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***Prognostic importance of temporal changes in resting heart rate in heart failure patients: an analysis of the CHARM program***

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**Abstract**

**Background** Resting heart rate (HR) is a predictor of adverse outcome in patients with heart failure (HF). Whether changes in HR over time in patients with chronic HF are also associated with adverse outcome is unknown. We explored the relationship between changes in HR from a preceding visit, time-updated HR (i.e. most recent available HR value from a clinic visit) and subsequent outcomes in patients with chronic HF.

**Methods and results** We studied 7599 patients enrolled in the candesartan in heart failure: assessment of reduction in mortality and morbidity program. We calculated change in HR from the preceding visit and explored its association with outcomes in Cox proportional hazards models, as well the association between time-updated HR and outcome. An increase in HR from preceding visit was associated with a higher risk of all-cause mortality and the composite endpoint of cardiovascular death or hospitalization for HF (adjusted hazard ratio 1.06, 95% confidence intervals, CI: 1.05–1.08, $P < 0.001$, per 5 b.p.m. higher HR), with lowering of HR being associated with lower risk, adjusting for covariates, including time-updated β-blocker dose and baseline HR. Time-updated resting HR at each visit was also associated with risk (adjusted hazard ratio 1.07, 95% CI: 1.06–1.09; $P < 0.001$, per 5 b.p.m. higher HR).

**Conclusions** Change in HR over time predicts outcome in patients with chronic HF, as does time-updated HR during follow-up. These data suggest that frequent outpatient monitoring of HR, and identification of changes over time, possibly with remote technologies, may identify patients with HF who may be at increased risk of rehospitalization or death.

**Introduction**

Resting heart rate (HR) is a known risk factor for adverse outcome in patients with cardiovascular (CV) disease.[1–5] In addition to being a marker for increased occurrence of adverse outcomes, resting HR may be a modifiable risk factor in patients with heart failure (HF), and strategies that reduce HR, including β-blockers and an $I_f$ inhibitor, also reduce fatal and non-fatal events in this population.[6–8]

The association between temporal changes in HR and mortality has been assessed in subjects without known CV disease[9,10] and also in subjects with hypertension.[11] These studies showed that a rise in HR over time was associated with a higher risk of adverse events. However to date, there have been no studies to assess whether temporal changes in HR are of prognostic importance in patients with chronic HF, particularly in patients on modern therapy for HF and in those with preserved ejection fraction. The availability of new remote monitoring strategies that can measure and track HR provides a compelling rationale for determining the utility of temporal changes in HR as a biomarker for HF severity.

We previously demonstrated that HR measured at baseline visit was of prognostic importance in patients enrolled in the CHARM (candesartan in heart failure: assessment of reduction in mortality and morbidity) program.[1] The objective of this analysis was to determine whether temporal changes in HR from the preceding visit are also of prognostic importance in patients with chronic HF.

**Methods**

**The overall CHARM program**

The details of the design and overall findings have been previously reported.[12] In brief, the overall CHARM program enrolled a total of 7599 patients with symptomatic chronic HF [New York Heart Association (NYHA) class II-IV] on standard therapy. The CHARM program comprises three component clinical trials and differed from one another according to LVEF and angiotensin-converting enzyme inhibitor (ACE-I) treatment. The component trials included the CHARM-alternative (*n* = 2028 with LVEF ≤40% not receiving an ACE-I due to previous intolerance), CHARM-added (*n* = 2548 with LVEF ≤40% already receiving an ACE-I) and the CHARM-preserved study (*n* = 3023 with LVEF >40%).[12–15] For each of the component trials, patients were randomized to candesartan or placebo at the enrolment visit.

The main exclusion criteria for the overall program were serum creatinine 3 mg/L (265 μmol/L) or more, serum potassium of 5.5 mmol/L or more; known bilateral renal artery stenosis, symptomatic hypotension, critical aortic or mitral stenosis, recent myocardial infarction (MI) (within 4 weeks), stroke or heart surgery.

The overall program consisted of up to 14 trial visits, these included an initial visit, followed by visit 2, 3, and 4 occurring at two weekly intervals and followed by visit 5 at 6 months from initial visit, subsequent visits occurred every 4 months up to visit 14. Therefore, the median time interval between visits was 119 days (interquartile range, IQR: 21–125 days). The follow-up time from the initial visit was a median of 38 months for the overall CHARM program. Resting HR was recorded at each visit. Heart rate at each visit was recorded after 5 min of rest, by palpation for at least 30 s or from auscultation of the heart or from the ECG.

