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ORIGINAL PAPER

# Resting heart rate is an independent predictor of all-cause mortality in the middle aged general population

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**Abstract**
*Background* High resting heart rate (RHR) predicts cardiovascular outcomes in patients with vascular disease and heart failure. We evaluated the prognostic value of RHR in a large contemporary population-based, prospective cohort of individuals without known coronary artery disease.
*Methods and results* Resting heart rate (RHR) was determined in 4091 individuals (mean age 59.2 ± 7.7; 53 % women) from the Heinz Nixdorf RECALL study, of whom, 3348 were free of heart rate lowering medication. During 10.5 years of follow-up (median), 159 (3.9 %) individuals developed a coronary event and 398 (9.7 %) died of any cause. Persons without any event ($n = 3603$) had similar heart rates as persons with coronary events (69.5 ± 11 versus 69.9 ± 11 bpm, $p = 0.51$) but lower heart rates than persons who died (72.3 ± 13 bpm, $p < 0.0001$). In individuals without heart rate lowering medication, an increase in heart rate by 5 bpm was associated with an increased hazard ratio (HR) for all-cause mortality of 13 % in unadjusted analysis and also upon adjustment for traditional cardiovascular risk factors, including coronary artery calcification [full model: HR (95 % CI) 1.13 (1.07–1.20), $p < 0.0001$], but not for coronary events [HR 1.02 (0.94–1.11), $p = 0.60$]. In individuals without heart rate lowering medication, the HR (full model) for heart rate ≥70 versus <70 bpm with regard to all-cause mortality and coronary events was 1.68 (1.30–2.18), $p < 0.0001$, and 1.20 (0.82–1.77), $p = 0.35$. Analysis of the entire cohort revealed a continuous relationship of heart rate with all-cause mortality [HR for lowest to highest heart rate quartile 1.64 (1.22–2.22), $p = 0.001$, full model] but not with coronary events [HR 1.04 (0.65–1.66), $p = 0.86$].
*Conclusions* In the general population without known coronary artery disease and heart rate lowering medication, elevated RHR is an independent risk marker for all-cause mortality but not for coronary events.

**Keywords** Resting heart rate · Mortality · Coronary events

**Abbreviations**

| | |
|---|---|
| CAC | Coronary artery calcium |
| CAD | Coronary artery disease |
| CVD | Cardiovascular disease |
| PAD | Peripheral arterial disease |
| RHR | Resting heart rate |

On behalf of the Heinz Nixdorf Recall Study Investigators.

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## Introduction

Resting heart rate (RHR) is a determinant of cardiovascular function and contributes to the pathogenesis of myocardial and vascular disease [21]. Increased heart rate is closely linked to endothelial dysfunction and atherosclerosis in experimental animal models and in humans [6, 9].

Epidemiological and interventional studies investigated the association between RHR and outcomes in different populations, and there is evidence from large studies that elevated RHR is predictive of cardiovascular outcomes, independently of standard risk factors or co-morbidities, in patients with established cardiovascular diseases [4, 10, 18, 22, 25].

Most epidemiological studies addressing RHR in a primary prevention setting were conducted prior to the broad implementation of cardiovascular protective therapies [10, 18, 22, 25]. Data from contemporary cohorts are sparse [26]. In patients with heart failure, RHR has emerged both as a powerful marker of risk in patients with impaired ejection fraction and a treatment target that is easily available through clinical examination, thus qualifying heart rate as being a risk factor [2–4, 35]. Therefore, we evaluated the association of RHR with all-cause mortality and coronary events in the Heinz Nixdorf risk factors, evaluation of coronary calcium, and lifestyle (RECALL) study, a population-based, prospective cohort study of the comparative value of risk stratification techniques for cardiovascular events [34].

## Methods

### Participants

Participants were randomly selected from mandatory city registries in Essen, Bochum, and Mülheim and invited to participate in the study as previously reported [11, 12]. Physician- or self-referral was not allowed to avoid selection bias. A total of 4814 subjects aged 45–75 years (50 % females) were included between December 2000 and August 2003. All subjects with physician-diagnosed coronary artery disease (CAD), i.e. a history of myocardial infarction or coronary revascularization ($n = 327$) or stroke ($n = 135$) were excluded from the study as well as persons with atrial fibrillation in the resting ECG ($n = 80$). In six individuals a resting ECG was unavailable, and 227 persons had no valid information on heart rate lowering medication, leaving 4091 persons for the present analysis. All participants provided written informed consent, and the study was approved by the Ethical Committee at the University Essen, Germany.

### Heart Rate, Cardiovascular Risk Factors and Questionnaires

RHR was obtained from standardized automated measurements from 12-lead resting ECGs after 5 min rest using a MAC 5000® ECG recorder (GE Healthcare, Freiburg, Germany) as previously reported [29]. Blood pressure was determined from the mean of the second and third measurements taken at least 3 min apart (Omron 705-CP, OMRON, Germany). Body mass index (BMI) was calculated from standardized measurements of height and weight. Current smoking was defined as a history of cigarette smoking during the past year. Former smoking was defined as a history of ever smoking. Standard enzymatic methods were used to measure total cholesterol, LDL- and HDL-cholesterol, and triglycerides. Participants were considered diabetic if they reported a physician diagnosis of diabetes or were taking anti-diabetic medication. HsCRP was measured using a standardized assay (Roche Diagnostics, Basel, Switzerland).

All subjects were queried about known cardiovascular disease (CVD) using a physician-based questionnaire and about regular cardiovascular medication including antihypertensive medication, heart rate lowering medication including beta-blockers, glycosides, and dihydropyridine-calcium channel blockers.

### Electron-beam computed tomography (EBCT)

To quantify CAC, non-enhanced EBCT scans were performed with a C 100 or C-150 scanner (GE Imatron, South San Francisco, US). Prospective ECG-triggering was done at 80 % of the RR-interval. Contiguous 3 mm thick slices to the apex of the heart were obtained at an image acquisition time of 100 ms. CAC was defined as a focus of at least four contiguous pixels with a CT density $\geq$130 Hounsfield Units. The CAC Agatston Score was computed by summing the CAC scores of all foci in the epicardial coronary system and was log-transferred because of skewed data distribution [1, 27, 33]. The CAC score was not communicated to either the participants or their treating physicians.

### Follow-up

Annual postal questionnaires assessed the morbidity status during follow-up, i.e. medication, hospital admissions, and outpatient diagnoses of CVD. Self-reported incident cardiovascular morbidity and fatal events were validated by review of hospital records and records of the attending physicians (see below). All death certificates of the three cities under study were regularly screened. In parallel,

deceased participants were tracked back to obtain as much information as possible to verify the causes of death.

### Study endpoints and verification of study endpoints

Primary endpoints for this study were based on unequivocally documented incident coronary events that met predefined study criteria [11, 12, 34]. We considered a myocardial infarction event based on symptoms, electrocardiographic signs, and enzymes [levels of creatine kinase (CK-MB)] as well as troponin T or I, and necropsy as: (1) non-fatal acute myocardial infarction or (2) coronary death [11, 12]. For all primary study endpoints, hospital and nursing home records including electrocardiograms, laboratory values, and pathology reports were collected. For deceased subjects, death certificates were collected, and interviews with general practitioners, relatives, and eyewitnesses were undertaken where possible. Medical records were obtained for all reported endpoints. An external criteria and endpoint committee blinded for conventional risk factor status and CAC scores reviewed all documents and classified the endpoints thereafter.

