to the institutional protocol (MISSION!) and was used by 93% of the patients treated with beta-blockers at discharge.

Interestingly, gender differed significantly between the heart rate groups and women were more likely to have a higher heart rate at discharge compared to men (Table 1). Overall, there was a significant difference between beta-blocker dosage in men and women (77 ± 41 vs. 68 ± 32, p <0.001). Table 2 shows the differences in beta-blocker dosage between men and women more in detail for heart rate at discharge divided by quartile. Of note, significant differences were only observed for the 2 highest quartiles of heart rate at discharge (heart rate 70 – 78 bpm: male 80 ± 38 mg vs. female 69 ± 34 mg, P=0.03, heart rate ≥ 78 bpm: male 96 ± 49 mg vs. 75 ± 32 mg, p <0.001). The higher beta-blocker dosages in men compared to women may be explained by the fact that women were overall older than men and therefore lower levels of beta-blocker dosages were tolerated in women (Table 2).

Follow-up

Follow-up was completed in 1436 (99%) patients. The median follow-up duration was 40 months (interquartile range 20 – 48 months). During the follow-up period, 83 (6%) patients died from all-cause mortality. More in detail, 52 (4%) patients died from cardiovascular disease and 21 (2%) patients died from non-cardiac causes.
Survival analysis showed an overall survival of 97% (95% CI 96 – 98%) at 1 year, 95% (95% CI 94 – 96%) at 2 years, 94% (95% CI 92 – 95%) at 3 years and 93% (95% CI 92 – 95%) at 4 years follow-up. In addition, the survival free of cardiovascular mortality was 98% (97% CI 90 – 99%) at 1 year, 97% (95% CI 96 – 98%) at 2 years, 96% (95% CI 95 – 97%) at 3 years and 96% (95% CI 95 – 97%) at 4 years.

Heart rate at discharge and adverse outcome

Kaplan-Meier curves for heart rate at discharge divided by quartiles and all-cause and cardiovascular mortality at 1 year and 4 years are shown in Figure 1.

Table 2. Differences between beta-blocker dosage and age in gender according to heart rate at discharge

Heart rate at discharge	*Gender*	*β-blocker dosage (mg/day)*	*P*	*Age (years)*	*P*
<62bpm	Male	66 ± 35	0.06	60 ± 12	0.10
	Female	57 ± 28		63 ± 13	
62–70bpm	Male	70 ± 35	0.32	60 ± 12	<0.001
	Female	65 ± 29		66 ± 13	
70–78bpm	Male	80 ± 38	0.03	60 ± 12	0.04
	Female	69 ± 34		63 ± 13	
≥ 78bpm	Male	96 ± 49	<0.001	59 ± 11	<0.001
	Female	75 ± 32		66 ± 13	

Beta-blocker dosage was reported for metoprolol, which is the beta-blocker of preference according to the institutional protocol (MISSION!) and was used by 93% of the patients treated with beta-blockers at discharge.

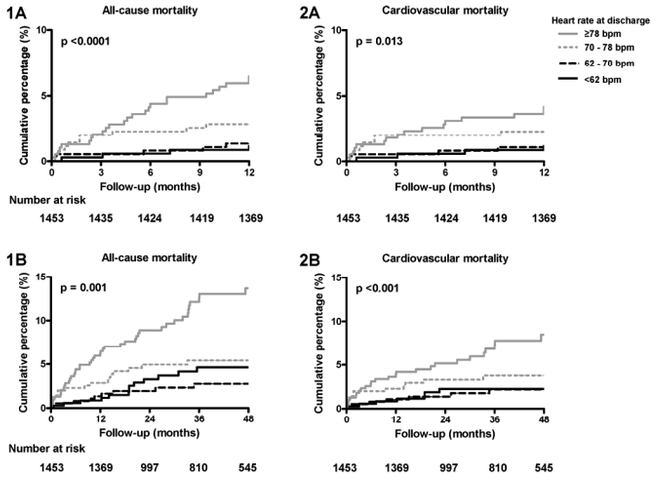

Figure 1.

Kaplan-Meier time-to-event plots for heart rate at discharge divided by quartiles and all-cause mortality (1) and cardiovascular mortality (2) at 1 year (A) and 4 years (B) follow-up.

Patients in the highest quartile with a heart rate of 78 bpm or higher showed significant higher event rates for both all-cause mortality (6% vs. 1% at 1 year and 14% vs. 5% at 4

years) and cardiovascular mortality (4% vs. 1% at 1 year 9% vs. 2% at 4 years) compared to patients in the lowest quartile with a heart rate lower than 62 bpm.
Multivariable analysis was performed to assess the prognostic value of discharge heart rate and adverse outcome after adjusting for age, the presence of heart failure (reflected by Killip class ≥2 and left ventricular ejection fraction) and the infarct size (reflected by left anterior descending coronary artery as culprit vessel and left ventricular ejection fraction).