**Heart rate at any clinic visit and calculation of temporal changes in heart rate**

In order to assess temporal changes in HR, we created a time-updated covariate representing the most recent available HR value for each patient at each visit over the course of the trial. We named this variable as HR at any visit. A patient's baseline HR was carried forward until the day of the first follow-up visit, at which time the new ‘current’ value was used and then subsequently carried forward until the next visit. As there were up to 14 trial visits in the program, the resting HR was updated up to 13 times after baseline for each patient.

We calculated temporal changes in resting HR from the preceding visit (ΔHR) by subtracting the time-updated visit HR value from the value from the preceding visit. These changes in HR reflect short-term changes occurring in between visits.

**Statistical analysis**

We modelled ΔHR as continuous covariate and also categorized ΔHR into five categories of HR (drop of >10 b.p.m., drop of 5–10 b.p.m., <5 b.p.m. change, increase of 5–10 b.p.m., increase >10 b.p.m.) based on the rationale that changes in HR of >5 b.p.m. would be considered as clinically meaningful. The resting HR at any visit represented by the time-updated HR was modelled both continuously and also categorized into tertiles, similar to our previous analysis of resting baseline HR.[1] Because patients' changing post-baseline HR values may cause them to spend time in more than one HR category, only the total time spent in each category and the associated numbers of events are presented for the time-updated analysis.

We related resting baseline HR, HR at any visit and ΔHR to several outcomes. These included all-cause mortality (the primary endpoint of the overall CHARM program) and the composite outcome of CV death or hospitalization for HF, whichever occurred first (the primary endpoint of each component trial), and also the outcome of CV death, hospitalization for HF, non-CV deaths, fatal and non-fatal MI and stroke. The rationale for using the non-CV death as an outcome was to assess whether or not ΔHR was predictive of general ill health or whether it would be specific to CV outcomes alone. Incidence rates were calculated, per 100 patient-years. The association between outcomes and resting baseline HR, HR at any visit and ΔHR were assessed using multivariable Cox proportional hazards models. As continuous covariates the

estimated hazard ratio for each of these covariates correspond to a 5 b.p.m. difference in HR. In models using categorical covariates, the no change in HR category (<5 b.p.m. change) was used as the reference for changes in HR from the preceding visit, and the lowest tertile was used as the reference for HR at any visit. The multivariable analysis adjusted for the established predictors of outcome, previously identified in the overall CHARM program.[16] These included age, LVEF, history of diabetes mellitus, previous history of HF hospitalization, NYHA functional class, body mass index, diastolic BP, sex, cardiomegaly on chest X-ray and candesartan treatment. We also included time-updated β-blocker dose and use of digoxin to control for starting or stopping rate limiting drugs and also for variation in dose of β-blocker. Our model also adjusted for the presence of atrial fibrillation at baseline. We controlled for baseline HR when modelling for HR at anytime; however, we replaced baseline HR with HR from the preceding visit when modelling ΔHR. Interval non-fatal MI was also included in the model when we considered endpoints that did not include non-fatal MI.

An adjusted model using a restricted cubic spline with five-knots was constructed to flexibly display the relationship between the hazards of developing outcome and continuous covariate of HR at anytime, using a reference value of 60 b.p.m. For ΔHR, 0 was used as the reference. Interaction testing was used to determine whether the relationship between ΔHR and outcomes varied in different subgroups (patients with or without atrial fibrillation at baseline, those with reduced vs. preserved ejection fraction, patients with or without diabetes at baseline, with and without pacemaker at baseline and β-blocker use at anytime). Continuous variables were described using median and IQRs and categorical variables were expressed as counts and percentages. All *P*-values were two sided, and a *P*-value of <0.05 was used to determine statistical significance. Analysis was performed using STATA (version 13.1, StataCorp LP, College Station, TX, USA).

## Results

### Baseline characteristics of the patients

The baseline characteristic of the study group has been previously described.[12] However, we have summarized key characteristics in *Table 1*. The mean age of the cohort was 65 ± 11 years, and almost a third of the population was female. Patients were treated with contemporary medication for HF, with 55% treated with β-blocker and 43% on digitalis/digoxin at the time of the baseline visit. The use of β-blockers and digoxin increased throughout the study, to 69 and 50%, respectively, at anytime during the follow-up.