### Statistical analysis

Demographic data and risk factors are expressed as means (standard deviation, SD) or medians (25th, 75th percentile), frequencies are given as counts (%). Differences in proportions were statistically evaluated using Chi square or Fisher's exact test, trends in proportions using the Cochran-Armitage trend test; location measures of continuous quantities were compared using Student's $t$ test or Mann–Whitney $U$ statistics.

Observed 12-year cumulative risks are given in quartiles of heart rate ($Q1$–4) and in 10 bpm categories of heart rate, plotting observed risks, and a parabolic fit curve to assess characteristic deviations from linearity. We used univariate and multivariable Cox proportional hazard regression to calculate unadjusted and adjusted hazard ratios (HRs) and corresponding 95 % confidence intervals (CI) for the occurrence of endpoints (death or coronary event). HR estimates for heart rates were adjusted for conventional risk factors, i.e. age, sex, hypertension, current smoking, diabetes, BMI, known PAD, LDL-cholesterol, lipid-lowering medication, heart rate lowering medication (where applicable), and CAC. Kaplan–Meier survival curves were calculated per quartile of heart rate, and statistically evaluated using a Log-rank test of trend. All calculations were performed with SAS (Cary, NC, version 9.4).

## Results

### Study population

Baseline characteristics and distribution of CVD risk factors by RHR quartile are shown in Table 1. Mean RHR in the study population was 69.7 ± 11 bpm. At study entry, 18.2 % of subjects were taking heart rate lowering medication. Individuals with lower RHRs were more likely to be on heart rate lowering drugs. In the lowest quartile ($Q1$) there were more men than in $Q2$–4. The prevalence of cardiovascular risk factors, e.g. systolic blood pressure, LDL-cholesterol, diabetes mellitus, and hsCRP increased with heart rate quartiles (Table 1). $Q4$ contained almost twice as many individuals with diabetes mellitus than $Q1$ and hsCRP levels were almost twice as high. CAC scores and the prevalence of PAD showed a J-shaped distribution across heart rate quartiles since persons with heart rate lowering medication had a higher prevalence of CAC and known PAD than those without (77 versus 66 %, $p < 0.0001$, and 2.5 versus 1.3 %, $p = 0.03$, respectively). Persons with heart rate lowering medication had lower heart rates than those without (66.0 ± 11 versus 70.6 ± 11 bpm, $p < 0.001$).

### Predictors of events

During a median follow-up of 10.5 years ($Q1$/$Q3$: 10.2/13.0 years), 159 (3.9 %) subjects developed a coronary event, and 398 (9.7 %) subjects died of any cause. Persons without any events had a similar mean heart rate (69.5 ± 11 bpm) as persons with coronary events (69.9 ± 11 bpm, $p = 0.51$) but lower mean heart rates than persons who died (72.3 ± 13 bpm, $p < 0.0001$). In the entire cohort using a multivariate full model, age, current smoking, known PAD, log(CAC + 1), and RHR [$Q4$ versus $Q1$, HR = 1.64 (1.22–2.22), see Table 2] were independent predictors of all-cause mortality (hazard ratios other than for heart rate not shown). Age, sex, known PAD, and log(CAC + 1), but not RHR, were independent predictors of a coronary event (hazard ratios not shown).

Persons with HR lowering medication had higher all-cause mortality rates (Fig. 1a; Table 3) and higher coronary event rates (Fig. 1b; Table 4) than persons without. This was also seen in HR quartiles for all-cause mortality except for $Q4$ and for coronary events in $Q1$, but not in $Q2$–4 (data not shown).

In individuals with heart rate lowering medication, only age and log(CAC + 1) were independent predictors of all-cause mortality, with known PAD having borderline statistical significance [HR = 2.39 (0.97–5.92), $p = 0.059$].

**Table 1** Baseline characteristics and distribution of CVD risk factors by heart rate quartiles

| Variable | All ($n = 4091$) | $Q1$ (≤62 bpm) ($n = 1093$) | $Q2$ (63–≤ 69 bpm) ($n = 1072$) | $Q3$ (70–≤ 76 bpm) ($n = 925$) | $Q4$ (> 76 bpm) ($n = 1001$) | $p$ value for trend |
|---|---|---|---|---|---|---|
| Heart rate (bpm) | 69.7 ± 11.1 | 57.1 ± 4.1 | 66.0 ± 2.0 | 72.8 ± 2.0 | 84.7 ± 7.5 | n.a. |
| Age (years) | 59.2 ± 7.7 | 58.9 ± 7.6 | 59.4 ± 7.8 | 59.0 ± 7.7 | 59.6 ± 7.8 | 0.09 |
| Female (%) | 53 | 46 | 57 | 57 | 55 | <0.0001 |
| BMI (kg/m$^2$) | 27.8 ± 4.6 | 27.3 ± 4.1 | 27.8 ± 4.5 | 27.9 ± 4.7 | 28.5 ± 5.0 | <0.0001 |
| Waist circumference (cm) | 94 ± 13 | 93 ± 12 | 93 ± 13 | 94 ± 13 | 96 ± 14 | <0.0001 |
| Systolic blood pressure (mmHg) | 132 ± 21 | 130 ± 20 | 131 ± 20 | 132 ± 20 | 137 ± 22 | <0.0001 |
| Diastolic blood pressure (mmHg) | 81 ± 11 | 80 ± 11 | 81 ± 11 | 81 ± 10 | 84 ± 11 | <0.0001 |
| Known hypertension (%) | 54.3 | 53.3 | 50.0 | 52.2 | 62.0 | <0.0001 |
| Total cholesterol (mg/dL) | 231 ± 39 | 229 ± 38 | 230 ± 40 | 234 ± 39 | 234 ± 39 | 0.0007 |
| LDL-cholesterol (mg/dL) | 147 ± 36 | 146 ± 35 | 146 ± 36 | 149 ± 36 | 149 ± 37 | 0.015 |
| HDL-cholesterol (mg/dL) | 59 ± 17 | 59 ± 17 | 59 ± 17 | 59 ± 17 | 59 ± 17 | 0.86 |
| Triglycerides (mg/dL) | 148 ± 103 | 137 ± 98 | 147 ± 110 | 151 ± 98 | 158 ± 102 | <0.0001 |
| Diabetes (%) | 7.3 | 5.8 | 5.6 | 7.7 | 10.5 | <0.0001 |
| HbA1c (mg/dL) | 5.5 ± 0.8 | 5.4 ± 0.7 | 5.5 ± 0.8 | 5.5 ± 0.8 | 5.6 ± 0.9 | 0.003 |
| hsCRP (mg/dL) | 0.31 ± 0.9 | 0.22 ± 0.4 | 0.32 ± 1.5 | 0.31 ± 0.7 | 0.40 ± 0.7 | <0.0001 |
| Never smoking (%) | 43.5 | 41.2 | 45.2 | 42.1 | 45.4 | < 0.01 |
| Former smoking (%) | 33.0 | 37.9 | 31.1 | 32.1 | 30.5 | |
| Active smoking (%) | 23.5 | 20.9 | 23.6 | 25.8 | 24.1 | |
| CAC Score [Agatston units, median ($Q1$/$Q3$)] | 11.9 (0/112) | 14.2 (0/118) | 8.8 (0/104) | 7.7 (0/83) | 20 (0/128) | 0.12 |
| Known peripheral artery disease (%) | 1.5 | 1.7 | 1.2 | 1.4 | 1.7 | 0.77 |
| Blood pressure lowering medication (%) | 32.5 | 38.2 | 31.3 | 28.3 | 31.4 | 0.0003 |
| Lipid-lowering medication (%) | 9.3 | 9.8 | 9.4 | 8.3 | 9.6 | 0.67 |
| Heart rate lowering medication (%) | 18.2 | 27.5 | 18.4 | 14.9 | 10.7 | <0.0001 |

Independent predictors of coronary events were sex and log(CAC + 1), while a high hazard in persons with known PAD [HR = 3.03 (0.95–9.68), $p = 0.061$] did not reach statistical significance.

