Resting Heart Rate and the Risk of Heart Failure in Healthy Adults:
The Rotterdam Study

Nanchen et al: Resting Heart Rate and Heart Failure

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Abstract

**Background**—An elevated resting heart rate is associated with re-hospitalization for heart failure and is a modifiable risk factor in heart failure patients. We aimed to examine the association between resting heart rate and incident heart failure in a population-based cohort study of healthy adults without pre-existing overt heart disease.

**Methods and Results**—We studied 4,768 men and women aged 55 years or older from the population-based Rotterdam Study. We excluded participants with prevalent heart failure, coronary heart disease, pacemaker, atrial fibrillation, atrio-ventricular block, and those using beta-blockers or calcium channel blockers. We used extended Cox-models allowing for time-dependent variation of resting heart rate along follow-up. Over a median of 14.6 years of follow-up, 656 participants developed heart failure. The risk of heart failure was higher in men with higher resting heart rate. For each increment of 10 beats per minute, the multivariable adjusted hazard ratios in men were 1.16 (95% confidence interval [CI], 1.05-1.28, p=0.005) in the time-fixed heart rate model and 1.13 (95% CI 1.02-1.25, p=0.017) in the time-dependent heart rate model. The association could not be demonstrated in women (p for interaction = 0.004). Censoring participants for incident coronary heart disease, or using time-dependent models to account for the use of beta-blockers or calcium channel blockers during follow-up did not alter the results.

**Conclusions**—Baseline or persistent higher resting heart rate is an independent risk factor for the development of heart failure in healthy older men in the general population.

**Key Words:** resting heart rate, heart failure, population-based, cardiovascular disease
Heart failure is a major public health problem that is associated with substantial mortality and morbidity. In the aging population of Western countries, the incidence of heart failure hospitalization is increasing despite the improvements in health care for heart failure patients. Therefore, it is important to develop strategies to detect adults at risk of heart failure in order to better tailor preventive measures and treatment.

Resting heart rate is a very accessible biological parameter with potential predictive capacity for heart failure and cardiovascular disease. Among patients suffering from heart failure, resting heart rate is a modifiable risk factor to prevent re-hospitalization for heart failure. However, studies examining the association between resting heart rate and heart failure have not included adults from the general population, or have included adults with cardiovascular disease, or conduction disorders such as atrial fibrillation, or adults using anti-arrhythmics or beta-blockers. This research question is important to study in a prospective manner because in cardiac patients, a subclinical decompensated state might enhance a hemodynamic response that increases heart rate. This biological interaction between resting heart rate and subclinical heart failure may limit the interpretation of the role of heart rate in the etiology of heart failure, because of potential reverse causality. Thus, it is still uncertain whether the association between resting heart rate and heart failure can be extrapolated to healthy adults from the general population.

We examined whether higher resting heart rate is independently associated with the development of heart failure among adults without pre-existing heart disease or heart-rate modifying medication use in the general population.
Methods

Study sample

This study was performed within the framework of the Rotterdam Study, a prospective population-based cohort study designed to evaluate the determinants and consequences of chronic diseases in the elderly. Details regarding the objectives and methods of the Rotterdam Study have been reported previously. Briefly, all inhabitants aged 55 and over of a well-defined suburb in the city of Rotterdam, the Netherlands, were invited to participate and 7,983 (78%) were enrolled. The Medical Ethics Committee of the Erasmus Medical Center approved the study and participants gave written informed consent to participate in the study and to obtain information from their treating physicians, separately. From 1990 until 1993, baseline data were collected using standardized home-interviews and established cardiovascular risk factors were subsequently assessed at the research center.