Table 1

Characteristics of patients within the Candesartan in heart failure: assessment of reduction in mortality and morbidity program

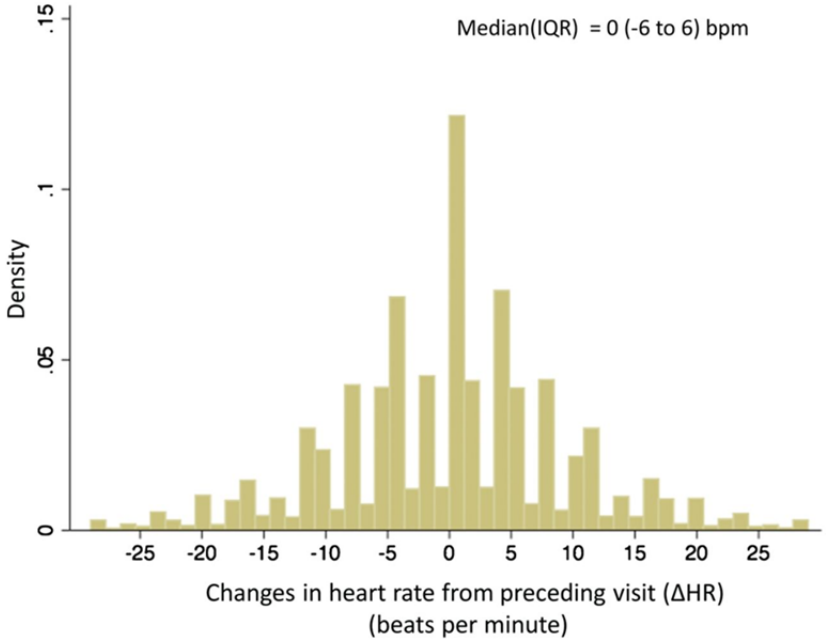
| **Baseline characteristics** | **Total cohort (*N* = 7599)** |
|---|---|
| Age (years) | 65 ± 11 |
| Females, *n* (%) | 2400 (32) |
| NYHA class, *n* (%) | |
| II | 3416 (45) |
| III/IV | 4183 (55) |
| LVEF (%) | 39 ± 15 |
| LVEF ≤40%, *n* (%) | 4578 (60) |
| LVEF >40%, *n* (%) | 3020 (40) |
| Baseline HR (b.p.m.) | 72 (64–80) |

| **Baseline characteristics** | **Total cohort (*N* = 7599)** |
|---|---|
| HR at any time (b.p.m.) | 72 (64–80) |
| ΔHR (b.p.m.) | 0 (−6 to 6) |
| Blood pressure (mmHg) | |
| Systolic | 131 ± 19 |
| Diastolic | 77 ± 5 |
| Body mass index (kg/m$^2$) | 28 ± 5 |
| Medical history, *n* (%) | |
| Hospitalization for CHF | 5426 (71) |
| Myocardial infarction | 4004 (53) |
| Current angina | 1808 (24) |
| Stroke | 663 (9) |
| Diabtetes mellitus | 2163 (29) |
| Hypertension | 4186 (55) |
| Atrial fibrillation | 2083 (27) |
| Pacemaker | 637 (8) |
| Implantable defibrillator | 191 (3) |
| PCI | 1228 (16) |
| CABG | 1791 (24) |
| Current smoker | 1114 (15) |
| Previous cancer | 513 (7) |
| Medical treatment at randomization, *n* (%) | |
| ACE-I | 3125 (41) |
| Angiotensin receptor blocker | 3796 (50) |
| β-Blocker | 4203 (55) |
| Spironolactone | 1272 (17) |
| Diuretic | 6286 (83) |
| Digoxin/digitalis | 3254 (43) |
| Calcium antagonist | 1542 (20) |
| Other vasodilators | 2964 (39) |
| Antiarrhythmic agents | 893 (12) |
| Oral anticoagulants | 2338 (31) |
| Bronchodilators | 674 (9) |

**Resting heart rate measured at any time and temporal changes in heart rate**

The median values of HR measured at any visit for the cohort were identical to the resting baseline HR value of 72 b.p.m. (IQR: 64–80 b.p.m.), *Table 1*. The distribution of ΔHR is summarized in *Figure 1*. The majority of patients within the cohort did not change their HR from the preceding visit (median of zero (−6 to 6) b.p.m.).

Figure 1.




Histogram of the distribution of changes in heart rate from preceding visit (ΔHR). The majority of patients have no change in heart rate from the preceding visit.

**Temporal changes in heart rate from the preceding visit (ΔHR) and outcomes**

With a median follow-up of 38 months, a total of 1831 patients died and 2459 experienced the composite endpoint of CV death or hospitalization for HF. The number events for other outcomes are summarized (*Table 1*). The ΔHR reflects changes in HR occurring over a median of 119 (IQR: 21–125) days.

