

# Elevated heart rate at 24–36 h after admission and in-hospital mortality in acute in non-arrhythmic heart failure



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## ARTICLE INFO

### Article history:

Received 4 August 2014

Received in revised form 5 January 2015

Accepted 9 January 2015

Available online 10 January 2015

### Keywords:

Heart failure

Heart rate

Risk stratification

Outcome

Treatment

## ABSTRACT

**Background:** Elevated resting heart rate is associated with worse outcomes in chronic heart failure (HF) but little is known about its prognostic impact in acute setting. The main aim of the present study was to examine the relationship between resting heart rate obtained 24–36 h after admission for acute non-arrhythmic HF and in-hospital mortality.

**Methods and results:** We examined the association of heart rate with in-hospital mortality in a cohort of 712 patients admitted for acute HF. None of the patients had significant arrhythmias, required invasive ventilation, or presented with acute coronary syndrome or primary valvular disease. Forty patients (5.6%) died during the hospital stay. Those patients were significantly older ( $78 \pm 9$  vs.  $72 \pm 12$  years;  $p = 0.0021$ ), had higher heart rate ( $92 \pm 22$  vs.  $78 \pm 18$  bpm;  $p < 0.0001$ ), NT pro-BNP ( $p = 0.0005$ ), creatinine ( $p = 0.023$ ), were often diabetics ( $p = 0.026$ ) and had lower systolic and diastolic blood pressures ( $p < 0.05$ ). There was a significant graded relationship between the increase in mortality rate and tertile of heart rate ( $p < 0.01$ ). With multivariable analysis, age ( $p = 0.037$ ), heart rate ( $p < 0.0001$ ), diastolic blood pressure ( $p < 0.001$ ), prior ischemic heart disease ( $p = 0.02$ ) and creatinine ( $p = 0.019$ ) emerged as independent predictors of in-hospital mortality. After adjusting for predictors of poor prognosis, patients in the highest heart rate tertile had worst outcomes when compared with those in the lowest heart rate group ( $p = 0.007$ ).

**Conclusions:** Higher heart rate 24–36 h after admission for acute non-arrhythmic HF is associated with increased risk of in-hospital mortality. Early targeting of elevated heart rate might represent a complementary therapeutic challenge.

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## 1. Introduction

Acute heart failure (HF) is a common and growing medical problem associated with major morbidity and mortality [1]. Options for the management of these patients remain limited with high in-hospital mortality rates. Accurate individual risk stratification can thus help physicians choose the intensity of care needed and promote tailored medical decision-making [2]. Previous studies have identified a number of variables that are associated with increased morbidity and mortality in HF [3,4]. However, most of these studies examined heterogeneous cohorts of patients with severe illness conditions such as cardiogenic shocks, acute coronary syndromes, and HF-related arrhythmias. Elevated resting heart rate has been recently recognized as a strong independent predictor of reduced life expectancy in patients with chronic HF and reduced left ventricular ejection fraction. Being also related to sympathetic overactivity, atherosclerosis and plaque vulnerability,

resting heart rate mediated arterial stress has progressively become a fascinating medical target per se, which has been further stressed by the recent results of the Systolic Heart failure treatment with the If inhibitor ivabradine Trial (SHIFT) [5]. In acute non-arrhythmic HF, little is known about the impact of elevated heart rate on in-hospital outcome [6]. However, higher heart rate at hospital discharge in patients with HF has been associated with greater risk of all-cause and cardiovascular mortality up to 1-year follow-up, and elevated risk of 30-day readmission for HF and cardiovascular disease [7]. The main aim of the present study was to examine the relationship between resting heart rate obtained in survivors 24–36 h after admission for acute non-arrhythmic HF and in-hospital mortality.

## 2. Methods

### 2.1. Patients

The present study collected detailed hospitalization data from computerized medical records of patients presenting with acute HF at CHU of Liège, Belgium, between 2010 and 2012. Patients ( $n = 1611$ ) were eligible for the first round of selection if they were  $> 18$  years of age, had a suspected diagnosis of HF and were alive 24–36 h after admission. After a second round of selection, 899 patients with  $\geq 1$  following criteria were further disqualified: respiratory support, cardiogenic shock, acute coronary syndrome, inotropic support, primary valvular heart disease, permanent pacemaker pacing, atrial fibrillation,

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<sup>1</sup> This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