Of the 7,129 individuals in the Rotterdam Study who visited the research center at baseline, heart rate measurement was available for 6,966 participants. To account for endogenous heart rate variation only, we further excluded 873 participants using beta-blockers and 173 using calcium channel blockers. Because we aimed to examine the association between heart rate and the development of heart failure in participants free of heart disease, we also excluded participants with a pacemaker, second or third degree atrio-ventricular block on the baseline electrocardiogram (ECG), a history of heart failure, atrial fibrillation, and those with known coronary heart disease (CHD) defined as a history of myocardial infarction, coronary artery bypass grafting, or percutaneous coronary intervention. The final sample for analysis comprised 4,768 participants.
Measurement of heart rate

In all participants, baseline resting pulse was measured for 30 seconds at the right radial artery between two consecutive blood pressure measurements at the research center, with the subject in a sitting position. To obtain heart rate in beats per minute (bpm), the obtained pulse count was multiplied by two. Repeated examinations of heart rate were performed every 3-4 years and were available for 3 additional follow-up visits, from 1993 to 1995, from 1997 to 1999, and from 2002 to 2004. For sensitivity analysis, resting heart rate was further measured from a 10 seconds 12-lead ECG at baseline in 4,127 participants. Repeated measurements of ECG were available for all 3 additional follow-up visits. All ECGs were recorded with an ACTA Gnosis IV ECG recorder (Esaote Biomedica, Florence, Italy) at a sampling frequency of 500 Hz and stored digitally. All ECGs were processed using the validated modular ECG analysis system (MEANS). MEANS locates the QRS complexes and determines a stable reference point in each complex. The QRS detector of MEANS operates on multiple simultaneously recorded leads, which are transformed to a detection function that brings out the QRS complexes among the other parts of the signal. RR intervals are taken as the intervals between the reference points in adjacent QRS complexes. The median RR interval was computed, after exclusion of RR intervals that immediately precede and follow any premature ventricular complex.

Heart failure assessment

Prevalent and incident heart failure was determined as defined previously. For prevalent cases, a validated score was used based on the heart failure definition of the
European Society of Cardiology.\textsuperscript{13} This score was based on the presence of at least two signs or symptoms suggestive of heart failure or use of medication for the indication of heart failure.\textsuperscript{10} Cases of incident heart failure were obtained by continuously monitoring participants during follow-up through automated linkage with files from general practitioners. All available data on heart failure, such as hospital discharge letters and notes from general practitioners, were copied from the medical records. Heart failure was adjudicated in accordance with the criteria of the European Society of Cardiology\textsuperscript{13} based on the combination of signs and symptoms, and objective evidence of cardiac dysfunction, including chest radiographs or echocardiography. Two independent research physicians adjudicated all potential heart failure cases. In case of disagreement the judgment of a cardiologist was sought and considered decisive.\textsuperscript{10} Only definite and probable cases of heart failure were included in the analyses. The date of incident heart failure was the first occurrence of symptoms suggestive of heart failure, or the day of receipt of a first prescription of a loop diuretic or an angiotensin-converting enzyme inhibitor for heart failure. For the present analysis, incident heart failure was adjudicated until 1\textsuperscript{st} January, 2009.

\textit{Covariables}

Hypertension was defined as a systolic blood pressure $\geq$140 mmHg or a diastolic blood pressure $\geq$90 mmHg or use of blood pressure lowering drugs with the indication of hypertension. Diabetes mellitus was defined as a random or post-load blood glucose measurement exceeding 11.0 mmol/L, or the use of anti-diabetic drugs. Body mass index was calculated by dividing measured weight by height squared. Assessment of incident
fatal and non-fatal CHD has been previously described. For the present analysis, incident CHD events, including myocardial infarction and myocardial revascularization procedures have been adjudicated until 1st January, 2009. For all medication use from 1st January 1991 onwards, eight fully automated pharmacies in the research area provided data on use, dosage, duration of use, and date of first prescription, using a single computer network to register all prescriptions, as previously described. Moreover, data on medication use were collected during the baseline home interview.