In persons without heart rate lowering medication, age, smoking, diabetes, log(CAC + 1), and RHR [HR = 1.84 (1.28–2.65), $p < 0.0001$ for $Q4$ versus $Q1$] were independent predictors of all-cause mortality. In this subgroup, independent predictors of coronary events were age, sex, smoking, known PAD, and log(CAC + 1), but not RHR.

### Effect of heart rate quartiles on outcome

In the entire cohort, all-cause mortality risk but not coronary event risk increased with heart rate quartiles (Table 2; Fig. 2a, d). The increased mortality risk was particularly driven by events in persons without heart rate lowering medication (Table 4; Fig. 2c), but not in persons with heart rate lowering medication (Table 3; Fig. 2b, e).

### Risk associated with heart rate ≥70 vs <70 bpm

In the entire cohort, individuals with heart rate ≥70 bpm had 50 % increased hazards for dying than persons with heart rate <70 bpm (HR = 1.53, 1.23–1.90, $p = 0.0001$). The HR for coronary events was 1.07 (0.77–1.51), $p = 0.68$, in persons with heart rate ≥70 versus <70. In persons with heart rate lowering medication, the risk of all-cause mortality was HR = 1.25 (0.81–1.95), $p = 0.32$, and of coronary events HR = 0.76 (0.35–1.67), $p = 0.49$, for heart rate ≥70 versus <70 bpm, respectively. In persons without heart rate lowering medication, the risk of all-cause mortality was HR = 1.68 (1.30–2.18), $p < 0.0001$, and of coronary events HR = 1.20 (0.82–1.77), $p = 0.35$, for heart rate ≥70 versus <70 bpm, respectively.

**Table 2** Incidence of events and hazard ratios by heart rate quartile in the entire cohort

| Type of event | All persons ($n = 4091$) | Model | $Q1$ (≤62 bpm) ($n = 1093$) $n = 90/8.2$ % | $Q2$ (63–≤ 69 bpm) ($n = 1072$) $n = 81/7.6$ % | $Q3$ (70–≤ 76 bpm) ($n = 925$) $n = 90/9.7$ % | $Q4$ (>76 bpm) ($n = 1001$) $n = 137/13.7$ % |
|---|---|---|---|---|---|---|
| All-cause mortality | 398 (9.7 %) | Unadjusted | | 0.92 (0.68–1.25) | 1.22 (0.91–1.63) | 1.77 (1.35–2.30) |
| | | Adjusted for age and sex | 1.0 (ref.) | 0.93 (0.69–1.26) | 1.25 (0.93–1.68) | 1.69 (1.30–2.21) |
| | | Full model | | 0.94 (0.67–1.30) | 1.31 (0.96–1.79) | 1.64 (1.22–2.22) |
| Type of event | All persons ($n = 4091$) | Model | $Q1$ (≤62 bpm) ($n = 1093$) $n = 45/4.1$ % | $Q2$ (63–≤ 69 bpm) ($n = 1072$) $n = 35/3.3$ % | $Q3$ (70–≤ 76 bpm) ($n = 925$) $n = 38/4.1$ % | $Q4$ (>76 bpm) ($n = 1001$) $n = 41/4.1$ % |
| Coronary events | 159 (3.9 %) | Unadjusted | | 0.79 (0.51–1.23) | 1.03 (0.67–1.58) | 1.05 (0.69–1.60) |
| | | Adjusted for age and sex | 1.0 (ref.) | 0.87 (0.56–1.36) | 1.15 (0.75–1.78) | 1.10 (0.72–1.68) |
| | | Full model | | 0.99 (0.62–1.58) | 1.10 (0.69–1.77) | 1.04 (0.65–1.66) |

Full model: age, sex, hypertension, current smoking, diabetes, BMI, known PAD, lipid-lowering medication, heart rate lowering medication, LDL-cholesterol, and CAC

### Risk per 5 and 10 bpm increase in resting heart rate

For the entire cohort, an increase of heart rate by 5 bpm was associated with increased all-cause mortality in unadjusted, age, and gender adjusted as well as traditional risk factor adjusted models [HR 1.10 (1.05–1.15), $p < 0.0001$, full model]. The risk for coronary events was not significantly increased [HR 1.01 (0.94–1.09), $p = 0.82$, full model]. In persons with heart rate lowering medication, the HR of all-cause mortality was 1.02 (0.92–1.13), $p = 0.70$, and for coronary events HR was 0.97 (0.82–1.14), $p = 0.71$ for an increase in heart rate by 5 bpm. In persons without heart rate lowering medication, the HR of all-cause mortality was 1.13 (1.07–1.20), $p < 0.0001$, and for coronary events HR was 1.02 (0.94–1.11), $p = 0.60$ for an increase in heart rate by 5 bpm.

To better understand the relationship between RHR and outcomes across the RHR spectrum, we also plotted events in 10 bpm RHR intervals (Fig. 3a–f). In the entire cohort—driven by persons without heart rate lowering medication—the relationship between RHR and all-cause mortality was non-linear, while we observed no association of RHR with coronary events. These results were confirmed when repeating the analyses for either sex.

## Discussion

The main finding of the present study is a positive and continuous association between RHR and mortality but not coronary events in a contemporary population-based prospective cohort. The study demonstrates that risk clearly increases at heart rates far below the common definition of tachycardia. These results support earlier studies that showed an association between RHR and mortality endpoints in cohorts free of CAD and were confirmed when repeating the analyses for either sex [5, 24]. Importantly, the observed association between baseline heart rate and risk is continuous and displays a J-shaped relation with a signal of increasing risk for heart rate below 60 bpm. Similar observations were found in other study populations indicating a non-linear relation between heart rate and mortality risk [17]. An increased risk in the lower heart rate range may reflect an indicator of underlying cardiovascular disease and may partially be associated with bradycardia related adverse events. Even though these findings represent epidemiologic data, the observation that risk may increase with low heart rate is supported by data from interventional studies. Recently, an interventional trial testing the prognostic importance of a pronounced heart rate reduction induced by ivabradine in a CHD population showed an increase in the incidence of the primary endpoint among patients with angina [14].