As a continuous covariate, increases in HR from the preceding visit were associated with all outcomes measures (*Table 2*). For example for each 5 b.p.m. increase in HR from the preceding visit was associated with 9% higher risk of all-cause mortality and a 6% higher risk of the composite of CV death or hospitalization for HF. Furthermore, for each 5 b.p.m. increase HR from the preceding visit was also associated with a 9, 6 and 10% higher risk of CV death, hospitalization for HF and non-CV death, respectively (*Table 2*).

Table 2

Number of events, event rate, and adjusted hazard ratio with 95% confidence interval for per 5 b.p.m. increase in baseline heart rate, heart rate at any visit, changes in heart rate from preceding visit as continuous covariates and outcomes

| | **Events (*n*)** | **Event rate[a] (95% CI)** | **Adjusted hazard ratio (95% CI)** | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | **Baseline HR** | ***P*-value** | **HR at any visit** | ***P*-value** | **ΔHR** | ***P*-value** |
| All-cause mortality | 1831 | 8.5 (8.1–8.9) | 1.03 (1.01–1.05) | 0.002 | 1.09 (1.07–1.11) | <0.001 | 1.09 (1.07–1.11) | <0.001 |
| CV death or hospitalization for HF | 2459 | 12.7 (12.2–13.2) | 1.04 (1.02–1.05) | <0.001 | 1.07 (1.06–1.09) | <0.001 | 1.06 (1.05–1.08) | <0.001 |

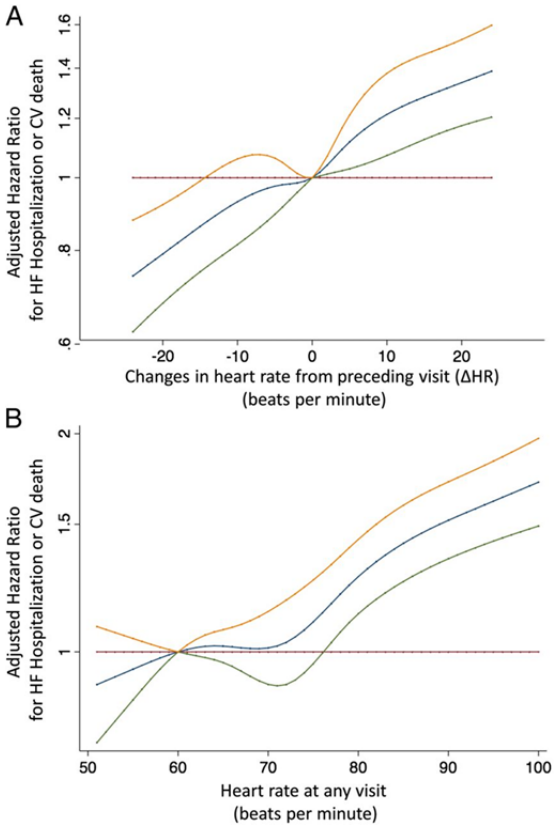
| | Events (*n*) | Event rate[a] (95% CI) | Adjusted hazard ratio (95% CI) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Baseline HR | *P*-value | HR at any visit | *P*-value | ΔHR | *P*-value |
| CV death | 1460 | 6.8 (6.4–7.1) | 1.03 (1.01–1.05) | 0.003 | 1.08 (1.06–1.10) | <0.001 | 1.09 (1.06–1.11) | <0.001 |
| Hospitalization for HF | 1674 | 8.6 (8.2–9.0) | 1.04 (1.02–1.06) | <0.001 | 1.07 (1.05–1.09) | <0.001 | 1.06 (1.04–1.08) | <0.001 |
| Non-CV death | 371 | 1.7 (1.5–1.9) | 1.01 (0.97–1.05) | 0.596 | 1.11 (1.07–1.15) | <0.001 | 1.10 (1.05–1.15) | <0.001 |
| Fatal and non-fatal MI | 366 | 1.7 (1.6–1.9) | 1.02 (0.98–1.06) | 0.396 | 1.05 (1.01–1.10) | 0.031 | 1.06 (1.01–1.16) | 0.014 |
| Fatal and non-fatal stroke | 287 | 1.3 (1.2–1.5) | 0.99 (0.95–1.04) | 0.835 | 1.08 (1.03–1.13) | 0.002 | 1.07 (1.02–1.13) | 0.009 |

CI, confidence interval; HR, heart rate; HF, heart failure; CV, cardiovascular; MI, myocardial infarction, ΔHR, change in HR from the preceding visit.