**Statistical analysis**

Resting heart rate values at baseline were grouped into tertiles. This was done separately for men and women, because women are known to have a higher resting heart rate than men. One-way ANOVA and χ² tests or the Kruskal-Wallis rank test were used for baseline comparisons between tertiles. We calculated incidence rates per 1,000 person-years of follow-up in participants categorized according to their resting heart rate and constructed Kaplan-Meier cumulative incidence curves. The associations between baseline resting heart rate and heart failure were examined in a time-fixed analysis using multivariable Cox proportional hazard models. A quadratic mixed-effect model was used to estimate change in average heart rate per year of follow-up. Among different polynomial models, we chose the quadratic one which minimized the BIC criterion. Moreover, we used an extension of the Cox model allowing for introduction of repeated measurements of heart rate over time in a time-dependent analysis. With this version of the Cox model, the risk of event at any time \( t \) depends upon the last available measure of heart rate before time \( t \).
P for trend across categories was obtained by entering heart rate tertiles as a continuous variable. In the first model, we only adjusted for age. In the second model, we entered traditional cardiovascular risk factors, including age, smoking status, systolic blood pressure, antihypertensive treatment, diabetes mellitus, body mass index, total cholesterol, and high-density lipoprotein cholesterol. Among participants, 302 (6.3%) had missing values for one or more covariables. The multivariable adjusted analysis was restricted to those participants with complete information on cardiovascular risk factors at baseline. Participants were followed until the occurrence of heart failure, death, or the end of the study period. In order to evaluate the association between heart rate and incident heart failure not mediated through CHD, we additionally censored participants at the occurrence of non-fatal CHD. Furthermore, we conducted time-dependent analyses to assess the association between heart rate and incident heart failure not mediated by the use of heart rate influencing medication, as the indication for the prescription of beta-blockers or calcium channel blockers might be associated with the risk of heart failure and these medications affect resting heart rate measurements. This was done by changing the exposure of the participants whenever they filled-out a prescription of beta-blockers or calcium channel blockers during follow-up. In the sensitivity analyses, we repeated all analyses using time-fixed and time-dependent resting heart rate measured by ECG, since ECG-derived heart rate is more accurate. We report estimates with 95% confidence intervals (CIs). All hypothesis tests are two-sided and the significance level set at 5%. Statistical analyses were performed using STATA statistical software® (Version 12, STATA Corp, College Station, Tex) and R (Version 2.15.2, http://www.r-project.org).
Results

Gender-specific baseline characteristics with respect to resting heart rate categories are presented in Table 1. Mean age of the participants was 68.5 years and 62% were females. In men, heart rate was 68 bpm or less for the first tertile, 69 to 78 bpm for the second tertile, and 79 bpm or more for the third tertile. In women, these rates were 72 bpm or less, 73 to 80 bpm, and 81 bpm or more, respectively. Participants in the highest heart rate tertile were more likely to smoke, and to have elevated blood pressure, and diabetes mellitus. No differences in the use of anti-hypertensive drugs was found across heart rate categories, but a higher heart rate was more frequently noted in male users of anti-asthmatics and female users of oral corticosteroids. Average resting heart rate decreased similarly in both genders during follow-up, but tended to stabilize over time (Supplemental Figure).

During a median (interquartile range) 14.6 (7.6) years of follow-up, 656 participants developed incident heart failure. Crude incidence rates of heart failure were higher in men with higher heart rate than in men with lower heart rate, with 13.7 versus 9.9 per 1,000 person-years. In women, crude incidence rates of heart failure were similar across heart rate categories, except when heart rate was measured with ECG (Figure). Accordingly, there were remarkable differences in adjusted hazard ratios (HRs) between men and women. The multiplicative interaction term between heart rate as a continuous variable and gender was significant both in the age- and gender adjusted model (p=0.011) and in the multivariable adjusted model (p=0.004). For each increment of 10 beats per minute, the multivariable adjusted HRs in men were 1.16 (95% confidence interval [CI], 1.05-1.28) in the time-fixed heart rate model and 1.13 (95% CI 1.02-1.25) in the time-
dependent heart rate model (Table 2). Further adjustment for use of anti-asthmatic drugs and corticosteroids use did not change the estimates. In women, resting heart rate was not associated with a higher heart failure risk (Table 2).

To assess the heart failure risk not mediated by CHD, we additionally censored 328 participants at the occurrence of non-fatal CHD during follow-up. This yielded similar results (Table 3). We also examined the risk of heart failure taking into account follow-up time until the first prescription of common heart rate lowering drugs. This represented 1,700 first prescriptions, including 248 prescriptions prior to the diagnosis of heart failure. In this analysis, men with a heart rate in the upper tertile compared to those with a heart rate in the lower tertile had a higher risk of heart failure with a multivariable adjusted HR of 1.47, 95% CI 1.08 to 2.01. Relative risk estimates were not significant and unchanged in women (Table 3).