Early epidemiologic studies such as NHANES I or the Framingham study suggested an association between RHR and risk for coronary mortality [19, 25]. In our analysis RHR did not affect the risk for coronary events, a finding that is supported by contemporary studies investigating populations without underlying cardiovascular disease [13]. Data from the National FINRISK Study show a significant association between heart rate and risk associated with coronary heart disease. However, a fundamental reduction in the strength of the relationship was seen when

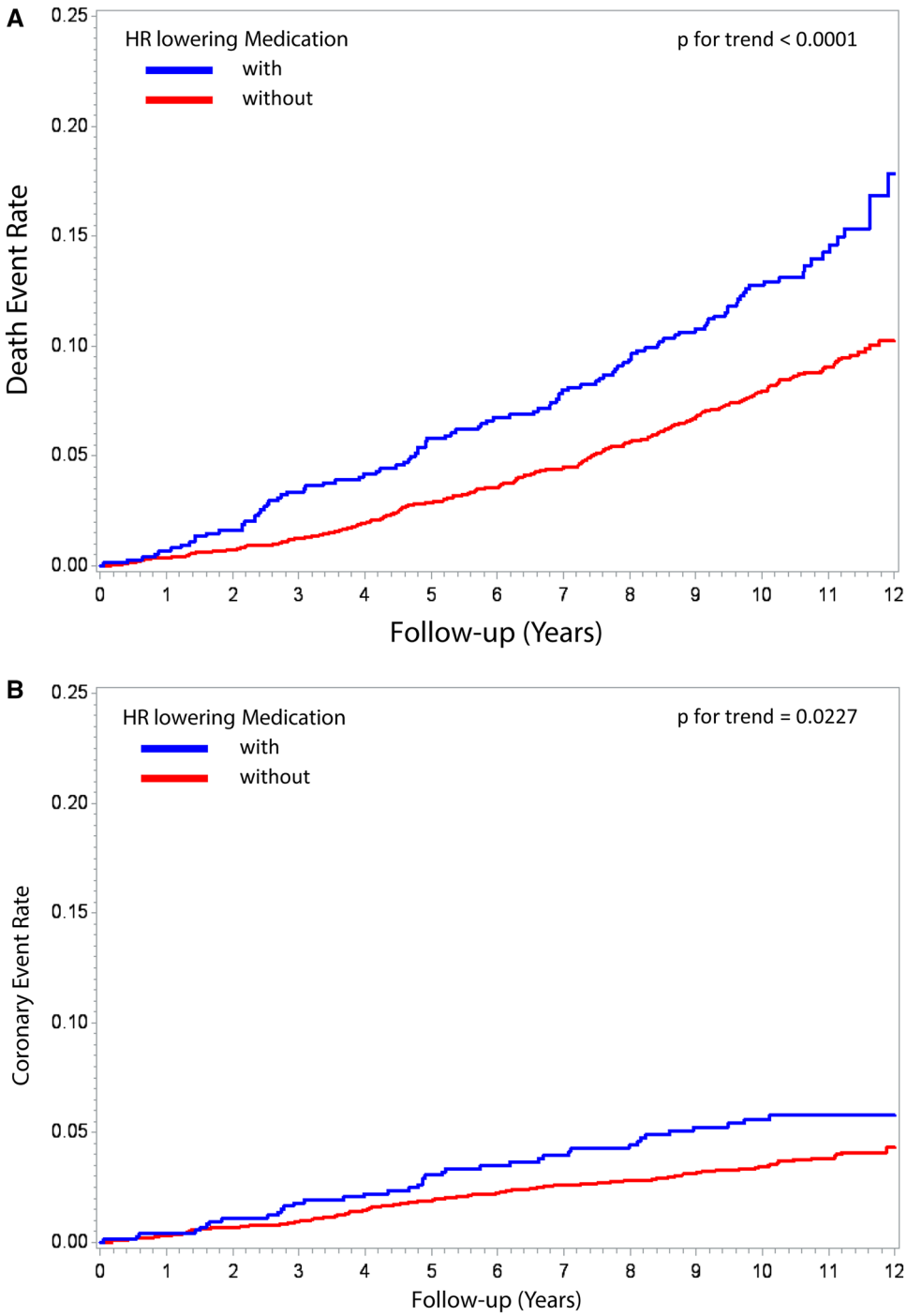



**Fig. 1** Kaplan–Meier time-to-event plots for all-cause mortality (**a**) and coronary events (**b**) in the subgroups of persons with heart rate lowering medication and persons without heart rate lowering medication

myocardial infarction was integrated in the analysis [5]. Interestingly even in high risk populations with clinically manifest atherosclerotic vascular disease, RHR was associated with increased risk for mortality but not for myocardial infarction or stroke [23, 26]. Furthermore, a targeted heart rate reduction did not affect coronary events and outcome in patients with stable coronary artery disease in an interventional trial [14]. Differing findings regarding coronary events may result from methodical differences concerning endpoint definition. To our knowledge, the Heinz Nixdorf RECALL study is the first and only study that included enzymatic methods [levels of creatine kinase (CK-MB), troponin T or I] or characteristic signs in resting 12-lead ECG to define a myocardial infarction event. All

**Table 3** Incidence of events and hazard ratios by heart rate quartile in individuals with heart rate lowering medication

| Type of event | All persons ($n = 743$) | Model | $Q1$ (≤62 bpm) ($n = 301$) $n = 40/13.3$ % | $Q2$ (63–≤ 69 bpm) ($n = 197$) $n = 26/13.2$ % | $Q3$ (70–≤ 76 bpm) ($n = 138$) $n = 22/15.9$ % | $Q4$ (>76 bpm) ($n = 107$) $n = 16/15.0$ % |
|---|---|---|---|---|---|---|
| All-cause mortality | 104 (14.0 %) | Unadjusted | | 0.99 (0.60–1.62) | 1.21 (0.72–2.03) | 1.21 (0.68–2.16) |
| | | Adjusted for age and sex | 1.0 (ref.) | 1.03 (0.63–1.70) | 1.24 (0.74–2.09) | 1.19 (0.67–2.13) |
| | | Full model | | 1.05 (0.60–1.83) | 1.38 (0.79–2.42) | 1.13 (0.58–2.21) |
| Type of event | All persons ($n = 743$) | Model | $Q1$ (≤62 bpm) ($n = 301$) $n = 18/6.0$ % | $Q2$ (63–≤ 69 bpm) ($n = 197$) $n = 9/4.6$ % | $Q3$ (70–≤ 76 bpm) ($n = 138$) $n = 7/5.1$ % | $Q4$ (>76 bpm) ($n = 107$) $n = 5/4.7$ % |
| Coronary events | 39 (5.3 %) | Unadjusted | | 0.77 (0.35–1.72) | 0.86 (0.36–2.06) | 0.83 (0.31–2.22) |
| | | Adjusted for age and sex | 1.0 (ref.) | 0.89 (0.40–1.99) | 0.99 (0.41–2.39) | 0.90 (0.33–2.42) |
| | | Full model | | n.a. | n.a. | n.a. |

Full model: age, sex, hypertension, active smoking, diabetes, BMI, known PAD, lipid-lowering medication, LDL-cholesterol, and CAC

*n.a* not applicable (power too low for full model)

**Table 4** Incidence of events and hazard ratios by heart rate quartile in individuals without heart rate lowering medication