**Table 1**  
Demographic, clinical and biologic data.

Variables	1st tertile	2nd tertile	3rd tertile	p
Age, years	72 ± 12	72 ± 12	72 ± 13	0.94
Systolic blood pressure, mm Hg	121 ± 28	121 ± 22	124 ± 23	0.47
Diastolic blood pressure, mm Hg	66 ± 11	67 ± 13	71 ± 15	0.0023
Left ventricular ejection fraction, %	46 ± 17	44 ± 16	44 ± 15	0.24
Left ventricular ejection fraction < 45%, n (%)	56 (33)	158 (43)	79 (45)	0.37
Medical history				
Diabetes, n (%)	25 (15)	60 (16)	47 (27)	0.029
Ischemic heart disease, n (%)	82 (48)	158 (43)	58 (33)	0.013
Medications				
ACE inhibitor, n (%)	78 (46)	126 (35)	49 (28)	0.0021
Beta-blocker, n (%)	85 (50)	138 (37)	55 (31)	0.0015
Laboratory findings				
NT-proBNP, pg/mL	9306 ± 9063	9735 ± 15133	9562 ± 10179	0.99
Creatinine, mg/dL	17.3 ± 15.5	14 ± 10	13 ± 8	0.003

atrial flutter, other significant arrhythmias, resting heart rate < 40 bpm or > 150 bpm, end-stage renal failure requiring dialysis, and cancer. A total of 712 patients in sinus rhythm at 24–36 h after admission were qualified for final inclusion in the study. The following clinical data were abstracted from hospital records: demographic information, the use of beta-blockers or angiotensin-converting enzyme (ACE) inhibitor at admission, medical history, prior myocardial infarction, prior heart failure hospitalization, laboratory findings (hemoglobin, sodium, creatinine, NT-proBNP), heart rate and blood pressure at 24–36 h after admission, left ventricular ejection fraction, and in-hospital mortality. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

## 2.2. Definitions

Hospital heart rate was defined as the first reported heart rate in the medical record obtained at 24–36 h after admission. It derived from either electrocardiogram or cardiac monitoring. Hospital heart rates were categorized into tertiles. The diagnosis of HF was based upon the following conditions to be satisfied: symptoms typical of HF, signs of HF, either reduced left ventricular ejection fraction or diastolic dysfunction with structural heart disease and increased NT-proBNP (> 300 pg/mL) [8]. Hemoglobin, sodium and creatinine levels were obtained the day of heart rate evaluation. Left ventricular ejection fraction was also extracted from the closest echocardiography report to hospital heart rate assessment. Patients were classified as newly hospitalized if no history of HF was reported in the medical record. The primary end-point of the study was the in-hospital death, defined as any cause of death occurring during the hospitalization.

## 2.3. Statistical methods

Data are reported as mean ± standard deviation for continuous variables or percentages of patients for categorical variables. Heart rates were tested for distribution normality with the Kolmogorov–Smirnov test. Group comparisons for categorical variables were

obtained with chi-square test and for continuous variables with t-test or 1-way analysis of variance with a Tukey post-hoc test. A logistic model was applied to identify significant predictors of in-hospital mortality. In order to avoid overfitting the multivariable model, we have only included significant univariable parameters. Values of  $p < 0.05$  were considered significant. All statistical analyses were performed with STATISTICA version 7 (StatSoft Inc, Tulsa, OK). Sensitivity and specificity for prediction of in-hospital mortality were determined for various cut-off values of hospital heart rate level using receiver operating characteristic (ROC) curves. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

## 3. Results

### 3.1. Patients' characteristics

Among the 712 patients included (72 ± 12 years, 60% males), 46% had hypertension, 19% were diabetics, 18% previously experienced myocardial infarction, 42% had ischemic heart disease and 44% had prior HF diagnosis (Table 1). Left ventricular systolic dysfunction (ejection fraction < 45%) was identified in 293 (41%) patients. ACE-inhibitor and beta-blocker were taken at the time of admission by 253 and 278 patients, respectively.