[a]Event rate per 100 patient-years. Adjusted for age, sex, randomization to candesartan, ejection fraction, previous hospitalization for HF, history of diabetes mellitus at baseline, body mass index, diastolic blood pressure, NYHA functional class, β-blocker dose and digoxin use at anytime during the study, cardiomegaly on chest X-ray, atrial fibrillation at baseline and baseline or preceding HR. For changes in HR from the preceding visit the preceding HR was used in the model instead of baseline HR. For outcomes without MI, interval MI was also included in the model.

The restricted cubic spline model showed that the relationship between ΔHR and the composite of CV death or hospitalization for HF was near linear (*Figure 2A*). For example, any rise in HR above a preceding HR value was associated with elevated risk and conversely a drop in HR of >10 b.p.m. from the preceding HR with a significantly lower risk.

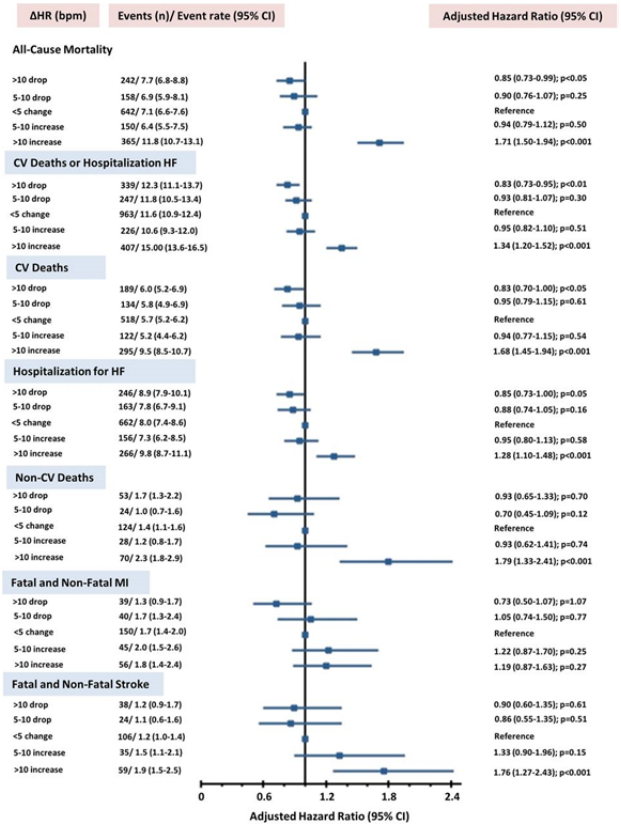
Figure 2.




(*A*) Association of changes in heart rate from preceding visit (ΔHR) and the composite of cardiovascular death or heart failure hospitalization in an adjusted cubic spline model. The adjusted cubic spline model demonstrates the flexible relationship between changes in heart rate from preceding visit (ΔHR) and the hazard of developing cardiovascular death or hospitalization for heart failure, when no change in heart rate is taken as the reference (i.e. 0 b.p.m.). This curve (blue line) displays a near linear relationship between ΔHR and risk of the composite of cardiovascular death or hospitalization for heart failure, such that any rise in heart rate (>1 b.p.m.) from the preceding visit appears to increase the risk significantly. However, a drop in heart rate of >15 b.p.m. from the preceding visit significantly reduced risk. The yellow and green curves represent the upper and lower 95% confidence limits, respectively. The horizontal red line represents the hazard ratio of 1. The domain was defined by excluding the smallest 1% and the largest 1% of values of ΔHR values. (*B*) Association of heart rate at any visit (time-updated heart rate) and the composite of cardiovascular death or heart failure hospitalization in an adjusted cubic spline model. The adjusted cubic spline model demonstrates the flexible relationship between resting heart rate at any visit and the hazard of developing cardiovascular death or heart failure hospitalization, when a resting heart rate of 60 b.p.m. is taken as the reference. This curve (blue line) displays that a resting heart rate of 60–76 b.p.m. was not associated with an elevated risk of cardiovascular death or heart failure hospitalization relative to an heart rate of 60 b.p.m. However, a resting heart rate >76 b.p.m. appears to be associated with a steep rise in risk with higher resting heart rate values. The yellow and green curves represent the upper and lower 95% confidence limits, respectively. The horizontal red line represents the hazard ratio of 1.

