Clinically recorded heart rate and incidence of 12 coronary, cardiac, cerebrovascular diseases and mortality in 233,970 men and women: a linked electronic health record study

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Abstract

Background*:* In healthy population cohorts, resting heart rate above 90bpm is associated with mortality from coronary heart disease (CHD) but it is not clear whether associations are present at lower heart rates or whether these associations differ between women.

Methods: Linked electronic health records from primary care, hospitalisations, myocardial infarction, and cause-specific mortality records in UK were used to assess associations between RHR and 12 fatal and non-fatal coronary, cardiac, cerebral and peripheral vascular CVDs and death using Cox proportional hazard models.

Results: Among 233,970 patients, 29,690 fatal and non-fatal events occurred. Fully adjusted models showed that RHR was not associated in men or women with cerebrovascular events. In men a RHR 70-79bpm (29.1% of all men) vs <60bpm was associated with increased risk of heart failure (HR=1.65 (95% CI: 1.26-2.16)), unheralded coronary death (HR=1.65 (95% CI: 1.13-2.41)), total cardiovascular events (HR=1.22 (95% CI: 1.15-1.28)) and all-cause mortality (HR=1.39 (95% CI: 1.22-1.58)). Women with a higher RHR level of 80-89bpm vs 60bpm had higher risk of total CVD events (HR=1.17 (95% CI: 1.07-1.24)) and all-cause mortality (HR=1.21 (95% CI: 1.07-1.35)) compared to RHR <60bpm. The risk was also present at higher heart rates (>90) for HF and sudden cardiac death.

Conclusions*:* A clinically recorded RHR in the general population is specifically associated with the incidence of certain major CVDs and death with the risk starting at lower RHR levels in men compared to women. Further research is required to evaluate whether interventions to lower RHR are warranted to prevent disease.
The study is registered at: clinicaltrials.gov (ID: NCT01947361)

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Introduction

Heart rate is a biomarker, increasingly recorded by people monitoring their own health with mobile devices and phone applications and an easily accessible routinely collected clinical marker in general practice (1-3). In epidemiological studies conducted under conditions tailored for research purposes, resting heart rate above 90bpm was clearly associated with mortality from coronary heart disease (CHD)(4) and all-causes (4-8), but have not established thresholds (for public health education or clinical practice) defining a "normal" heart rate at which risk of cardiovascular events is at its lowest. About a third of the adult population has a resting heart rate measured in clinical practice of 70-79 beats per minute, yet reliable estimates of risk at this level are lacking.

Currently, there is a lack of large scale population based studies of clinically recorded resting heart rate and it is not known whether such records replicate findings from cohorts in which heart rate is measured under research conditions (9). Furthermore, little is known about the specificity of the associations between clinical resting heart rate and the incidence of specific CVDs with the majority of studies examining aggregated cardiovascular outcomes (4, 10) (**Table S1 (**in Supplement)). It is well known that women have higher resting heart rates than men (7, 11), but there is a lack of sufficiently large studies powered to reliably detect sex differences.

The objectives therefore of our research were i) to determine the extent to which heart rate measured in clinical practice is associated with the incidence of 12 different cardiac, coronary, cerebrovascular and peripheral vascular diseases; ii) to identify potential differences in associations between women and men; and iii) to determine whether there is evidence of a threshold in risk and whether this risk extends into lower heart rate ranges. We used large scale, population based linked primary-hospital care electronic health records (EHRs) in the CALIBER (ClinicAL disease research using LInked Bespoke studies and EHRs) resource (12), We have previously demonstrated the validity of these data for a wide range of cardiovascular risk factors (age, and sex (13), systolic and diastolic blood pressure (14), and smoking(15)) across a wide range of incident CVDs (13-15).

Methods

Data resource

CALIBER links patient records from four different data sources: Primary care (Clinical Practice Research Database (CPRD)(16), the Myocardial Ischaemia National Audit Project registry (MINAP)(17), Hospital Episodes Statistics (HES)(18), and the Office for National Statistics (ONS)(19). CPRD data were used to obtain heart rate measurements, demographic variables and other risk factors. CPRD patients are representative of the UK population in terms of sex, age, ethnicity (20) and overall mortality (21) and have been validated for

epidemiological research (22). A description of the CALIBER approach and phenotyping algorithms combining Read, ICD-10, drug and procedure codes to define risk factors and endpoints are available at http://www.caliberresearch.org/portal/.