### 3.2. Heart rate categories

Mean heart rate was 78.9 ± 18.2 bpm (median 76 bpm, range: 43–150 bpm, Table 2). According to heart rate tertile (1st tertile: 43–

**Table 2**  
Univariable analysis: predictors of in-hospital mortality.

Variables	Whole cohort (n = 712)	Survivors (n = 672, 94%)	Death (n = 40, 5.6%)	p
Age, years	72 ± 12	72 ± 12	78 ± 9	0.0021
Male gender, n (%)	425 (59)	396 (58)	29 (72)	0.08
Heart rate, bpm	79 ± 18	78 ± 18	92 ± 22	< 0.0001
Systolic blood pressure, mm Hg	121 ± 24	122 ± 24	113 ± 30	0.046
Diastolic blood pressure, mm Hg	68 ± 13	68 ± 13	58 ± 16	0.0002
Left ventricular ejection fraction, %	44 ± 16	44 ± 16	46 ± 15	0.46
Left ventricular ejection fraction < 45%, n (%)	293 (41)	276 (41)	16 (40)	0.64
Medical history				
Hypertension, n (%)	331 (46)	314 (47)	17 (43)	0.17
Diabetes, n (%)	132 (19)	118 (18)	14 (35)	0.026
COPD, n (%)	177 (25)	166 (25)	11 (28)	0.96
Ischemic heart disease, n (%)	298 (42)	274 (41)	24 (60)	0.017
Prior HF, n (%)	311 (44)	287 (43)	24 (60)	0.032
Medications				
ACE inhibitor, n (%)	253 (36)	245 (36)	8 (20)	0.035
Beta-blocker, n (%)	278 (39)	269 (40)	9 (22.5)	0.027
Laboratory findings				
Hemoglobin, g/L	12 ± 2	12 ± 2	12 ± 2	0.63
NT-proBNP, pg/mL	9615 ± 12872	8488 ± 10660	24692 ± 26433	0.0005
Creatinine, mg/dL	14 ± 11	14 ± 10	18.5 ± 18	0.023
Sodium, mmol/L	140.7 ± 4.4	141 ± 4.2	140 ± 6.3	0.71

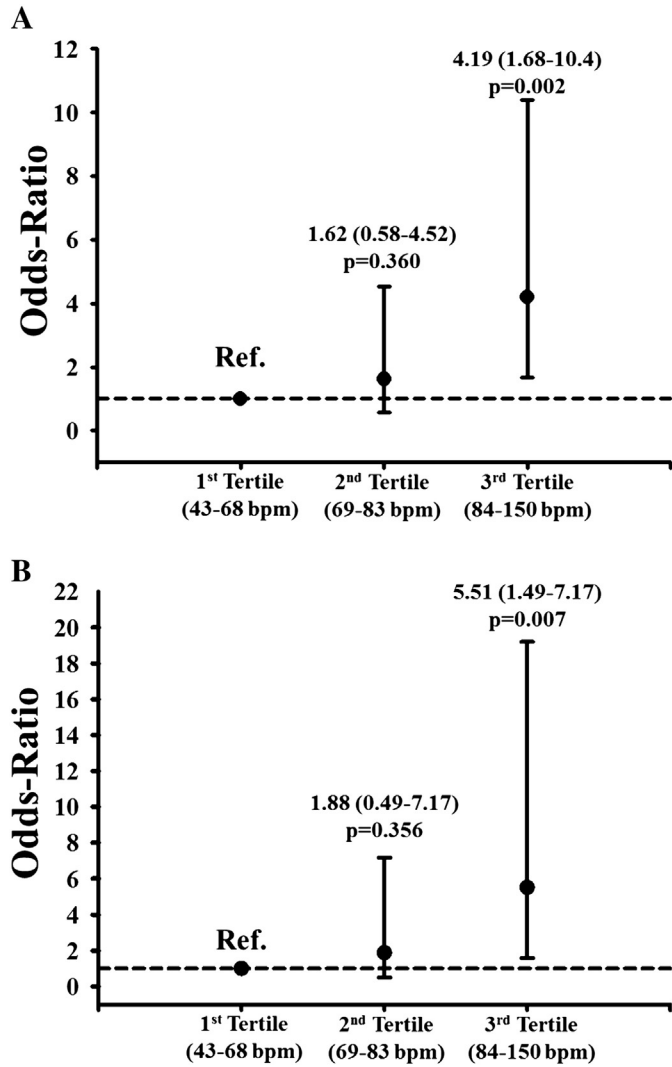


Fig. 1. Impact of tertile of 24–36 h heart rate on in-hospital mortality in both univariable (Panel A) and multivariable (Panel B) analyses.