When we analyzed the data categorically, ΔHR was also associated with outcomes (*Figure 3*). A >10 b.p.m. drop in HR from the preceding visit was associated significantly with a 17% lower risk of both CV death or hospitalization for HF and the risk of CV death when compared with the no change in HR group (*Figure 3*). A drop of >10 b.p.m. when compared with the no change in HR group was also associated with 15% lower risk of all-cause mortality and also hospitalization for HF (*Figure 3*). Conversely, a >10 b.p.m. rise in HR from the preceding visit compared with the no change in HR group was associated with a 35% higher risk of CV death or hospitalization and a 68 and 28% higher risk of CV death or hospitalization for HF, respectively (*Figure 3*). Furthermore, a >10 b.p.m. rise in HR from the preceding visit compared with the no change in HR group was also associated with 76% higher risk of fatal and non-fatal stroke, 80% higher risk of non-CV death and 71% higher risk of all-cause mortality relative to no change in HR (*Figure 3*).

Figure 3.




Association between changes in heart rate from the preceding visit and outcomes. Adjusted hazard ratio and 95% confidence intervals and also events with event rates (95% confidence intervals) given for six outcomes across the five categories of changes in heart rate from preceding visit (ΔHR).

The use of β-blocker at anytime in the study did not affect the relationship between ΔHR and outcomes (*P* for interaction of 0.72 for all-cause mortality and 0.87 for CV death or hospitalization for HF) nor did the presence of atrial fibrillation at the time of randomization (*P* for interaction 0.90 for all-cause mortality and 0.46 for CV death or hospitalization for HF) or pacemaker implantation at baseline (*P* for interaction of 0.39 for all-cause mortality and *P* for interaction of 0.35 for CV death or hospitalization for HF). The relationship between HR and outcomes was similar in patients with reduced and preserved ejection fraction (*P* for interaction 0.55 for all-cause mortality and 0.81 for CV death or hospitalization for HF). No other interactions were detected between the other specified subgroups and ΔHR.

**Heart rate at any time and outcomes**

As a continuous covariate, time-updated HR, which represents HR at any visit, and also baseline HR predicted both all-cause mortality and the composite outcome of CV death or hospitalization for HF (*Table 2*). For every 5 b.p.m. higher HR at any time, the risk of all-cause mortality and the composite of CV death or hospitalization for HF was 9 and 7% higher, respectively.

We found that a resting HR between 60 and 76 b.p.m. at any time during follow-up was not associated with a higher risk of CV death or hospitalization for HF compared with an HR of 60 b.p.m. (*Figure 2B*). However, a resting HR >76 b.p.m. at any time during follow-up was associated higher risk of CV death or hospitalization for HR (*Figure 2B*). This is further supported when HR at any visit is categorized into tertiles, such that the upper tertile of HR at any visit (>76 b.p.m.) was associated with the highest risk, 49% increase in all-cause

mortality (adjusted hazard ratio of 1.49 (1.30–1.70): $P < 0.001$) and 37% increase in composite of CV death or hospitalization for HF (adjusted hazard ratio of 1.37 (1.22–1.53); $P < 0.001$), relative to lowest tertile (HR < 65 b.p.m.).

In patients with AF at baseline, HR at anytime was associated with outcomes. Such that for every 5-b.p.m. difference in HR at any time, the adjusted hazard ratio for all-cause mortality was of 1.06 (1.03–1.10); $P < 0.001$ and for composite of CV death and hospitalization for HF, the adjusted hazard ratio was 1.04 (1.01–1.07); $P = 0.004$.

**Discussion**

In a large cohort of patients with reduced and preserved ejection fraction HF, we found that changes in HR from the preceding clinic visit occurring over a median of 119 (21–125) days, predicted all-cause mortality, the composite endpoint of CV death or hospitalization for HF, and non-CV outcomes. While increases in HR were associated with higher risk, reduction in HR was associated with lower risk. Heart rate at any time was also predictive of outcomes. These findings suggest that HR may be a useful and easily measured biomarker in the management of HF patients.

Our study further supports that changes in HR over time from the preceding clinic visit are of prognostic importance in patients with chronic HF with reduced or preserved ejection fraction, irrespective of cardiac rhythm. Epidemiological studies have suggested that high HR is associated with increased risk of mortality, with increased sympathetic activity as a proposed mechanism.[5] Increases in HR in patients with HF may reflect higher sympathetic tone due to further progression of HF or even decompensation.[17] They could also suggest the onset of new or paroxysms of atrial arrhythmias such as atrial fibrillation. In contrast, a drop in HR may reflect improving cardiac function and lower sympathetic tone. Importantly, While use or up-titration of HR-reducing drugs such as β-blockers and digoxin are possible explanations for reduction in HR from the preceding visit, especially as β-blocker use became more frequent over the course of the study, in our analysis, we have controlled for β-blocker using in a time-updated analysis, taking into account both use of β-blockers and β-blocker dose. Thus, the importance of HR change appears to be independent of β-blocker use. Furthermore, β-blocker use at anytime during the study did not alter the relationship between ΔHR and outcome. Another factor which might play a role in change in HR over time (and its relationship with outcomes) is physical activity.[18] Unfortunately, details of physical activity were not measured during the follow-up period. An increase in HR from the preceding visit was also associated with increased risk of the composite of non-CV death, perhaps suggesting that ΔHR is likely to be a non-specific signal of deteriorating health or other non-CV related episodes such as exacerbations of chronic obstructive pulmonary disease or infection.