Sensitivity analysis (heart rate measured with ECG)

Using resting heart rate measured by ECG instead of pulse measurement, baseline heart rate was generally somewhat lower resulting in 62 bpm or less for the first tertile, 63 to 73 bpm for the second tertile, and 74 bpm or more for the third tertile in men, and 69 bpm or less, 69 to 76 bpm, and 77 bpm or more in women, respectively (Supplemental Table). However, for each increment of 10 bpm in men, we still found a significant 13% higher heart failure rate for the time-fixed heart rate model and 18% higher rate for the time-dependent heart rate model (Table 4). In women, the association did not reach statistical significance in the multivariable models. Further excluding 10 men and 7 women with a resting heart rate lower than 50 bpm, e.g. with bradycardia, yielded similar results.
Discussion

In a large population-based cohort study of healthy adults, higher resting heart rate measured with pulse palpation (and alternatively by ECG) was independently associated with incident heart failure in men during follow-up, and this association was not mediated through overt CHD. The association was found significant in men both with single and repeated heart rate measurement over time. In women, the association could not be demonstrated. Our study highlights the importance of resting heart rate as an independent marker of future heart failure in middle-aged and older healthy men from the general population.

Previous studies have reported that heart rate is a prognostic and potentially modifiable marker in patients suffering from heart failure or CHD. In a convenient sample of patients with CHD, Diaz and colleagues demonstrated that heart rate was associated with incident heart failure hospitalization. However, both the basic hemodynamic response to a decompensated state and the excessive neuroendocrine activation cause tachycardia in patients with subclinical heart failure. Thus, the etiologic nature of the association between heart rate and incident heart failure can only be examined in subjects without pre-existing overt cardiac disease at baseline. In line with our results, investigators from the EPIC-Norfolk study recently reported on a positive association between a single heart rate measurement and heart failure in middle-aged adults from the general population. In addition to the EPIC-Norfolk study, we could demonstrate that the association was not influenced by variation of resting heart rate over time or by the measurement method used to assess heart rate. Furthermore,
participants of the EPIC-Norfolk study may still have had subclinical heart disease, because they relied on use of medication only to define prevalent heart failure cases, as well as self-reported CHD, and they did not exclude adults with pre-existing atrial fibrillation or other conduction disorders based on ECG. Finally, the EPIC-Norfolk study examined only incident heart failure hospitalization, without including diagnoses of heart failure made by general practitioners or nursing home physicians as in our study.

As confirmed in our data, resting heart rate is higher in women than in men.14 Gender differences have also been proposed in heart failure etiology: in men CHD is considered the most important determinant, whereas in women hypertension plays a more predominant role.21 In our study sample, resting heart rate showed a stronger association in men than in women for the development of heart failure, but hypertension was associated with incident heart failure both in men and women without a significant gender difference (p for interaction 0.77). Resting heart rate in women may be less precise due to more important endogenous variations and previous experiences with cardiac volume overload during pregnancy. Indeed, the healthy female heart might have an advantage to adapt to elevated heart rate and volume overload related to pregnancy, offering protection against heart failure.22 Our results are in line with those from the EPIC-Norfolk study examining adults from the general population, in which the investigators could not find a statistically significant association between heart rate and heart failure in women not taking heart rate lowering drugs, with a p for trend of 0.055 across heart rate categories.7

We could further demonstrate that higher heart rate was an independent marker of heart failure that was not preceded by CHD, or by the use of beta-blockers or calcium
channel blockers during follow-up. Through mechanisms linked to oscillatory shear stress in the coronary arteries, an elevated heart rate might promote coronary atherosclerosis. In our study, it seems unlikely that the higher incidence of heart failure that we observed in adults with a higher heart rate was mediated by CHD. Current guidelines for the prevention of heart failure classify heart rate as a minor clinical risk factor, probably because the pathophysiological pathways between heart rate and heart failure remain speculative. Recently, two clinical trials reported the additional benefit of a specific heart rate lowering drug on outcomes in patients with heart failure and heart rate above 75 bpm. Interestingly, in the SHIFT trial, women seemed to derive equal benefit than men from the heart rate lowering drug to avoid re-hospitalization for heart failure. Specific heart rate reducing therapy should be considered for evaluation in healthy adults with elevated heart rate to prevent or postpone the development of heart failure.