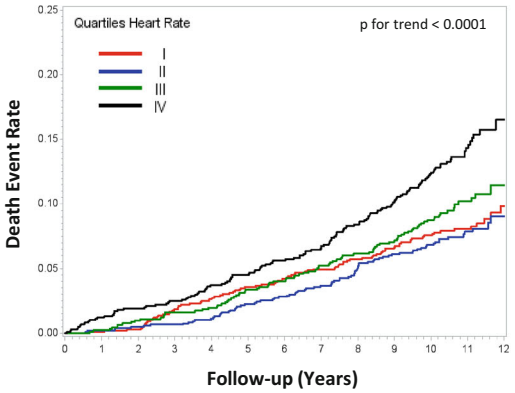
| Type of event | All persons ($n = 3348$) | Model | $Q1$ (≤62 bpm) ($n = 792$) $n = 50/6.3$ % | $Q2$ (63–≤ 69 bpm) ($n = 875$) $n = 55/6.3$ % | $Q3$ (70–≤ 76 bpm) ($n = 787$) $n = 68/8.6$ % | $Q4$ (>76 bpm) ($n = 894$) $n = 121/13.5$ % |
|---|---|---|---|---|---|---|
| All-cause mortality | 294 (8.8 %) | Unadjusted | | 1.01 (0.69–1.48) | 1.43 (0.99–2.06) | 2.30 (1.65–3.20) |
| | | Adjusted for age and sex | 1.0 | 0.99 (0.67–1.45) | 1.42 (0.98–2.04) | 2.09 (1.50–2.91) |
| | | Full Model | | 0.95 (0.63–1.43) | 1.39 (0.94–2.05) | 1.84 (1.28–2.65) |
| Type of event | All persons ($n = 3348$) | Model | $Q1$ (≤62 bpm) ($n = 792$) $n = 27/3.4$ % | $Q2$ (63–≤ 69 bpm) ($n = 875$) $n = 26/3.0$ % | $Q3$ (70–≤ 76 bpm) ($n = 787$) $n = 31/3.9$ % | $Q4$ (>76 bpm) ($n = 894$) $n = 36/4.0$ % |
| Coronary events | 120 (3.6 %) | Unadjusted | | 0.87 (0.51–1.50) | 1.21 (0.72–2.02) | 1.26 (0.77–2.08) |
| | | Adjusted for age and sex | 1.0 | 0.94 (0.55–1.61) | 1.32 (0.78–2.21) | 1.28 (0.78–2.12) |
| | | Full model | | 1.02 (0.57–1.80) | 1.24 (0.70–2.19) | 1.19 (0.69–2.06) |

Full model: age, sex, hypertension, active smoking, diabetes, BMI, known PAD, lipid–lowering medication, LDL-cholesterol, and CAC

comparable studies used ICD codes based on national registries or death certificates resulting in attenuated precision.

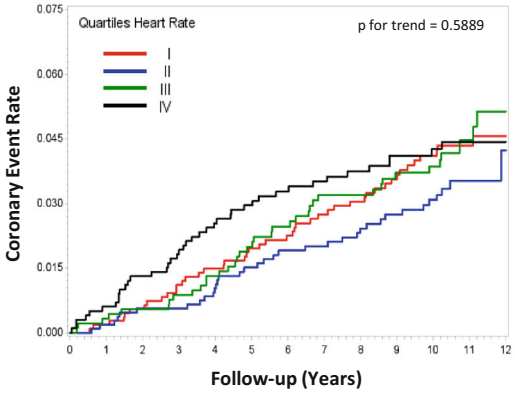
A considerable proportion of participants received heart rate lowering medication, which constitutes a fundamental part of several CV disease drug regimens. Consequently, we stratified risk analysis for individuals with and without such medication. Interestingly, the observed effect of heart rate on mortality risk was essentially driven by persons not taking heart rate lowering medication. Moreover, overall mortality risk and coronary event risk was higher in persons taking heart rate lowering medication. Our data suggest that persons with underlying CV disease—other than excluded known myocardial infarction, coronary revascularization, stroke, or atrial fibrillation—were the ones receiving heart rate lowering medication. It appears that such medication may attenuate risk, but not enough to achieve risk levels of otherwise healthy individuals. Hence, the effect of heart rate on mortality risk can especially be seen in low risk persons where risk is not predominantly driven by risk factors with a higher impact than that of heart rate. To the best of our knowledge, the present analysis is the first that analyzed risk in relation to heart rate lowering medication in the general population.

**A** Entire Cohort



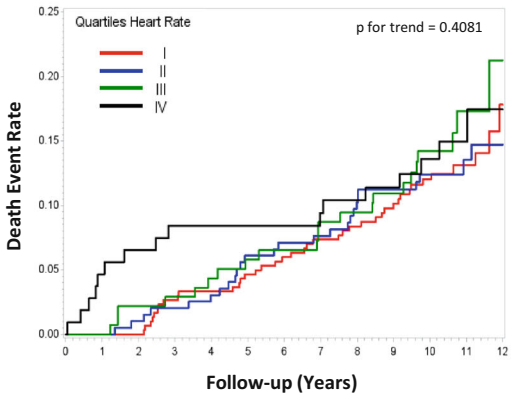

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Q1 | 1093 | 1090 | 1063 | 1037 | 1002 | 881 | 172 |
| Q2 | 1072 | 1067 | 1060 | 1024 | 982 | 868 | 135 |
| Q3 | 925 | 915 | 904 | 865 | 832 | 725 | 108 |
| Q4 | 1001 | 982 | 963 | 919 | 874 | 729 | 86 |

**D** Entire Cohort



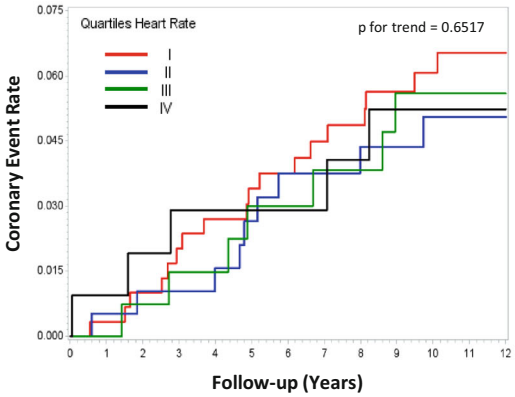

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Q1 | 1093 | 1081 | 1045 | 992 | 948 | 828 | 154 |
| Q2 | 1072 | 1058 | 1045 | 985 | 933 | 817 | 126 |
| Q3 | 925 | 907 | 889 | 812 | 764 | 658 | 97 |
| Q4 | 1001 | 971 | 943 | 863 | 801 | 657 | 79 |

**B** With HR Lowering Medication



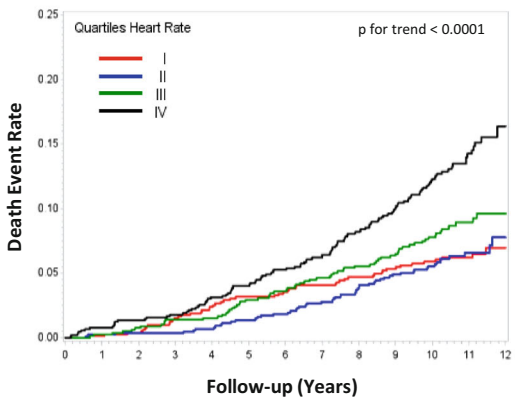

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Q1 | 301 | 301 | 291 | 279 | 264 | 222 | 39 |
| Q2 | 197 | 195 | 191 | 180 | 173 | 152 | 20 |
| Q3 | 138 | 135 | 132 | 128 | 123 | 104 | 15 |
| Q4 | 107 | 100 | 97 | 92 | 90 | 75 | 6 |