Our observation is in keeping with two longitudinal studies looking at subjects without known CV disease, the first of which showed that a change in HR between two visits over a 5-year period in 5139 healthy middle-aged men was associated with mortality over a 20-year follow-up.[10] In the second example, a large epidemiological study, which included 29 325 subjects without known CV disease, increase in resting HR between two visits over a 10-year period was associated with higher risk of all-cause mortality and death from ischaemic heart disease.[9] Our data are also consistent with a study performed in 4065 hypertensive patients, where ΔHR was calculated by measuring the difference between the HR at the baseline visit and the mean HR of follow–up visits. They found that increase in HR of >5 b.p.m. over time was associated with mortality.[11] In our study, ΔHR were calculated, and used to predict events over a median interval of ∼4 months, a period shorter than previously published studies. Our study also showed that a temporal drop in HR over a short period of time was beneficial, not shown in any previous study.

Our analysis provides additional evidence that the value of HR recorded at anytime during the study was also of prognostic importance, in keeping with our previous study looking at baseline HR.[1] In our cohort, patients with HR at anytime <76 b.p.m. had lowest risk similar to other published studies. In the *post hoc*

analysis of the COMET trial, that included patients with chronic HF and reduced ejection fraction, an HR <68 b.p.m., was associated with better outcome compared with HR >68 b.p.m.[19] and in the placebo arm of SHIFT, an HR of 70–71 b.p.m. was associated with lower events compared with HR ≥72 b.p.m.[2]

We found that in patients with AF at baseline, there was a weaker relationship between HR at anytime and outcomes compared with patients in sinus rhythm. Our findings are somewhat similar to previous studies on baseline HR in which patients with AF at baseline had a weak or no significant relationship between baseline HR and outcome.[1,20] Although our analysis suggest that the use of HR at anytime, which represents the most recent HR value (i.e. time updated) is a better predictor of outcomes in patients with AF compared with baseline HR as shown in our previous analysis.[1]

Our observation suggest that monitoring of HR over time, as a biomarker of severity of HF, in the clinic setting or remotely may be useful in identifying HF patients at greatest risk of readmission and death. This is of importance especially as HR is potentially a modifiable risk factor and these patients could be considered for interventions that might improve their disease trajectory if guideline-based criteria for their use is met.[6,8] Whether remote monitoring devices that can assess HR more continuously might improve risk prediction in patients with HF will need further study.

Some limitations of our analysis should be noted. A limitation of time-updated analysis is that it hinders any detailed characterization of the patients' that have a rise or drop in HR from baseline or the preceding visit. This is because a patient's follow-up HR may rise or fall into different categories of HR; therefore, each patient may spend time in more than one HR category. Thus, we were limited to reporting the baseline characteristics of all patients, and the total time spent in each category with the associated number of events. However, an advantage of time-updated analysis is that it uses HR data from all visits allowing the calculation of changes in HR over short periods of time, something that other studies did not perform.[9–11] Furthermore, some predictors of outcome were not time updated.

We relied on investigator-reported HR at each visit. This may have been measured in different ways, at different times of the day, and under different circumstances. Estimating ventricular rates in patients with atrial fibrillation may be less reliable than measurement of resting HR in patients with sinus rhythm. In our analysis, we have controlled for β-blocker using in a time-updated analysis, taking into account both use of β-blockers and β-blocker dose. Thus, the importance of HR change appears to be independent of β-blocker use. Other strengths of this study include the fact that the CHARM program studied patients with both reduced and preserved EF on modern HF therapy and also the large number of outcome events in this population.

**Conclusions**

In a cohort of chronic HF patients with reduced and preserved ejection fraction, inclusive of patients with atrial fibrillation, changes in HR over time from the preceding clinic visit were associated with outcome, such that a rise in HR were associated with elevated risk and a drop in HR associated with reduced risk. Moreover, resting HR independent of the time it is measured is a predictor of adverse events in this population. Our findings further support the importance of measuring resting HR in every day clinical practice, and potentially with remote monitoring, as a way to identify HF patients at greatest risk for readmission and death.