Table 3. Adjusted hazard ratios for elevated heart rate at discharge

		Events, n (%)	*Hazard Ratio (95% CI)*	*P*
1 year	All-cause mortality	44 (3%)		
	Heart rate ≥70 versus <70bpm		3.16 (1.44–6.97)	0.004
	Heart rate higher by 5bpm		1.35 (1.22–1.50)	<0.001
	Cardiovascular mortality	32 (2%)		
	Heart rate ≥70 versus <70bpm		2.44 (1.02–5.84)	0.04
	Heart rate higher by 5bpm		1.29 (1.13–1.46)	<0.001
4 year	All-cause mortality	83 (6%)		
	Heart rate ≥70 versus <70bpm		2.29 (1.38–3.81)	0.001
	Heart rate higher by 5bpm		1.26 (1.16–1.36)	<0.001
	Cardiovascular mortality	52 (4%)		
	Heart rate ≥70 versus <70bpm		2.11 (1.10–4.04)	0.02
	Heart rate higher by 5bpm		1.24 (1.12–1.37)	<0.001

Multivariable models were constructed adjusting for age, Killip class ≥2, the left anterior descending coronary artery as culprit vessel and left ventricular ejection fraction.

Table 3 shows the increased risk of adverse events associated with an elevated heart rate at discharge. Analyses with heart rate as a continuous variable showed that every increase of 5 bpm resulted in a significant increased risk of 35% for all-cause mortality and 29% for cardiovascular mortality at 1 year. For 4 years follow-up, discharge heart rate remained an important predictor for adverse events and showed fairly similar hazard ratios with an increased risk of 26% for all-cause mortality and 24% for cardiovascular mortality for

every increase of 5 bpm. In addition, a heart rate of 70 bpm or higher demonstrated a HR of 3.16 (95% CI 1.44 –6.97, p = 0.004) for all-cause mortality and a HR of 2.44 (95% CI 1.02 – 5.84, p = 0.04) for cardiovascular mortality at 1 year follow-up and remained a strong predictor for all-cause mortality and cardiovascular mortality at 4 year follow-up (HR 2.29, 95% CI 1.38 – 3.81, p = 0.001 and HR 2.11, 95% CI 1.10 – 4.04, p = 0.002, respectively). Of note, the change in heart rate between admission and discharge was not related to all-cause mortality or cardiovascular mortality (HR 1.01, 95% CI 0.99 – 1.03, p = 0.22 and HR 1.01, 95% CI 0.99 – 1.03, p = 0.23, respectively). In addition, no differences in survival were observed between men and women for all-cause mortality or cardiovascular mortality (log rank p = 0.90 and p = 0.69, respectively) and the interaction term between gender and heart rate at discharge divided by quartiles was neither significant for cardiovascular mortality nor for all-cause mortality at 1 and 4 years follow-up.

Discussion

The main findings of the present study can be summarized as follows: 1) Discharge heart rate in STEMI patients treated with primary PCI was an independent predictor of cardiovascular mortality and all-cause mortality up to 4 year follow-up after adjusting for parameters reflecting an increased infarct size and the presence of heart failure. 2) Every increase of 5 bpm in heart rate at discharge was associated with a 29% and 24% increased risk of cardiovascular mortality at 1 and 4 year follow-up, respectively. 3) Patients with a heart rate of ≥70 bpm demonstrated a 2 times increased risk of cardiovascular mortality at 1 year and 4 year follow-up compared to patients with a heart rate <70 bpm.

Heart rate at discharge in acute myocardial infarction

The current results indicate for the first time the strong relationship between heart rate at discharge and adverse outcome up to 4 year follow-up in STEMI patients treated with primary PCI even after adjusting for parameters reflecting an increased infarct size and the presence of heart failure. All patients were treated with structurized medical therapy including a high level of beta-blockers and therefore, left ventricular systolic function was relatively preserved. It has been well established that the adherence to medical treatment including beta-blockers, angiotensin-converting enzyme inhibitors and statins improves the