Strengths of our study include the large sample size in a population-based setting with a long follow-up, the repeated measurement of resting heart rate over time, the concurrent assessment of resting heart rate by means of both arterial pulse and ECG recording, as well as the large number of heart failure cases adjudicated using standardized definitions. The detection of heart failure relied not only on hospitalization, but also included diagnoses of heart failure made by general practitioners and nursing home physicians. This systematic approach potentially reduced selection of severe cases only. Previous studies have evaluated risk factors for incident heart failure based on ECG measurement. The ECG provides important clinical information other than heart rate, such as presence of left ventricular hypertrophy, bundle branch blocks, or ST-T
abnormalities that might together improve cardiovascular risk prediction. In our study, we showed that a single or repeated assessment of heart rate based on arterial pulse was sufficient to identify men at higher risk of developing heart failure. However, our study also has some limitations. The association between heart rate and heart failure in our population of healthy older adults suggests that heart rate is not merely a surrogate marker of an underlying process leading to heart failure. However, even with a comprehensive assessment of traditional cardiovascular risk factors, we cannot rule out residual confounding. For example, we could not account for the circadian variation of resting heart rate in our analyses. However, the circadian variation of heart rate is small between 10 AM and 6 PM, and tends to diminish in older adults. Similarly to previous reports, we were also unable to account for the degree of physical activity performed by each participant, and therefore the associations found with heart rate may be confounded by physical fitness. Finally, we could not assess cardiac changes or differentiate between echocardiographic systolic and diastolic dysfunction in our study. Therefore, further studies should better characterize healthy men and women with elevated heart rate, for instance using echocardiography or B-type natriuretic peptide measurements.

In conclusion, in our population-based study of adults free of heart disease, both single and repeated measurements of resting heart rate based on pulse palpation or alternatively ECG identifies men at higher risk of developing heart failure, beyond other cardiovascular risk factors. Whether healthy older individuals with higher resting heart rate might benefit from preventive therapy that specifically reduces heart rate remains to be explored.
Acknowledgements

The dedication, commitment, and contribution of inhabitants, general practitioners, and pharmacists of the Ommoord district to the Rotterdam Study are gratefully acknowledged.

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None of the funders had any role in design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Disclosures

None.
References


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<th></th>
<th>Men (n=1,829)</th>
<th>Women (n=2,939)</th>
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<th></th>
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<tbody>
<tr>
<td></td>
<td>First tertile</td>
<td>Second tertile</td>
<td>Third tertile</td>
<td>P-value</td>
</tr>
<tr>
<td>Resting heart rate, median bpm (range)</td>
<td>64 (40-68)</td>
<td>74 (69-78)</td>
<td>86 (79-128)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>First tertile</td>
<td>Second tertile</td>
<td>Third tertile</td>
<td>P-value</td>
</tr>
<tr>
<td>Demographics</td>
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<td>Age, years</td>
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<td>67.6 (8.1)</td>
<td>67.2 (8.3)</td>
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<tr>
<td></td>
<td>69.3 (9.7)</td>
<td>68.9 (9.4)</td>
<td>69.1 (9.4)</td>
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<td>Smoking status, No. (%)</td>
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<td>Never</td>
<td>60 (8.7)</td>
<td>47 (8.6)</td>
<td>48 (8.6)</td>
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<td>640 (53.8)</td>
<td>417 (51.8)</td>
<td>450 (52.9)</td>
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<td>Former</td>
<td>452 (65.5)</td>
<td>335 (61.4)</td>
<td>287 (51.3)</td>
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<td></td>
<td>238 (29.6)</td>
<td>209 (24.6)</td>
<td></td>
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<tr>
<td>Current</td>
<td>181 (26.1)</td>
<td>164 (30.0)</td>
<td>224 (40.1)</td>
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<td></td>
<td>149 (18.5)</td>
<td>191 (22.5)</td>
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<td>Comorbidities</td>
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<td>Hypertension, No. (%)</td>
<td>289 (40.9)</td>
<td>257 (46.6)</td>
<td>293 (51.4)</td>
<td>0.001</td>
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<td>599 (49.1)</td>
<td>386 (46.2)</td>
<td>493 (56.0)</td>
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<td>Diabetes mellitus, No. (%)</td>
<td>37 (5.3)</td>
<td>51 (9.3)</td>
<td>60 (10.5)</td>
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<td></td>
<td>86 (7.1)</td>
<td>65 (7.9)</td>
<td>105 (12.0)</td>
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### Objective measures