Study Population and heart rate

An open cohort of 233,970 people was drawn from registrants between January 1997 and March 2010 with 225 primary care practices who consented to data linkage (**Figure S1)**. We included people aged ≥30 years at study entry ('index date'), with ≥1 year registration prior to the index date, no prior diagnosis of CVD and with at least one recorded heart rate measurement. Heart rate was prospectively recorded by general practice staff during consultations. Although the method of measurement is not recorded in the EHR, 82.6% of people with a heart rate record had a blood pressure measurement the same day, suggesting that a large proportion of heart rate measurements were obtained using an automated blood pressure device. The distributions of heart rate measured on the same and different dates as blood pressure is presented in **Fig S2**. Follow-up started from the date of their first heart rate measurement. Participants were censored on the earliest of the following dates: leaving the practice, last submission of data, death, or endpoint occurrence.

Cardiovascular risk factors

Information on cardiovascular risk factors was obtained from primary care, as recorded during consultations in primary care. Identical to previous reports we defined baseline cardiovascular risk factors using the most recent measurement (or prescription) recorded in CPRD up to one year before or on the date of study entry. Socioeconomic status was derived from the ONS using the Index of Multiple Deprivation (IMD) 2007 (23). It was divided into five categories (quintiles), the 1st quintile corresponding to the least deprived and the 5th quintile to the most deprived groups.

Incident cardiovascular diseases

We defined 12 CVDs identical to our previous reports (13, 14) using the four data sources to define first occurrence of non-fatal or fatal CVDs. Additional composite endpoints analysed were total CVD events, CVD deaths and all-cause mortality. Diagnoses were identified using codes from the International Classification of Diseases 10th Revision (ICD 10) for the hospital data (HES) and mortality data (ONS), from Read Codes for primary care data and bespoke variables in the ACS registry (MINAP).

Statistical Analysis

We analysed heart rate in categories (<60, 60-69, 70-79, 80-89, >90bpm) and used<60bpm as the reference level. Additionally, to explore whether digit preference might affect the results, we divided it into quintiles (30-65 bpm, 66-72 bpm, 73-79 bpm, 80-87 bpm, 88-150bpm). The association between

heart rate and each disease was assessed using Cox proportional hazard models, adjusted for baseline age (classified by sex) as the first step and then for established cardiovascular risk factors (age, sex, social deprivation, smoking, systolic blood pressure, BP lowering medication, total cholesterol, high-density lipoprotein, low-density lipoprotein, type 2 diabetes and body mass index [BMI]) and used multiple chained equations when data missing at random (S3). Sex specific estimates are reported due to evidence of interaction with sex. Models were stratified by primary care practice. Separate analyses excluding participants prescribed beta-blockers at baseline and similarly for Ca-channel blockers was carried out. Further analysis was done using as heart rate reference level the 70-79 bpm range (that is the level with the highest frequency of observations), and the heart rate of people with repeated heart rate measurements prior to their baseline measurement. To assess the shape of association between heart rate and 4 specific CVD endpoints in men and women, we used restricted cubic splines with 3 knots and the reference value of 60bpm. Statistical analyses were performed using Stata statistical software (StataSe v13 and R version 3.0.3).

Results

Baseline characteristics

We included 233,970 patients (58% women) with heart rate measurements available at baseline with mean (SD) heart rate in men 74.6bpm (14.5) and in

women 77.9bpm (14.0). There were 28,381 fatal and non-fatal incident CV events during 641,843.5 person-years of follow-up, (mean follow-up 3.26 years). **Table 1** shows that higher resting heart rates at baseline were associated with female sex, social deprivation, current smoking and type 2 diabetes and lower use of beta-blockers.

Specificity of associations for different incident CVDs

In age adjusted Cox analysis (**Table S4**) resting HR in men was associated with increased hazard of unheralded coronary death, heart failure, SCD, MI, peripheral arterial disease (PAD), cardiovascular mortality and all-cause mortality. These were stepwise relationships with no evidence of a threshold. The fully adjusted hazard ratios comparing a heart rate of >90bpm vs <60bpm were particularly strong for unheralded coronary death, SCD and heart failure (HF). Heart rate was not in adjusted analyses associated with the incidence of coronary diseases (stable angina, unstable angina, MI in women), cerebrovascular diseases (transient ischaemic attack, subarachnoid haemorrhage, ischaemic stroke, intracerebral haemorrhage), PAD or abdominal aortic aneurysm in men or women (**Figures 1 and 2).**

Associations in women compared to men

We found strong evidence in age adjusted (**Table S4**) and fully adjusted analyses that men (**Figure 1**) and women (**Figure 2**) differed in their heart rate-CVD associations, with associations being weaker or absent in women.

The fully adjusted hazard ratios comparing a heart rate of >90bpm vs <60bpm were particularly strong in men for unheralded coronary death (HR= 3.06 (95% CI: 2.07-4.52)), SCD (HR= 2.71 (95% CI: 1.90-3.83)) and heart failure (HF) (HR=3.26 (95% CI: 2.48-4.30)) whereas these associations were attenuated or not present in women (**Figures 1 and 2**). Interactions with sex were significant for stable angina, heart failure, unheralded coronary death, PAD, TIA, CVD death, total CVD events and all-cause mortality (**Fig 1, Table S4**). For stable angina, in women only heart rate above 60bpm was associated with lower risks.