**References**

1. Castagno D, Skali H, Takeuchi M, Swedberg K, Yusuf S, Granger CB, Michelson EL, Pfeffer MA, McMurray JJ, Solomon SD, Investigators C. Association of heart rate and outcomes in a broad spectrum of patients with chronic heart failure: results from the CHARM (Candesartan in Heart

Failure: Assessment of Reduction in Mortality and morbidity) program. J Am Coll Cardiol 2012;59:1785-1795.
2. Bohm M, Swedberg K, Komajda M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L, Investigators S. Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial. Lancet 2010;376:886-894.
3. Fox K, Borer JS, Camm AJ, Danchin N, Ferrari R, Lopez Sendon JL, Steg PG, Tardif JC, Tavazzi L, Tendera M; Heart Rate Working G. Resting heart rate in cardiovascular disease. J Am Coll Cardiol 2007;50:823-830.
4. Poole-Wilson PA, Uretsky BF, Thygesen K, Cleland JG, Massie BM, Ryden L; Atlas Study Group. Assessment of treatment with l, survival. Mode of death in heart failure: findings from the ATLAS trial. Heart 2003;89:42-48.
5. Palatini P, Julius S. Elevated heart rate: a major risk factor for cardiovascular disease. Clin Exp Hypertens 2004;26:637-644.
6. Swedberg K, Komajda M, Bohm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L, Investigators S. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet 2010;376:875-885.
7. Swedberg K, Komajda M, Bohm M, Borer J, Robertson M, Tavazzi L, Ford I, Investigators S. Effects on outcomes of heart rate reduction by ivabradine in patients with congestive heart failure: is there an influence of beta-blocker dose?: findings from the SHIFT (Systolic Heart failure treatment with the I(f) inhibitor ivabradine Trial) study. J Am Coll Cardiol 2012;59:1938-1945.
8. McAlister FA, Wiebe N, Ezekowitz JA, Leung AA, Armstrong PW. Meta-analysis: beta-blocker dose, heart rate reduction, and death in patients with heart failure. Ann Intern Med 2009;150:784-794.
9. Nauman J, Janszky I, Vatten LJ, Wisloff U. Temporal changes in resting heart rate and deaths from ischemic heart disease. JAMA 2011;306:2579-2587.
10. Jouven X, Empana JP, Escolano S, Buyck JF, Tafflet M, Desnos M, Ducimetiere P. Relation of heart rate at rest and long-term (>20 years) death rate in initially healthy middle-aged men. Am J Cardiol 2009;103:279-283.
11. Paul L, Hastie CE, Li WS, Harrow C, Muir S, Connell JM, Dominiczak AF, McInnes GT, Padmanabhan S. Resting heart rate pattern during follow-up and mortality in hypertensive patients. Hypertension 2010;55:567-574.
12. Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J, Yusuf S, Pocock S, Investigators C; Committees. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. Lancet 2003;362:759-766.
13. Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B, Ostergren J, Pfeffer MA, Swedberg K, Investigators C; Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet 2003;362:772-776.
14. McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, Olofsson B, Yusuf S, Pfeffer MA, Investigators C; Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. Lancet 2003;362:767-771.
15. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J, Investigators C; Committees. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 2003;362:777-781.

16. Pocock SJ, Wang D, Pfeffer MA, Yusuf S, McMurray JJ, Swedberg KB, Ostergren J, Michelson EL, Pieper KS, Granger CB. Predictors of mortality and morbidity in patients with chronic heart failure. ur Heart J 2006;27:65-75.
17. Kaye DM, Lambert GW, Lefkovits J, Morris M, Jennings G, Esler MD. Neurochemical evidence of cardiac sympathetic activation and increased central nervous system norepinephrine turnover in severe congestive heart failure. J Am Coll Cardiol 1994;23:570-578.
18. Black A, Murray L, Cardwell C, Smith GD, McCarron P. Secular trends in heart rate in young adults, 1949 to 2004: analyses of cross sectional studies. Heart 2006;92:468-473.
19. Metra M, Torp-Pedersen C, Swedberg K, Cleland JG, Di Lenarda A, Komajda M, Remme WJ, Lutiger , Scherhag A, Lukas MA, Charlesworth A, Poole-Wilson PA. Influence of heart rate, blood pressure, and beta-blocker dose on outcome and the differences in outcome between carvedilol and metoprolol tartrate in patients with chronic heart failure: results from the COMET trial. Eur Heart J 2005;26:2259-2268.
20. Cullington D, Goode KM, Zhang J, Cleland JG, Clark AL. Is heart rate important for patients with heart failure in atrial fibrillation? JACC Heart Fail 2014;2:213-220.