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<th>Measure</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>136 (21)</td>
<td>138 (21)</td>
<td>140 (22)</td>
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<td>0.009 **</td>
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<td>Diastolic blood pressure, mmHg</td>
<td>73 (11 )</td>
<td>75 (12 )</td>
<td>76 (12 )</td>
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<td>&lt;0.001 **</td>
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<td>Body mass index, kg/m²</td>
<td>25.5 (2.9)</td>
<td>25.6 (3.0)</td>
<td>25.2 (3.0)</td>
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<td>0.044</td>
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<td>Total cholesterol, mmol/L</td>
<td>6.3 (1.1)</td>
<td>6.3 (1.3)</td>
<td>6.3 (1.2)</td>
<td></td>
<td>0.70</td>
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<td>HDL-cholesterol, mmol/L</td>
<td>1.3 (0.3)</td>
<td>1.2 (0.3)</td>
<td>1.2 (0.3)</td>
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<td>0.144</td>
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<td>Creatinine, μmol/L</td>
<td>88 (14)</td>
<td>88 (15)</td>
<td>89 (22)</td>
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### Medication use

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<th>Group 3</th>
<th>Group 4</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Anti-hypertensive drugs, No. (%)</td>
<td>57 (8.1)</td>
<td>52 (9.4)</td>
<td>52 (9.1)</td>
<td></td>
<td>0.67</td>
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<tr>
<td>Anti-asthmatics, No. (%)</td>
<td>39 (5.5)</td>
<td>30 (5.4)</td>
<td>64 (11.2)</td>
<td></td>
<td>0.002 **</td>
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<td>Corticosteroids, No. (%)</td>
<td>11 (1.6)</td>
<td>10 (1.8)</td>
<td>17 (3.0)</td>
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<td>Thyroid therapy, No. (%)</td>
<td>1 (0.1)</td>
<td>3 (0.5)</td>
<td>2 (0.4)</td>
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<td>0.63</td>
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</table>

Data are given as mean (standard deviation) unless otherwise indicated.

1 Defined as a systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or use of blood pressure lowering drugs for the indication of hypertension.

2 Defined as a random or post-load blood glucose measurement of ≥11.1 mmol/L or the use of anti-diabetic drugs.

Abbreviations: bpm, beats per minute; HDL, high-density lipoprotein.
### Table 2. Heart failure risk for each increment of 10 bpm for time-fixed versus time-dependent heart rate measurement during follow-up

<table>
<thead>
<tr>
<th></th>
<th>Men (n=1,829)</th>
<th>Women (n=2,939)</th>
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<tr>
<td></td>
<td>N events</td>
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<td><strong>Baseline heart rate</strong></td>
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<tr>
<td>Age adjusted</td>
<td>261</td>
<td>1.14</td>
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<tr>
<td>Multivariable adjusted¹</td>
<td>1.16</td>
<td>(1.05 ; 1.28)</td>
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<tr>
<td>Additionally adjusted for treatment²</td>
<td>1.14</td>
<td>(1.03 ; 1.27)</td>
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<tr>
<td><strong>Time-dependent heart rate</strong></td>
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<tr>
<td>Age adjusted</td>
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<td>1.15</td>
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<tr>
<td>Multivariable adjusted¹</td>
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<td>(1.02 ; 1.25)</td>
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<tr>
<td>Additionally adjusted for treatment²</td>
<td>1.11</td>
<td>(1.00 ; 1.22)</td>
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</tbody>
</table>

¹Adjusted for age, smoking status, systolic blood pressure, diabetes, body mass index, total cholesterol, high-density lipoprotein cholesterol, and antihypertensive treatment.

²Additionally adjusted for systemic corticoid and anti-asthmatic treatment.

