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Heart rate prediction of outcome in heart failure following myocardial infarction depend on heart rhythm status an analysis from the high-risk myocardial infarction database initiative

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ABSTRACT

Background: Heart rate has been reported to be associated with adverse outcome in heart failure (HF) and myocardial infarction (MI), but conflicting evidence exists regarding its impact in patients with associated atrial fibrillation (AF).
Objectives: We investigated the differential impact of heart rate on clinical outcomes according to the presence or absence of AF in patients with reduced systolic function and/or HF after MI.
Methods: We studied the association of heart rate with outcome using Cox-models in a merged dataset ($n = 28,771$) of four randomized trials (CAPRICORN, EPHESUS, OPTIMAAL, and VALIANT).
Results: At baseline, 3736 (13%) patients had AF. We identified a significant interaction between AF and heart rate, and a decreasing effect of heart rate with time, heart rate being less associated with outcome after 1 year of follow-up (both p for interaction <0.001). We report associations with outcome separately in patients with and without AF. In addition, as neutral associations with outcome after 1 year were estimated after adjustment on confounding factors, only association for the first year follow-up were provided. 10-bpm increase in heart rate conferred increased risk for all-cause mortality (1.27 [1.21 to 1.33], $p < 0.0001$), CV-mortality (1.28 [1.22 to 1.34], $p < 0.0001$), and HF-hospitalisation (1.25 [1.19 to 1.31], $p < 0.0001$) in patients without AF. In contrast, in patients with AF, the incremental risk for 10-bpm increase in heart rate was attenuated for all-cause (1.14 [1.06 to 1.23], $p = 0.0007$), CV-mortality (1.12 [1.03 to 1.22], $p = 0.006$), and HF-hospitalisation (1.16 [1.07 to 1.26], $p = 0.0006$, p for interaction with AF <0.001 for all outcomes).
Conclusions: In patients with reduced systolic function and/or HF post-MI, higher heart rate predicts increased major cardiovascular events during the first year following MI in patients without AF. This association is markedly attenuated in subjects with AF.

1. Introduction

Despite major advances during the past few decades, the prognosis following myocardial infarction (MI) still carries an unfavourable prognosis when complicated by heart failure (HF), left ventricular (LV) dysfunction, or both.

Heart rate is associated with adverse outcome in cardiovascular disease (CV), including hypertension and MI [1–3]. Furthermore, the prognostic value of heart rate in patients with HF have been established through several clinical trials [4–7]. Data from the ONTARGET/TRANCEND trials suggests that a 10 bpm increase in resting heart rate in patients with stable CV disease confers 22–26% increase in risk of major cardiovascular events, 33–41% increase in risk of CV death, and 33–39% increase in risk of all-cause death [4].

Abbreviations: MI, myocardial infarction; LV-dysfunction, left ventricular dysfunction; HF, heart failure; AF, atrial fibrillation; SR, sinus rhythm; CV, cardiovascular; bpm, beats per minute; ESC, European Society of Cardiology.

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However, Cullington et al. provide evidence for a neutral impact of heart rate in chronic HF patients with atrial fibrillation (AF) [8]. They found that an elevated resting heart rate is associated with higher mortality in patients with sinus rhythm (SR), but not for those in AF. A study on patients with AF randomized to lenient rate control (<110 bpm) compared to strict control (<80 bpm) did not observe a higher risk for cardiovascular death, HF-hospitalisation, or stroke [8]. Yet, the impact of heart rate on outcome in patients with AF after incident HF complicating acute MI was not studied.

In this study, we analysed data from the "High-Risk MI database". This database contains individual patient data, from four major clinical trials, with acute MI complicated by LV systolic dysfunction and/or HF. All patients from the treatment and control arms in the original trials are included in this database. This database has the power to identify relevant interactions of moderate strength [9,10]. Consequently, we investigated the association between heart rate and outcome in patients with HF, LV dysfunction or both after MI according to the rhythm status (i.e. AF or no AF).

2. Methods

2.1. High-risk acute MI database

The "High-Risk MI database" contains individual patient data of 28,771 patients [9]. Mean follow-up time is 2.7 years. The database includes a substantial number of clinical events such as over 5000 deaths and over 15,000 hospital admissions, all adjudicated by independent endpoint committees. Heart rate was measured in accordance with original trial protocols, usually at index hospitalisation with an electrocardiogram. For patients with AF, heart rate was measured while in AF.

2.2. Clinical outcomes evaluated

We evaluated the association between baseline heart rate and cardiovascular mortality, all-cause mortality, and HF-related hospitalisations, in patients with and without AF, according to original trial definitions.

2.3. Statistical analysis

Statistical analyses were performed using the commercially available software SAS version 9.3 (SAS Institute Inc., Cary, N.C., USA). Continuous variables were expressed as means ± standard deviation, categorical variables as frequencies (percentages). Comparison of baseline characteristics were carried out using Mann Whitney, Kruskall Wallis or Pearson's Chi-Square tests as required.

Survival probabilities were calculated using the Kaplan-Meier Method. Associations between heart rate, used as continuous linear variable or according to pre-specified categories (<80, 80–110 and >110 bpm) as used previously [8], with the 3 aforementioned outcomes (cardiovascular mortality, all-cause mortality, and HF-related hospitalisations) were assessed using the Cox proportional hazards model. In addition, we evaluated the functional form of the association between heart rate and the risk for outcomes using heart rate as a non-linear continuous variable. To do so, as previously used by our group [11], we initially used smoothing cubic splines with 5 knots. Based on AIC criteria, a 3 knots cubic spline transformation was finally used. Hazard ratios were calculated and plotted according to the values of heart rate using 60 bpm as reference value**.** Survival curves taking into account competing risks were performed for all other endpoints than all cause death using the prodlim package (R Software).