68 bpm, 2nd tertile: 69–83 bpm and 3rd tertile: 84–150 bpm), patients with a higher heart rate were often diabetics and more likely to have suffered from previous ischemic heart disease. A higher resting heart rate was also associated with higher diastolic blood pressure. The proportion of patients treated with a betablocker or ACE-inhibitor decreased as heart rate increased, whereas the renal function was better in the 3rd heart rate tertile.

3.3. In-hospital outcome

Forty patients (5.6%) died during the hospital stay. There was a significant graded relationship between increase in mortality rate and

Table 3  
Multivariable analysis: predictors of in-hospital mortality.

Variables	Odds-ratio	95% confidence Interval	p
Age, per year	1.049	1.002–1.099	0.040
Diastolic blood pressure, per mm Hg	0.940	0.910–.972	<0.0001
Ischemic heart disease	2.899	1.125–7.471	0.028
Beta-blocker	0.313	0.012–8.079	0.484
ACE inhibitor	1.130	0.045–28.480	0.941
Creatinine, per mg/mL	1.040	1.011–1.071	0.007
Heart rate, per bpm	1.041	1.021–1.062	<0.0001

tertile of heart rate (1st tertile: 2.6%; 2nd tertile: 4.1% and 3rd tertile: 10%,  $p < 0.01$ ). Using ROC curves analysis, the best cut-off value of hospital heart rate to predict in-hospital mortality was 91 bpm (sensitivity = 55%; specificity = 81%; area under the curve = 0.7). Patients in tertile 3 of heart rate had a 4.19-fold increase in risk of in-hospital death, as compared to those in 1st tertile (Fig. 1, Panel A).

3.4. Predictors of in-hospital mortality

The comparison between patients with in-hospital death and survivors regarding demographic, clinical and biologic data is reported in Table 2. In-hospital survivors were significantly younger and often of male gender. Conversely, in-hospital death patients' were more frequently with diabetes, lower systolic and diastolic blood pressures, and higher heart rate at 24–36 h after admission. Of note, there was no significant difference between in-hospital death and survivors regarding chronic obstructive disease, prior myocardial infarction and heart failure episodes. Patients taking an angiotensin-converting enzyme inhibitor or beta-blocker at the time of admission faced lower risk of in-hospital mortality. Interestingly, patients were also at higher risk of death if they had higher NT-proBNP release and creatinine levels.

With multivariable analysis, age (OR = 1.05;  $p = 0.037$ ), heart rate (OR = 1.04;  $p < 0.0001$ ), diastolic blood pressure (OR = 0.94;  $p < 0.001$ ) prior ischemic heart disease (OR = 4.2;  $p = 0.02$ ) and creatinine (OR = 1.03;  $p = 0.019$ ) emerged as independent predictors of in-hospital mortality (Table 3). Similarly, after adjusting for predictors of poor