Abbreviations: N, number; HR, hazard ratio; CI, confidence interval;
Table 3. Hazard ratios for developing heart failure, with respect to gender-specific baseline resting heart rate tertile, and after considering heart rate modifying medication during follow-up, or censoring at the occurrence of myocardial infarction

<table>
<thead>
<tr>
<th></th>
<th>Men (n=1,829)</th>
<th>Women (n=2,939)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First tertile</td>
<td>Second tertile</td>
</tr>
<tr>
<td></td>
<td>Heart rate</td>
<td>Heart rate</td>
</tr>
<tr>
<td></td>
<td>&lt;69 bpm</td>
<td>69-78 bpm</td>
</tr>
<tr>
<td>Number of events</td>
<td>84</td>
<td>89</td>
</tr>
<tr>
<td>Incidence rate, per 1,000 person-years</td>
<td>9.9</td>
<td>13.6</td>
</tr>
<tr>
<td>Age adjusted HR</td>
<td>1.00 (ref)</td>
<td>1.36 (1.01 ; 1.83)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td>(1.01 ; 1.83)</td>
</tr>
<tr>
<td>Multivariable adjusted HR</td>
<td>1.00</td>
<td>1.35</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(ref)</td>
<td>(0.99 ; 1.84)</td>
</tr>
<tr>
<td>Additionally adjusted for treatment HR (95% CI)</td>
<td>1.00</td>
<td>1.34</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(ref)</td>
<td>(0.98 ; 1.83)</td>
</tr>
<tr>
<td>Using the prescription of beta-blockers and calcium channel blockers as time-dependent variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-adjusted HR</td>
<td>1.00</td>
<td>1.31</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(ref)</td>
<td>(0.97-1.77)</td>
</tr>
<tr>
<td>Multivariable adjusted HR</td>
<td>1.00</td>
<td>1.32</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(ref)</td>
<td>(0.97-1.80)</td>
</tr>
<tr>
<td>Censoring participants at the occurrence of coronary heart disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of events</td>
<td>74</td>
<td>76</td>
</tr>
<tr>
<td>------------------</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>Age adjusted HR</td>
<td>1.00</td>
<td>1.31</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(ref)</td>
<td>(0.95-1.81)</td>
</tr>
<tr>
<td>Multivariable adjusted HR</td>
<td>1.00 (ref)</td>
<td>1.33</td>
</tr>
<tr>
<td>(95% CI)¹</td>
<td>(0.95-1.86)</td>
<td>(1.12-2.19)</td>
</tr>
</tbody>
</table>

¹Adjusted for age, smoking status, systolic blood pressure, diabetes mellitus, body mass index, total cholesterol, high-density lipoprotein cholesterol, and antihypertensive treatment.

²Additionally adjusted for systemic corticoid and anti-asthmatic treatment.

Abbreviations: HR, hazard ratio; CI, confidence interval; bpm, beats per minute.
Table 4. Heart failure risk for each increment of 10 bpm for time-fixed versus time-dependent heart rate measurement during follow-up, as measured by ECG (n=4,127)

<table>
<thead>
<tr>
<th></th>
<th>Men (n = 1,574)</th>
<th>Women (n=2,553)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N events</td>
<td>HR</td>
</tr>
<tr>
<td>Baseline heart rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age adjusted</td>
<td>219</td>
<td>1.17</td>
</tr>
<tr>
<td>Multivariable adjusted(^1)</td>
<td>1.13</td>
<td>(1.01 ; 1.26)</td>
</tr>
<tr>
<td>Additionally adjusted for treatment(^2)</td>
<td>1.12</td>
<td>(1.00 ; 1.25)</td>
</tr>
<tr>
<td>Time-dependent heart rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age adjusted</td>
<td>219</td>
<td>1.21</td>
</tr>
<tr>
<td>Multivariable adjusted(^1)</td>
<td>1.18</td>
<td>(1.06 ; 1.31)</td>
</tr>
<tr>
<td>Additionally adjusted for treatment(^2)</td>
<td>1.16</td>
<td>(1.05 ; 1.29)</td>
</tr>
</tbody>
</table>

\(^1\) Adjusted for age, smoking status, systolic blood pressure, diabetes, body mass index, total cholesterol, high-density lipoprotein cholesterol, and antihypertensive treatment.

\(^2\) Additionally adjusted for systemic corticoid and anti-asthmatic treatment.