A clinical heart rate of 70-79bpm in men (29.1% of all men) vs <60bpm showed an increased risk in adjusted analyses of incident heart failure (HR=1.65 (95% CI: 1.26-2.16)), unheralded coronary death (HR=1.65 (95% CI: 1.13-2.41)) and PAD (1.45 (95% CI: 1.06-1.99)), total cardiovascular events (HR=1.22 (95% CI: 1.15-1.28)) and all-cause mortality (HR=1.39 (95% CI: 1.22-1.58)) (**Fig 1**). In women, heart rates of 70-79bpm (31% of all women) were not associated with any disease endpoint. Women with heart rates of 80-89bpm had higher total CVD events (HR=1.17 (95% CI: 1.07-1.24)) and all-cause mortality (HR=1.21 (95% CI: 1.07-1.35)) (**Fig 2**).

The shapes of the associations (**Fig 3**) further highlight these important differences, the hazard of unheralded coronary death and heart failure

increasing progressively, starting from higher heart rates in women compared to men.

Sensitivity analyses

Confining analyses to those men not prescribed beta-blockers showed consistent associations with heart rate 70-79bpm vs <60bpm and increased risk of incident heart failure (HR=1.61 (95% CI: 1.04-2.48)) and unheralded coronary death (HR=2.87 (95% CI: 1.44-5.72)) (**Figures S3 and S4**). Similar findings were present when we excluded those prescribed calcium channel blockers at baseline (data not shown). Removing events occurring within the first year of follow up (as a means of addressing reverse causation) showed consistent associations in men for a heart rate of 70-79bpm for unheralded coronary death (HR=1.85 (95% CI: 1.18-2.89)) and heart failure (HR=1.79 (95% CI: 1.29-2.49)) (**Figures S5 and 6).** Analyses using repeated heart rate measurements did not alter the results (**Figures S7 and S8** 0respectively) nor when we divided heart rate in quintiles to assess digit preference (**Fig S9**).

Discussion

Main findings

This study demonstrates the specificity of the heart rate associations across a wide range of pathologically diverse incident CVDs in clinical practice. In the largest healthy population cohort studied, we show that men have stronger

associations with major cardiac diseases and mortality at lower heart rate levels than women. Our findings suggest that resting heart rate of 70-79bpm, seen in 29.1% of men could be associated with a CVD risk, whereas for women risk was largely confined to heart rates >80bpm.

Associations between heart rate and stroke and PAD

There was no association of heart rate with cerebrovascular manifestations or with abdominal aortic aneurysm. For PAD in men we found that risk was similarly increased at all heart rate levels above 60bpm, with no evidence of a dose response relation. In contrast to a previous study of Woodward et al.(9) that used a population from the Asia-Pacific region and identified strong associations between heart rate and specific cerebrovascular outcomes, although we found strong associations with HF, CVD death and all-cause mortality, we did not find a link between heart rate (per 10bpm increase starting above 65bpm) and cerebrovascular event even after replicating their design and correcting for dilution bias (**Table S5**). However, in populations with a different lifestyle background compared with Western populations, the role of HR in predicting death may be different (24). Our findings were consistent with a previous study of approximately 20,000 people in France that had a free medical examination provided by the national health care system. The level of HR did not predict stroke mortality in men nor in women regardless of the BP level (25).

Associations between heart rate and contractility and rhythm disorders

In men we found a stepwise graded association between higher RHR and higher incident HF consistent with previous reports (26, 27). In patients with established heart failure, randomized controlled trials of rate reduction with beta-blockers and with ivabradine, have reported improvement in mortality and hospitalization for subsequent heart failure events (RR=0.58, P<0.001) regardless of sex (28). The present study further examined unheralded coronary death events. These are fatal MI events in which there has been no prior CVD events diagnosed. This definition, important in public health terms, has never been studied previously in large scale cohorts.

We found an association between resting heart rate >90bpm and SCD, consistent with some previous reports (29-31) particularly prominent to events occurring within one year after the heart rate measurement. Associations of heart rate with SCD may also be consistent with experimental data showing diminishing ventricular fibrillation thresholds as heart rate is increased in stimulation studies and increasing thresholds when heart rate is lowered with ivabradine (32).

Taken together these observations may have mechanistic implications, suggesting that damages of the myocardium and the electrical stability of the conduction system are more associated with higher heart rate and its autonomic drivers than to disease progression in the arterial wall, despite data

relating increased heart rates to a prothrombotic state (33), endothelial dysfunction and accelerated atherosclerosis (34).