**E** With HR Lowering Medication



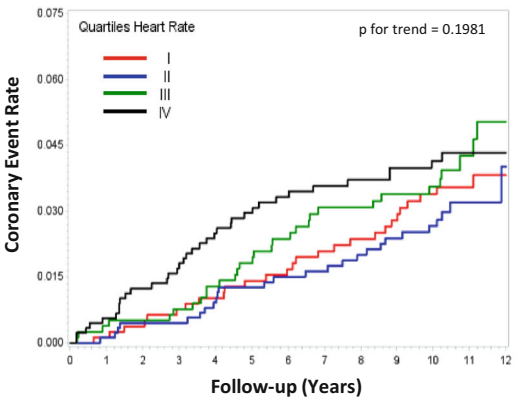

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Q1 | 301 | 297 | 285 | 265 | 248 | 209 | 35 |
| Q2 | 197 | 191 | 186 | 168 | 158 | 137 | 18 |
| Q3 | 138 | 134 | 131 | 119 | 111 | 92 | 14 |
| Q4 | 107 | 100 | 97 | 86 | 82 | 67 | 6 |

**C** Without HR lowering medication




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Q1 | 792 | 789 | 772 | 758 | 738 | 659 | 133 |
| Q2 | 875 | 872 | 869 | 844 | 809 | 716 | 115 |
| Q3 | 787 | 780 | 772 | 737 | 709 | 621 | 93 |
| Q4 | 894 | 882 | 866 | 827 | 784 | 654 | 80 |

**F** Without HR lowering medication




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Q1 | 792 | 784 | 760 | 727 | 700 | 619 | 119 |
| Q2 | 875 | 867 | 859 | 817 | 775 | 680 | 108 |
| Q3 | 787 | 773 | 758 | 693 | 653 | 566 | 83 |
| Q4 | 894 | 871 | 777 | 777 | 719 | 590 | 73 |

◀**Fig. 2** Kaplan–Meier time-to-event plots for all-cause mortality (**a**–**c**) and coronary events (**d**–**f**) in the prespecified subgroups (**a**, **d** entire cohort, **b**, **e** persons with heart rate lowering medication, **c**, **f** persons without heart rate lowering medication)

Findings from comparable studies would therefore be of great interest.

Despite a wealth of data from epidemiological and interventional studies regarding the relation between RHR

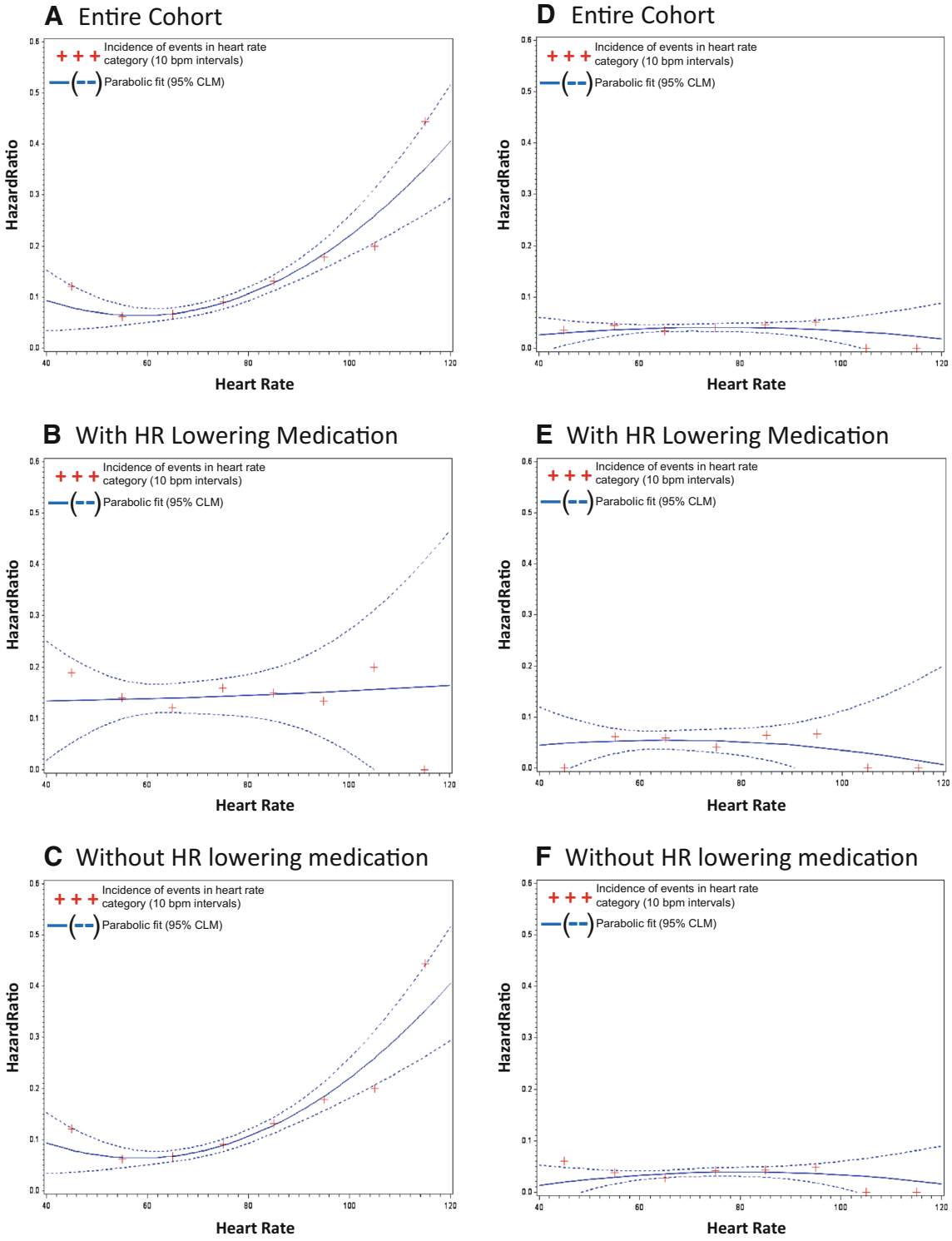



**Fig. 3** Relationship between heart rate as a continuous variable, all-cause mortality (**a**–**c**), and coronary events (**d**–**f**) as a result of modeling with parabolic fits in the prespecified subgroups [**a**, **d** entire cohort, **b**, **e** persons with heart rate lowering medication, **c**, **f** persons without heart rate lowering medication; incidence of events in heart rate category (10 bpm intervals), parabolic fit (95 % CLM)]

and cardiovascular risk, a distinct heart rate-threshold at which risk increases and the quantitative relation between heart rate increase and outcome has been debated. In patients with coronary artery disease and impaired left-ventricular function, elevated RHR of 70 bpm or greater increases cardiovascular mortality and the risk for coronary events [16]. In the Heinz Nixdorf RECALL study population, individuals with heart rates of 70 bpm or greater had an increased risk of all-cause mortality. Again, this risk was more pronounced in individuals without heart rate lowering medication. Whether RHR acts as a marker of underlying disease or may be seen as a risk factor independent of established cardiovascular risk factors has been a matter of debate. Here, our data show a relevant association between RHR and all-cause mortality after adjustment for common risk factors. Heart rate remained a prognosticator even after adjustment for atherosclerotic manifestations such as PAD and CAC.