Assumptions of log-linearity, absence of interaction between heart rate and adjustment variables mentioned later, absence of collinearity, and proportionality of hazards were verified. Specifically, log-linearity was assessed both recoding exposition variable using quintiles and using cubic splines. Baseline estimated Glomerular Filtration Rate (eGFR) and systolic blood pressure (SBP) were necessarily expressed as binary covariables (respectively < vs. ≥ 60 ml/min/1.73m^2 and < vs. ≥130 mm Hg) in order to meet the log-linearity assumption. As we identified both an interaction with time and a significant interaction between heart rate and AF, we fitted a time-dependent Cox model including an interaction term between heart rate and AF; Associations between heart rate and outcomes were derived from this model in AF an non AF and according to time intervals, before and after 1 year. Proportionality of the hazard ratio was assessed using both an interaction with time term in a time-dependent Cox model and inspecting Schoenfeld residuals. We identified significant interaction with time in the no AF group. From the Schoenfeld residuals graph inspection, a 1 year threshold appeared the most appropriate. Restricted cupic splines analyses were performed for each outcome and for each time interval.

The following baseline characteristics were considered in multivariable time to event analyses: heart rate, age, gender, Killip class (3–4 vs. 1–2), SBP, diabetes, hypertension, renal insufficiency, chronic obstructive pulmonary disease (COPD), peripheral artery disease (PAD), use of beta blockers, angiotensin-converting enzyme inhibitors (ACEI) and/or angiotensin receptor blockers (ARB), diuretics, haemoglobin, blood sodium, eGFR. The past medical history obtained at study entry was used to define the absence or presence

Table 1
Baseline characteristics of the study population.

	AF				No AF			
	HR < 80 $n = 2153$	HR 80–110 $n = 1465$	HR > = 110 $n = 118$	P-value	HR < 80 $n = 15{,}839$	HR 80–110 $n = 8810$	HR > = 110 $n = 305$	P-value
Demography								
Age (years), mean ± SD	70.9 ± 9.7	70.6 ± 9.8	69.8 ± 9.4	0.21	64.4 ± 11.3	63.6 ± 11.6	64.5 ± 11.2	< 0.0001
Female, n (%)	32	33.3	36.4	0.49	27.4	32.8	33.1	< 0.0001
Weight (kg), mean ± SD	78.6 ± 15.7	78.8 ± 15.6	83.4 ± 20.7	0.1	79.1 ± 15.1	79.2 ± 16.0	77.9 ± 15.0	0.54
Bmi (kg/m^2), mean ± SD	27.3 ± 4.6	27.4 ± 4.6	28.7 ± 6.2	0.093	27.4 ± 4.7	27.7 ± 4.8	27.2 ± 4.2	< 0.0001
Medical history n (%)								
Renal insufficiency	6	5.5	5.1	0.77	2.8	2.9	3.9	0.46
COPD	9.9	12.1	16.9	0.014	7	9.3	11.8	< 0.0001
Peripheral vascular disease	12.2	10.9	8.5	0.29	7.6	7.8	7.2	0.87
Diabetes	28.1	28.9	44.1	0.001	22.9	29.1	31.8	< 0.0001
Hypertension	61.1	60.2	63.6	0.71	53.6	52.6	47.9	0.055
Obesity (BMI > 30)	22.5	23.9	33.3	0.024	23.2	25.9	21.6	< 0.0001
Clinical								
Killip Class III, IV vs. I, II, n(%)	25.4	32.9	29.9	< 0.0001	15	21.7	30.6	< 0.0001
SBP (mmHg), mean ± SD	124 ± 18	123 ± 18	126 ± 19	0.56	122 ± 17	121 ± 17	122 ± 18	0.15
LVEF < 35%, n(%)	51.2	55.2	57.5	0.11	46.1	51.7	61.3	< 0.0001
Medications n (%)								
ACE or ARB	65.5	60.7	58.5	0.007	65.6	64.4	64.6	0.15
Beta blockers	64.4	51.8	50.4	< 0.0001	72.4	59.6	48.6	< 0.0001
Diuretics	58.2	62.6	58.5	0.028	39.6	48.8	56.1	< 0.0001
Biology								
eGFR (ml/min/1.73 m2)	62.8 ± 19.8	64.1 ± 20.1	64.4 ± 22.5	0.17	70.0 ± 20.1	70.9 ± 21.6	67.8 ± 20.2	0.014
Haemoglobin in g/dl	13.17 ± 1.76	13.31 ± 1.71	13.30 ± 2.62	0.21	13.39 ± 1.68	13.19 ± 1.75	12.87 ± 2.02	< 0.0001
Sodium (mmol/l)	139.5 ± 3.7	138.9 ± 3.8	139.3 ± 4.8	0.074	139.6 ± 3.4	138.8 ± 3.6	138.6 ± 3.1	< 0.0001
Hemocontration n (%)	30.8	33.5	25	0.62	33.7	30.4	28.1	0.066

P-values are obtained from Kruskall-Wallis test or Chi-2 test as required.

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