Evidence for different associations in men and women

We found strong evidence that heart rate has different associations with CVDs in women and men. We found significant sex differences for stable angina, HF, UCD, PAD and all-cause mortality. An increased hazard of HF that was greater in men and evident at heart rates >70bpm compared with women in whom the hazard was confined to heart rates >90bpm was also identified. Epidemiological studies on RHR and HF have shown weaker associations in women and in other smaller studies it was confined to men perhaps reflecting under-powering rather than a true sex difference (27).

Unlike heart failure risk that showed an increase starting at lower rates in men, SCD appeared increased when heart rate exceeded 90bpm in both men and women (29-31, 35, 36). This risk was still higher when restricted to those who were not on beta-blockers.

A "normal" heart rate of 70-79bpm, showed strong associations with UCD but only in men, whereas for women the risk was not present, implying a difference in disease pattern as was also showed by the shape of their associations in **Figure 3**. An increase in PAD risk present in men was found particularly for heart rates 80-89bpm. Women may not be at increased risk

due to haemodynamic resilience and a decrease in total peripheral resistance accompanying pregnancy (37).

Lack of associations between heart rate and MI

An important finding in the present study was that stepwise heart rate associations appeared to have some specificity to diseases of heart muscle and were not detected for atherothrombotic disorders, such as acute MI. In line with these findings, evidence from a clinical trial, the Study Assessing the Morbidity-Mortality Benefits of the If Inhibitor Ivabradine in Patients with Coronary Artery Disease (SIGNIFY) trial showed that heart rate reduction with ivabradine does not affect the risk of MI in patients with stable CAD (38). Mendelian randomization studies show that the genetic loci that are associated with heart rate are not associated with CAD or MI (39) questioning the causal relevance of heart rate in these diseases.

Stable angina

Despite the plausibility of an association between resting heart rate and the incidence of stable angina (beta blockers were developed because of the importance of rate control in myocardial oxygen demand) there has been a lack of large scale general population studies evaluating this question. We found that associations with stable angina were weak in men and in women there was some evidence that they were inverse (i.e. highest risk in lowest heart rate group). Restricting analyses to patients who underwent a Coronary

Artery Bypass Graft (to assess more severe angina), did not alter the results (data not shown).

Clinical implications

Our findings have three clinical implications. First they can be used to help establish normal values for men and women. Approximately 63% of men have heart rates >70bpm and are at risk of major CV events and death, whereas 43% of women that have heart rates >80bpm are at increased risk of total CVD events and all-cause mortality compared to heart rates <60bpm. These findings suggest that commonly considered as "normal" heart rate values particularly in men, cannot be considered harmless. Second, given the existence of behavioural (e.g. exercise) and pharmacological interventions which lower heart rate, our findings help specify the need for, and design of, endpoint trials that aim at lowering heart rate, as well as the revision of clinical guidelines in primary prevention for re-classification of HR as a greater risk factor for specific major outcomes such as heart failure. We found that men with RHR 70-79bpm that have not been prescribed beta-blockers medication were at increased risk of unheralded death and heart failure (**Fig S4**). Third, our findings suggest evaluation of the contribution that heart rate makes to risk prediction, taking account of specific outcomes of interest (e.g. HF) and recognizing that existing tools such as SCORE and Framingham include disorders with weak or absent associations with heart rate in their aggregate CVD endpoints (40).

Strengths and limitations

The main strength of this study lies in a population based large scale cohort of 233,970 men and women with clinical resolution of 12 different CVD presentations. It is the first study to use clinical heart rate measurements recorded using EHRs and therefore has intrinsic clinical relevance.

Our study has important limitations. Patients with a resting heart rate recorded within CALIBER were older than those without a heart rate record (see **Table S3).** However, the mean heart rate values that we observed of 74bpm in men and 77bpm in women were similar to those reported in general population samples based on resting heart rate measured under research conditions.(11) This supports the population representativeness of CALIBER heart rate recordings. To account for potential reverse causality effects, we excluded cardiovascular events that occurred within the first year of follow-up; with the exception of SCD associations were if anything stronger (**Figures S5, S6**). Additionally, electronic health records lack measures of physical activity or physical fitness, which may influence RHR levels.

Conclusions

Resting heart rate of 70-79bpm in men in the general population was associated with a higher risk of specific major CVDs and death, while in women, risks were mainly apparent at heart rates above 90bpm. Future

research should replicate our findings in other real world cohorts, while trials of interventions to lower heart rate for primary prevention are required.

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Competing interests

OA was funded by a PhD studentship from Servier laboratories. Servier had no access to the dataset and did not have a role in the data management, analysis or interpretation of the findings.

Contributors

OA, HH, MPR and AT conceived the study idea. OA, MPR and HH designed the study and OA performed the analysis and drafted the manuscript. All authors provided critical input in the writing of the manuscript, and read and approved the final version of manuscript.

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