In the HNR study population, increased RHR was associated with the presence of cardiovascular risk factors. Individuals with a high heart rate were more likely affected by hypertension and diabetes mellitus and showed higher LDL-C and triglyceride levels. Atherosclerotic manifestations (CAC and PAD) and higher CRP levels were more prevalent in high than in low heart rate groups. These relationships are consistent with previous studies that showed positive correlations between an unfavorable pattern of risk factors and heart rate [36]. The underlying mechanisms of such associations are not fully understood and conclusions about cause and effect remained speculative. Hypertension and insulin resistance may contribute to an autonomic imbalance (e.g. sympathetic overactivity) that causes increased RHR [30]. On the other hand, animal models such as stress-induced increase of heart rate suggest that cardiovascular structural alterations can be the symptom of increased heart rate [8]. Mechanistically, several potential links between RHR and cardiovascular mortality have been proposed. One of the most relevant seems to be an interference of increased heart rate with vascular integrity as experimental and clinical data suggest that sustained elevation of heart rate may contribute to the pathogenesis of vascular disease [9]. In animal studies, accelerated heart rate was associated with vascular oxidative stress and inflammation, endothelial dysfunction, acceleration of atherogenesis, and vascular stiffness [6, 7, 32]. In humans, high RHR was shown to be closely linked to systemic inflammation, arterial stiffness, and markers of endothelial dysfunction. Increased heart rate predisposed to coronary plaque rupture [20, 31, 37]. Earlier analyses of the present cohort characterized RHR as an independent predictor of coronary artery calcium (CAC), a measure of coronary plaque burden [28]. However, although there is ample experimental evidence for direct vascular effects, the potential weight for clinical practice remains elusive since interventional clinical studies investigating effects of a targeted heart rate reduction on vascular endpoints are lacking to date. Even with regard to large randomized controlled trials which assessed the prognostic role of heart rate reduction in patients with established coronary heart disease transformation of experimental findings into clinical impact still remains a future target [14, 15].

A possible limitation of the present study is the restricted number of HR recordings that was limited to a single measurement. As heart rate is susceptible to a large number of influences and effectors multiple recordings collected at shorter intervals could have shown a longitudinal course of RHR and may have increased the association between RHR and risk for events.

## Conclusion

In this prospective study of an unselected general population without known CAD, elevated heart rate is an independent marker of subsequent death. The relationship between RHR and risk was graded and persisted after adjustment for risk factors, PAD, and CAC. The association was particularly pronounced in individuals without heart rate lowering medication. RHR is easily and widely available and can therefore be used as a prognostic marker in the general population. Interventional trials are warranted to test whether heart rate can be used not only as a powerful marker of risk but also as a treatment target in populations with and without known cardiovascular disease.

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**Compliance with ethical standards**

**Conflict of interest** None of the authors have declared a conflict of interest or financial disclosures related to the study. Statistical analysis was supported by a grant by SERVIER Deutschland GmbH Germany.

**Ethical standards** All patients gave informed consent prior to their inclusion in the study; the study protocol conformed to the ethical guidelines of the 1964 Declaration of Helsinki and its later amendments.

## References


1. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R (1990) Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 15:827–832 **(0735-1097(90)90282-T [pii])**
2. Böhm M, Borer J, Ford I, Gonzalez-Juanatey JR, Komajda M, Lopez-Sendon J, Reil JC, Swedberg K, Tavazzi L (2013) Heart rate at baseline influences the effect of ivabradine on cardiovascular outcomes in chronic heart failure: analysis from the SHIFT study. Clin Res Cardiol 102:11–22. doi:10.1007/s00392-012-0467-8
3. Böhm M, Reil JC (2013) Heart rate: surrogate or target in the management of heart failure? Heart 99:72–75. doi:10.1136/heartjnl-2012-302301
4. Böhm M, Swedberg K, Komajda M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L (2010) 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 376:886–894. doi:10.1016/S0140-6736(10)61259-7
5. Cooney MT, Vartiainen E, Laatikainen T, Juolevi A, Dudina A, Graham IM (2010) Elevated resting heart rate is an independent risk factor for cardiovascular disease in healthy men and women. Am Heart J 159(612–619):e613. doi:10.1016/j.ahj.2009.12.029
6. Custodis F, Baumhäkel M, Schlimmer N, List F, Gensch C, Böhm M, Laufs U (2008) Heart rate reduction by ivabradine reduces oxidative stress, improves endothelial function, and prevents atherosclerosis in apolipoprotein E-deficient mice. Circulation 117:2377–2387. doi:10.1161/CIRCULATIONAHA.107.746537
7. Custodis F, Fries P, Müller A, Stamm C, Grube M, Kroemer HK, Böhm M, Laufs U (2012) Heart rate reduction by ivabradine improves aortic compliance in apolipoprotein E-deficient mice. J Vasc Res 49:432–440. doi:10.1159/000339547
8. Custodis F, Gertz K, Balkaya M, Prinz V, Mathar I, Stamm C, Kronenberg G, Kazakov A, Freichel M, Böhm M, Endres M, Laufs U (2011) Heart rate contributes to the vascular effects of chronic mental stress: effects on endothelial function and ischemic brain injury in mice. Stroke 42:1742–1749. doi:10.1161/STROKEAHA.110.598607
9. Custodis F, Schirmer SH, Baumhäkel M, Heusch G, Böhm M, Laufs U (2010) Vascular pathophysiology in response to increased heart rate. J Am Coll Cardiol 56:1973–1983. doi:10.1016/j.jacc.2010.09.014
10. Diaz A, Bourassa MG, Guertin MC, Tardif JC (2005) Long-term prognostic value of resting heart rate in patients with suspected or proven coronary artery disease. Eur Heart J 26:967–974. doi:10.1093/eurheartj/ehi190
11. Erbel R, Möhlenkamp S, Lehmann N, Schmermund A, Moebus S, Stang A, Grönemeyer D, Seibel R, Mann K, Volbracht L, Dragano N, Siegrist J, Jöckel KH (2008) Sex related cardiovascular risk stratification based on quantification of atherosclerosis and inflammation. Atherosclerosis 197:662–672. doi:10.1016/j.atherosclerosis.2007.02.031
12. Erbel R, Möhlenkamp S, Moebus S, Schmermund A, Lehmann N, Stang A, Dragano N, Grönemeyer D, Seibel R, Kälsch H, Bröcker-Preuss M, Mann K, Siegrist J, Jöckel KH (2010) Coronary risk stratification, discrimination, and reclassification improvement based on quantification of subclinical coronary atherosclerosis: the Heinz Nixdorf Recall study. J Am Coll Cardiol 56:1397–1406. doi:10.1016/j.jacc.2010.06.030
13. Floyd JS, Sitlani CM, Wiggins KL, Wallace E, Suchy-Dicey A, Abbasi SA, Carnethon MR, Siscovick DS, Sotoodehnia N, Heckbert SR, McKnight B, Rice KM, Psaty BM (2015) Variation in resting heart rate over 4 years and the risks of myocardial infarction and death among older adults. Heart 101:132–138. doi:10.1136/heartjnl-2014-306046
14. Fox K, Ford I, Steg PG, Tardif JC, Tendera M, Ferrari R, Investigators S (2014) Ivabradine in stable coronary artery disease without clinical heart failure. N Engl J Med 371:1091–1099. doi:10.1056/NEJMoa1406430
15. Fox K, Ford I, Steg PG, Tendera M, Ferrari R (2008) Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. Lancet 372:807–816. doi:10.1016/S0140-6736(08)61170-8
16. Fox K, Ford I, Steg PG, Tendera M, Robertson M, Ferrari R (2008) Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a subgroup analysis of a randomised controlled trial. Lancet 372:817–821. doi:10.1016/S0140-6736(08)61171-X
17. Fujiura Y, Adachi H, Tsuruta M, Jacobs DR Jr, Hirai Y, Imaizumi T (2001) Heart rate and mortality in a Japanese general population: an 18-year follow-up study. J Clin Epidemiol 54:495–500
18. Gillman MW, Kannel WB, Belanger A, D'Agostino RB (1993) Influence of heart rate on mortality among persons with hypertension: the Framingham Study. Am Heart J 125:1148–1154
19. Gillum RF, Makuc DM, Feldman JJ (1991) Pulse rate, coronary heart disease, and death: the NHANES I Epidemiologic Follow-up Study. Am Heart J 121:172–177
20. Heidland UE, Strauer BE (2001) Left ventricular muscle mass and elevated heart rate are associated with coronary plaque disruption. Circulation 104:1477–1482
21. Heusch G (2008) Heart rate in the pathophysiology of coronary blood flow and myocardial ischaemia: benefit from selective bradycardic agents. Br J Pharmacol 153:1589–1601. doi:10.1038/sj.bjp.0707673
22. Hjalmarson A, Gilpin EA, Kjekshus J, Schieman G, Nicod P, Henning H, Ross J Jr (1990) Influence of heart rate on mortality after acute myocardial infarction. Am J Cardiol 65:547–553 **(0002-9149(90)91029-6 [pii])**
23. Ho JE, Bittner V, Demicco DA, Breazna A, Deedwania PC, Waters DD (2010) Usefulness of heart rate at rest as a predictor of mortality, hospitalization for heart failure, myocardial infarction, and stroke in patients with stable coronary heart disease [data from the treating to new targets (TNT) trial]. Am J Cardiol 105:905–911. doi:10.1016/j.amjcard.2009.11.035
24. Jouven X, Empana JP, Schwartz PJ, Desnos M, Courbon D, Ducimetiere P (2005) Heart-rate profile during exercise as a predictor of sudden death. N Engl J Med 352:1951–1958. doi:10.1056/NEJMoa043012
25. Kannel WB, Kannel C, Paffenbarger RS Jr, Cupples LA (1987) Heart rate and cardiovascular mortality: the Framingham Study. Am Heart J 113:1489–1494
26. Lonn EM, Rambihar S, Gao P, Custodis F, Sliwa K, Teo KK, Yusuf S, Böhm M (2014) Heart rate is associated with increased risk of major cardiovascular events, cardiovascular and all-cause