Abbreviations: N, number; HR, hazard ratio; CI, confidence interval.
Figure Legend

Figure

Cumulative incidence of heart failure according to tertile of baseline heart rate, by gender

a) Heart rate measured at the radial artery for 30 seconds (n=4,768)

b) Heart rate measured from a 10 second ECG (n=4,127)
Resting Heart Rate and the Risk of Heart Failure in Healthy Adults: The Rotterdam Study
David Nanchen, Maarten J.G. Leening, Isabella Locatelli, Jacques Cornuz, Jan A. Kors, Jan Heeringa, Jaap W. Deckers, Albert Hofman, Oscar H. Franco, Bruno H.Ch. Stricker, Jacqueline C.M. Witteman and Abbas Dehghan

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Supplemental Material

**Supplemental Figure.** Changes of resting heart rate during follow-up estimated by a quadratic mixed-effect model (n=4,768)

<table>
<thead>
<tr>
<th></th>
<th>men</th>
<th>women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>73.52</td>
<td>76.43</td>
</tr>
<tr>
<td>Time(years)</td>
<td>-0.85 &lt; 0.001</td>
<td>-0.86 &lt; 0.001</td>
</tr>
<tr>
<td>Time*Time</td>
<td>0.04 &lt; 0.001</td>
<td>0.04 &lt; 0.001</td>
</tr>
</tbody>
</table>

Abbreviation: bpm, beat per minute.
**Supplemental Table.** Incidence rates and hazard ratios for developing heart failure, with respect to gender-specific resting heart rate tertile, as measured by baseline ECG (n=4,127)

<table>
<thead>
<tr>
<th></th>
<th>First tertile</th>
<th>Second tertile</th>
<th>Third tertile</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men (n=1,574)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of events</td>
<td>60</td>
<td>66</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>Incidence rate, per 1,000 person-years</td>
<td>8.9</td>
<td>10.3</td>
<td>16.3</td>
<td></td>
</tr>
<tr>
<td>Age adjusted HR (95% CI)</td>
<td>1.00 (ref)</td>
<td>1.12 (0.79-1.59)</td>
<td>1.66 (1.20-2.29)</td>
<td>0.002</td>
</tr>
<tr>
<td>Multivariable adjusted HR (95% CI)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>1.00 (ref)</td>
<td>1.07 (0.74-1.54)</td>
<td>1.50 (1.07-2.11)</td>
<td>0.015</td>
</tr>
<tr>
<td>Additionally adjusted for treatment&lt;sup&gt;2&lt;/sup&gt;</td>
<td>1.00 (ref)</td>
<td>1.07 (0.74-1.54)</td>
<td>1.46 (1.04-2.06)</td>
<td>0.023</td>
</tr>
<tr>
<td><strong>Women (n=2,553)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of events</td>
<td>104</td>
<td>110</td>
<td>124</td>
<td></td>
</tr>
<tr>
<td>Incidence rate, per 1,000 person-years</td>
<td>8.5</td>
<td>10.4</td>
<td>12.4</td>
<td></td>
</tr>
<tr>
<td>Age adjusted HR (95% CI)</td>
<td>1.00 (ref)</td>
<td>1.08 (0.82-1.41)</td>
<td>1.20 (0.93-1.56)</td>
<td>0.166</td>
</tr>
<tr>
<td>Multivariable adjusted HR (95% CI)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>1.00 (ref)</td>
<td>0.98 (0.74-1.30)</td>
<td>1.05 (0.80-1.39)</td>
<td>0.69</td>
</tr>
<tr>
<td>Additionally adjusted for treatment&lt;sup&gt;2&lt;/sup&gt;</td>
<td>1.00 (ref)</td>
<td>0.98 (0.74-1.30)</td>
<td>1.05 (0.80-1.39)</td>
<td>0.70</td>
</tr>
</tbody>
</table>

<sup>1</sup> Adjusted for age, smoking status, systolic blood pressure, diabetes, body mass index, total cholesterol, high-density lipoprotein cholesterol and antihypertensive treatment.

<sup>2</sup> Additionally adjusted for systemic corticoid and anti-asthmatics treatment.

Abbreviations: HR, hazard ratio; CI, confidence interval, ECG, electrocardiograph; bpm, beat per minute.