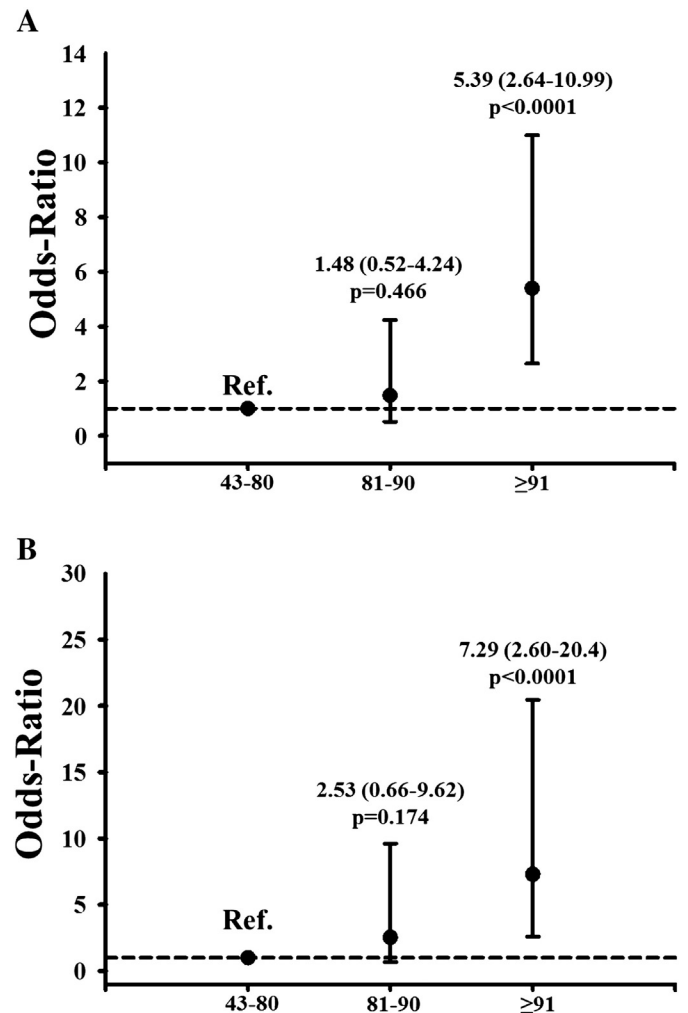


Fig. 2. Impact of categories of 24–36 h heart rate on in-hospital mortality in both univariable (Panel A) and multivariable (Panel B) analyses.

prognosis (i.e. as reported in Table 3), patients in the highest heart rate tertile had worse outcomes when compared with those in the lowest heart rate group (Fig. 1, Panel B).

As compared to patients with a heart rate  $\leq 80$  bpm, those with a heart rate  $>91$  bpm were at the highest risk of in-hospital death. Univariately, heart rate  $>91$  bpm was associated with 5.39-fold increase in risk of death (Fig. 2, Panel A). Using multivariable analysis, heart rate  $>91$  bpm was identified as independently associated with increased risk of in-hospital death (OR = 7.29,  $p < 0.0001$ , Fig. 2, Panel B).

#### 4. Discussion

Risk of in-hospital mortality for patients hospitalized with acute non-arrhythmic HF is high (5.6%) and varied significantly based upon 24–36 h heart rate levels. Heart rate levels provide risk prediction independently of numerous other clinical (older age, lower blood pressure, prior history of ischemic heart disease) and laboratory (increased serum creatinine) variables previously demonstrated to be predictive of in-hospital outcomes [9]. Our findings are the first to demonstrate that including heart rate evaluation early after admission for acute non-arrhythmic HF in patients with non-severely ill conditions (i.e. cardiogenic shock) provides incremental prognostic information for in-hospital mortality.

##### 4.1. Heart rate and outcome in HF

Previous studies have shown that elevated heart rate levels predict prognosis in patients presenting with HF [6,10]. Autonomic imbalance resulting from sympathetic overactivity and parasympathetic withdrawal is likely to be the underlying mechanism of increased heart rate in HF [11]. Several pathophysiologic mechanisms, including increased myocardial oxygen consumption, reduced diastolic filling times, compromised coronary perfusion with induction of myocardial ischemia, and precipitation of rhythm disturbances have been proposed to explain the association between higher heart rate and worse outcomes in patients with HF [5,12–15].

While the present study was generally consistent with previous reports, our data exclusively focused on acute HF patients surviving 24–36 h after admission who were not in cardiogenic shock, acute coronary syndrome, arrhythmias, or respiratory support. As a result, our mean hospital heart rate ( $79 \pm 18$  bpm) was lower than the mean heart rate at admission in the OPTIMIZE-HF ( $87 \pm 22$  bpm) [6], the Aronson's report ( $84 \pm 16$  bpm) [16], the ESC HF pilot study ( $88 \pm 24$  bpm) [17], and the IN-HF Italian registry ( $93 \pm 26$  bpm) [18]. The in-hospital mortality rate varied in these studies from 3.8% to 6.4%, which intriguingly remains close to ours.

For the first time, we reported the relationship between 24–36 h heart rate categories and hospital outcome. Specifically, heart rates exceeding 91 bpm were associated with higher in-hospital mortality while lower thresholds portended better hospital prognosis. Several factors were associated with higher hospital heart rate. Some of them were paradoxically predictors of in-hospital survival (i.e. lower frequency of prior ischemic heart disease, higher diastolic blood pressure, and lower serum creatinine level), whereas others were markers of in-hospital mortality (i.e. diabetes, lower rate of beta-blockers and ACE inhibitors use). Conversely, there was no interaction between resting heart rate and left ventricular ejection fraction, indicating that the value of elevated heart rate in predicting in-hospital mortality was independent of left ventricular systolic function. In-hospital mortality was thus similar in patients with reduced or preserved LV ejection function. Similar to some prior reports, patients with a de novo HF hospitalization tended to be at lower risk for in-hospital mortality [19]. Of particular interest, the use of beta-blockers or ACE inhibitors at the time of admission predicted improved in-hospital survival in the lower heart rate groups. These data underline again the importance of heart rate control in HF. In patients surviving the acute HF phase, higher heart rate at

discharge but not at admission emerged as a potent predictor of 30-day mortality in the study of Habal et al. Interestingly, this trend reached significance at heart rates above 90 bpm, a cut-off close to ours [7]. However, the impact of heart rate at admission on in-hospital mortality was not examined in that study. Whether the hospital heart rate is rather a predictor of in-hospital mortality and the discharge heart rate a predictor of short-term outcome needs to be addressed in specific studies.