death in patients with stable chronic cardiovascular disease: an analysis of ONTARGET/TRANSCEND. Clin Res Cardiol 103:149–159. doi:10.1007/s00392-013-0644-4

27. Möhlenkamp S, Lehmann N, Moebus S, Schmermund A, Dragano N, Stang A, Siegrist J, Mann K, Jöckel KH, Erbel R, Heinz Nixdorf Recall Study I (2011) Quantification of coronary atherosclerosis and inflammation to predict coronary events and all-cause mortality. J Am Coll Cardiol 57:1455–1464. doi:10.1016/j.jacc.2010.10
28. Möhlenkamp S, Lehmann N, Schmermund A, Roggenbuck U, Moebus S, Dragano N, Bauer M, Kälsch H, Hoffmann B, Stang A, Bröcker-Preuss M, Böhm M, Mann K, Jöckel KH, Erbel R, Heinz Nixdorf Recall Study I (2009) Association of exercise capacity and the heart rate profile during exercise stress testing with subclinical coronary atherosclerosis: data from the Heinz Nixdorf Recall study. Clin Res Cardiol 98:665–676. doi:10.1007/s00392-009-0054-9
29. Möhlenkamp S, Schmermund A, Lehmann N, Roggenbuck U, Dragano N, Stang A, Moebus S, Beck EM, Schluter C, Sack S, Meinertz T, Taylor A, Jöckel KH, Erbel R (2008) Subclinical coronary atherosclerosis and resting ECG abnormalities in an unselected general population. Atherosclerosis 196:786–794. doi:10.1016/j.atherosclerosis.2007.01.012
30. Palatini P, Casiglia E, Pauletto P, Staessen J, Kaciroti N, Julius S (1997) Relationship of tachycardia with high blood pressure and metabolic abnormalities: a study with mixture analysis in three populations. Hypertension 30:1267–1273
31. Rogowski O, Shapira I, Shirom A, Melamed S, Toker S, Berliner S (2007) Heart rate and microinflammation in men: a relevant atherothrombotic link. Heart 93:940–944. doi:10.1136/hrt.2006.101949
32. Schirmer SH, Degen A, Baumhäkel M, Custodis F, Schuh L, Kohlhaas M, Friedrich E, Bahlmann F, Kappl R, Maack C, Böhm M, Laufs U (2012) Heart-rate reduction by If-channel inhibition with ivabradine restores collateral artery growth in hypercholesterolemic atherosclerosis. Eur Heart J 33:1223–1231. doi:10.1093/eurheartj/ehr255
33. Schmermund A, Möhlenkamp S, Berenbein S, Pump H, Moebus S, Roggenbuck U, Stang A, Seibel R, Grönemeyer D, Jöckel KH, Erbel R (2006) Population-based assessment of subclinical coronary atherosclerosis using electron-beam computed tomography. Atherosclerosis 185:177–182. doi:10.1016/j.atherosclerosis.2005.06.003
34. Schmermund A, Möhlenkamp S, Stang A, Grönemeyer D, Seibel R, Hirche H, Mann K, Siffert W, Lauterbach K, Siegrist J, Jöckel KH, Erbel R (2002) Assessment of clinically silent atherosclerotic disease and established and novel risk factors for predicting myocardial infarction and cardiac death in healthy middle-aged subjects: rationale and design of the Heinz Nixdorf RECALL Study. Risk factors, evaluation of coronary calcium and lifestyle. Am Heart J 144:212–218 **(S0002870302000698 [pii])**
35. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L (2010) Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet 376:875–885. doi:10.1016/S0140-6736(10)61198-1
36. Tverdal A, Hjellvik V, Selmer R (2008) Heart rate and mortality from cardiovascular causes: a 12 year follow-up study of 379,843 men and women aged 40–45 years. Eur Heart J 29:2772–2781. doi:10.1093/eurheartj/ehn435
37. Whelton SP, Blankstein R, Al-Mallah MH, Lima JA, Bluemke DA, Hundley WG, Polak JF, Blumenthal RS, Nasir K, Blaha MJ (2013) Association of resting heart rate with carotid and aortic arterial stiffness: multi-ethnic study of atherosclerosis. Hypertension 62:477–484. doi:10.1161/HYPERTENSIONAHA.113.01605