outcome of STEMI patients.[12] In addition, previous studies have shown that prescription of medication before discharge increased the compliance during follow-up.[16] In patients with left ventricular systolic dysfunction, an elevated heart rate has been described as an important risk factor for long-term outcome.[5] However, data about the relationship between heart rate and patients with preserved left ventricular function after STEMI are scarce, because most studies describing the role of heart rate in relationship to adverse outcome have been performed before or in the thrombolytic era.[17-19] Recently, Fosbol et al. reported in 1518 patients with heart failure and 1510 patients with myocardial infarction and left ventricular dysfunction, that baseline heart rate was independently associated with an increased risk of overall mortality during 10 years follow-up. Interestingly, the prognostic importance of heart rate was stronger in patients with myocardial infarction compared to patients with heart failure.[4] To our best knowledge, the only other study that investigated the relationship between heart rate and adverse outcome in patients with STEMI treated with primary PCI was performed by Parodi et al.[8] The authors report that an elevated heart rate of 80 bpm or greater was associated with an increased risk of mortality at 6 months follow-up. However, the percentage of patients treated with beta-blockers was significantly lower compared to the patient population described in the current study (29% vs. 95%). Although the association of heart rate and outcome has been investigated extensively, understanding the relationship between heart rate and adverse events remains challenging. It is likely that heart rate is both a causative factor and an indicator of pathophysiologic processes. Heart rate influences myocardial oxygen demand and supply and consequently, also myocardial perfusion which may explain the strong relationship that has been observed in between heart rate and infarct size.[1 20] A higher heart rate at discharge frequently reflects a larger infarct size and therefore correlates with a more impaired clinical condition, which leads to an increased risk of mortality up to a follow-up duration of 4 years. However, in the current study the relationship between heart rate and mortality up to 4 year follow-up remained very strong even after adjustment for parameters reflecting an increased infarct size and the presence of heart failure. These results support the fact that heart rate is not merely an indicator of impaired clinical condition, but heart rate itself may also influence an adverse outcome. Most likely, heart rate reduction reduces myocardial oxygen consumption and increases mechanical efficiency of the left ventricle. In a murine heart

failure model, Mulder et al. showed that long-term heart rate reduction improved left ventricular function and increased stroke volume with preservation of the cardiac output.[21]

Heart rate reduction in acute myocardial infarction

Several large trials have demonstrated the relationship between beta-blocker treatment and decreased mortality after myocardial infarction.[22-24] Cucherat reported in a meta-regression of 14 randomized clinical trials of beta-blockers and calcium channel blockers in myocardial infarction patients, that the benefit of drugs modifying heart rate was strongly related to the magnitude of heart rate reduction.[24] In the current study, no relationship was observed between the change in heart rate between admission and discharge and adverse outcome, however, heart rate at discharge was a strong predictor of all-cause and cardiovascular mortality during a 4 year follow-up period. Interestingly, differences in heart rate at discharge were observed between men and women. Women were more likely to have a higher heart rate at discharge compared to men and subanalysis showed that the difference was related to a difference in age and dosage of beta-blocker at discharge. A high resting heart rate is a modifiable risk factor, but existing medications including beta-blockers have other cardiovascular effects besides decreasing the heart rate. Recently, the BEAUTIFUL investigators reported that ivabradine reduced the incidence of adverse events in patients with stable coronary artery disease, left ventricular dysfunction and a heart of 70 bpm or higher.[5 6] Thus far, only 1 study has been performed in patients after myocardial infarction with ivabradine demonstrating that the treatment was safe, feasible and well tolerated by the patients. Evidently, large prospective studies are needed to further determine whether a reduction in heart rate by ivabradine, beta-blockers or another strategy is the best approach to reduce the occurrence of adverse events in STEMI patients treated with primary PCI

Clinical implications

Heart rate is a simple cardiovascular risk factor which provides important prognostic information in STEMI patients treated with primary PCI. In the current study, heart rate at discharge was an independent predictor of adverse outcome during 4 year follow-up including cardiovascular and all-cause mortality despite the high level of treatment with

beta-blockers and adjustment for parameters reflecting an increased infarct size and the presence of heart failure. The results emphasize the importance of targeting a low heart rate in the contemporary population of STEMI patients and provide more evidence on the prognostic relevance of heart rate. However, more studies are needed to confirm these findings in larger clinical registries. In addition, large randomized trials are needed to compare different treatment strategies for the reduction in heart rate after myocardial infarction and the effect on long-term outcome.

Limitations

The major limitation of the current study is the small number of events that occurred during the follow-up. However it is in line with previous reports from our registry and probably related to the optimized treatment and standardized care according to the institutional protocol.[13 25 26] In addition, the event rates are in line with recent published data concerning STEMI patients in Western Europe. For example, the OPERA registry reported an in-hospital mortality of 4.6% and a 1-year mortality of 9.0%.[27] In addition very recently, Damman et al. evaluated 1024 STEMI patients where the cumulative event rate including in-hospital events was 14.1% during a median follow-up time of 901 days.[28] Nevertheless, in order to avoid overfitting, not all variables that have proven to be clinical predictors of adverse outcome could be included in the multivariable models due to the low event rate. However, multivariable analysis was performed adjusting for the most important parameters reflecting increased infarct size and the presence of heart failure. Furthermore, the exclusion of patients presenting with congestive heart failure could be seen as a limitation of the current study. However, this is in line with previous studies evaluating the value of heart rate.[29] Finally, left ventricular ejection fraction was assessed early after STEMI and therefore may be underestimated due to myocardial stunning. However, several studies have demonstrated the prognostic value of left ventricular ejection fraction assessed early after STEMI.[30 31]

Conclusions

In STEMI patients treated with primary PCI and optimal medical therapy, heart rate at discharge was an important predictor of mortality up to 4 years follow-up

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