##### 4.2. Clinical implications

The continued high mortality rate for patients hospitalized with acute HF provides a compelling indication for accurate risk stratification to potentially improve individual management and hospital outcome. Recent studies have suggested heart rate reduction per se as a mechanism responsible for improvement of clinical outcomes in patients with chronic HF [5]. Although cautious interpretation is required, the results of the present study might support the concept that heart rate reduction might also represent a specific therapeutic target per se soon after hospitalization for acute HF, especially in patients with prior ischemic heart disease [20]. In our study, one third of patients in the higher heart rate quartile had prior ischemic heart disease, a population in whom rigorous heart rate control improves outcome. Either reduction of adrenergic tone by beta-blockers or pure heart rate-lowering by  $I_f$  current inhibitor ivabradine, which selectively blocks the sinus node to lower heart rate, might be targeted. In practice, beta-blockers remain the first-line therapy in HF patients and should be started as soon as possible after stabilization and if blood pressure and heart rate permit [8]. Ivabradine represents a second line treatment if heart rate remains  $>70$  bpm despite beta-blockers, but might represent a potential alternative approach in the early stage of HF hospitalization since it affects less the hemodynamic status.

##### 4.3. Limitations

This study has a number of limitations. Our results do not pertain to all patients presenting with acute HF (i.e. cardiogenic shock). Only patients surviving at 24–48 h after admission were evaluated, which excluded severely ill patients presenting with an early death. Early mortality is known to occur in very frail patients with several comorbidities, which represent significant confounding findings. Therefore, measuring heart rate at admission does not likely provide a meaningful assessment of the independent prognostic value of this parameter. In our study, the heart rate at admission was not evaluated as well as the time course of changes in heart rate during the hospital stay. In fact, the scope of the present study was to evaluate in-hospital mortality in relation with heart rate obtained in survivors 24–36 h after admission for acute HF. However, it should be acknowledged that although the heart rate was measured late after admission, all survivors were not necessarily hemodynamically stabilized. All this suggests that persistent elevated heart rate at 24–36 h likely represents an independent critical prognostic marker in non-completely stabilized patients. Therefore, the prognostic impact of elevated heart rate at 24–36 h may also reflect persisting precarious hemodynamic status. Furthermore, the optimal timing for the measurement of heart rate remains to be addressed. This is particularly true at admission. Whether the clinical meaning of heart rate measured at hospital arrival in the emergency department, or in the intensive care, or before or after treatment initiation is similar remains unknown. The advantage of measuring heart rate at a fixed period after admission (24–36 h) allows standardization of data collection mode, which is more reliable for comparative studies. The exclusion of patients with atrial fibrillation is actually the strength of this analysis on HR and outcome. The influence of any antiarrhythmic drugs was not evaluated; the use of them did not represent an exclusion criterion. Before 2012, NT-proBNP was not routinely measured in our hospital, resulting in small number of patients with these data available. In this regard, we have decided not to include NT-proBNP in the multivariable model in order to

save statistical power and reach meaningful conclusion. However, when available, blood concentrations of these biomarkers were confirmed to be significantly increased in both worsening and de novo HF patients. The reasons for lower baseline use of beta-blockers and ACE inhibitor were unknown. Also, LV ejection fraction was the sole robust echocardiographic measurement available in all patients. As a result, the relationships between diastolic function and LV filling pressure with heart rate categories have not been evaluated.

## 5. Conclusions

Higher heart rate 24–36 h after admission for acute non-arrhythmic HF is associated with increased risk of in-hospital mortality. Early targeting of elevated heart rate might thus represent a complementary therapeutic challenge in non-severely ill patients (i.e. cardiogenic shock). Further studies are needed to confirm our data and to define the potential beneficial impact of heart rate lowering interventions.

## Conflict of interest

None declared.

## Funding

None.

## Disclosure

None.

## Acknowledgment

The authors would like to thank CHU Sart Tilman Liège IT/DMI team, Belgium.

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