Heart rate as a marker of incidence and prognosis of cardiovascular diseases in different populations: Evidence from Linked Electronic Health Records using the CALIBER platform and the 4C clinical cohort

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Declaration

I, Olga Archangelidi confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

Background:

Resting heart rate (RHR) is an easily accessible clinical parameter. In spite of the well-established association between resting heart rate and mortality in men and women, potential links between the marker and more specific cardiovascular diseases (CVDs) have not yet been explored. No previous research has used clinically collected RHR measurements from primary care settings. Normal RHR values have not been firmly established, although this is crucial in clinical practice and promotion of personalised health care.

Objectives:

The main objectives of this PhD are to:

- Examine the association between RHR and the onset of specific fatal and non-fatal cardiovascular diseases
- Examine the association between RHR and the prognosis of people with coronary artery disease (CAD)
- Investigate the association between RHR and the onset and prognosis of atrial fibrillation
- Describe the establishment of a consented clinical cohort resource of patients with CAD (4C)
- Compare electronic health records (EHR) processes and data with the 4C consented clinical cohort

Methods:

I used CALIBER, a linked electronic health records (EHR) platform that links primary and secondary care data, myocardial infarction disease registry and mortality data. Additionally, to establish a clinical cohort of people with CAD, I consented, recruited and collected anthropometric and biomarker data including RHR from patients attending chest pain clinics and angiography labs in London.

Results:

RHR was associated with myocardial and arrhythmic disorders, but not with coronary disease or peripheral arterial disease. An average RHR of >70bpm in the general population was associated with increased hazards of specific CVDs and mortality particularly in men and should not be considered as normal. Additionally, increased RHR was strongly associated with higher risk of cardiovascular outcomes not currently considered as primary endpoints in trials, such as heart failure. Finally, higher HR is strongly associated with atrial fibrillation in men, but not in women.

Conclusions:

EHR provides a wealth of primary care data, so far unexplored that give insight into associations of heart rate with CVDs in healthy and CAD populations. Average RHR of >70bpm in the general male population is associated with increased myocardial and arrhythmic disorders risk, but not with coronary disease. Disaggregation of CVDs into its constituent phenotypes contributes to our understanding of disease mechanisms with implications for clinical practice and interpretation of clinical trials.

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Abbreviations

AAA	Abdominal Aortic Aneurysm
BMI	Body Mass Index
BP	Blood Pressure
BPM	Beats Per Minute
CAD	Coronary Artery Disease
CHD	Coronary Heart Disease
CI	Confidence Interval
CPRD	Clinical Practice Research Datalink
CVD	Cardiovascular Disease
DM	Diabetes Mellitus
GP	General Practitioner
HDL	High density lipoprotein
HES	Hospital Episodes Statistics
HF	Heart Failure
ICD-10	International Classification of Diseases, 10th Edition
IHD	Ischaemic Heart Disease
IMD	Index of Multiple Deprivation
LDL	Low density lipoprotein
MI	Myocardial Infarction
MINAP	Myocardial Ischaemia National Audit Project registry
nSTEMI	Non-ST elevated Myocardial Infarction
ONS	Office of National Statistics
PAD	Peripheral Arterial Disease
RHR	Resting Heart Rate
SA	Stable Angina
SCD	Sudden Cardiac Death
STEMI	ST-elevated Myocardial Infarction
TIA	Transient Ischaemic Attack
UA	Unstable Angina
UCD	Unheralded Coronary Death

Overview and aims of this PhD

The aims of this PhD are to determine the association of resting heart rate (RHR) with:

- The onset of specific fatal and non-fatal cardiovascular diseases using a platform of linked electronic health records (CALIBER platform)
- The prognosis of people with coronary artery disease (CAD) using CALIBER data
- The onset and prognosis of atrial fibrillation using CALIBER data
- To describe the establishment of a consented clinical cohort of patients with CAD (4C) that records parameters such as quality of life, genetic variants and diagnostic imaging
- Compare linked electronic health records processes and data with the 4C consented clinical cohort

An overview of these objectives and the overall PhD structure is illustrated in **Figure 1** at the end of this section. Below, a more detailed description of each chapter is presented.

Heart rate mechanisms of action

Resting heart rate is an easily accessible clinical parameter increasingly recorded by healthy people monitoring personal fitness with mobile devices and phone applications. Heart rate affects the human system on many levels. It is an indirect metabolic marker and "decides" how much energy the body is consuming. It is controlled by the central nervous system (CNS) and an increase in heart rate is accompanied by autonomic imbalance (increase of sympathetic and a decrease of the parasympathetic activity). HR reduction also plays a pivotal role at the cellular level. Experimental studies demonstrate several vascular responses accounting for the detrimental effects of accelerated heart rate [1]. From vascular risk factors to endothelial function, coronary blood flow to atherosclerotic plaque development, plaque rupture, and myocardial infarction, heart rate affects several stages of the cardiovascular disease continuum[2-4] (**Chapter 1**).

Literature findings

In addition, a significant amount of epidemiological data support the predictive value of resting heart rate on several fatal and non-fatal, cardiovascular and no cardiovascular events[5]. The first data on the adverse role of heart rate was reported as early as 1945 by Levy et al. when they investigated the association between elevated heart rate and increased risk of mortality[3]. They found that cardiovascular death was much more frequent among subjects with transient tachycardia defined as persistent heart rate over 100 beats per minute (bpm), than it was among subjects with a heart rate of less than 100 bpm, however this association was not statistically significant. Since then, a large part of the literature devoted on heart rate has identified associations between the marker and the experience of cardiovascular diseases. These associations were observed in the general healthy population but also in hypertensive

patients as well as in patients with clinically evident coronary artery disease. [6-9] The most commonly investigated cardiovascular diseases (besides fatal cardiovascular events) examined by literature as having affected by increased heart rate are coronary diseases (stable angina, myocardial infarction), cardiac diseases such as heart failure, and vascular diseases particularly stroke.

Although Cardiovascular Diseases and more specifically coronary disease are not a single unified condition but rather a set of different syndromes under which a wide range of atherosclerotic and non-atherosclerotic mechanisms might lie, they are collapsed by literature and treated as pooled, unified phenomena with a common root. For this indicator, aggregate analytical methods and techniques have been proposed and implemented. Furthermore, clinical research so far has presented conflicting evidence regarding the types of CVDs that heart rate is associated with. To that effect, the mechanistic implications of increased heart rate and its underlying processes remain speculative. Furthermore, normal heart rate values have not been firmly established and as a result clinical practice underrates the use of heart rate as marker of diseases and collects it in non-routine patterns. Additionally, the prognostic value of heart rate in patients with stable coronary artery disease has drawn limited attention. A recent trial conducted in sCAD population with left ventricular ejection fraction >40% (SIGNIFY) on the prognosis of heart rate and future cardiovascular events, altered the so far established belief that heart rate is strongly correlated with coronary artery disease, which consequently questions the atherosclerotic nature of the underlying mechanism. All available literature has been presented in **Chapter 2**.

To address these issues of the lack of specificity of cardiovascular diseases in current literature, this PhD thesis sets out to investigate all the potential associations between heart rate and incidence and prognosis of a number of different cardiovascular diseases and cardiac endpoints such as different phenotypes of CAD (stable/unstable angina, Myocardial Infarction), cerebrovascular diseases (Ischaemic, subarachnoid stroke, Transient Ischaemic Attack), Abdominal Aortic Aneurysm, heart failure and mortality from sudden or unheralded death in different populations (healthy, sCAD, atrial fibrillation).

Data from CALIBER: A linked electronic health records platform

To explore the above aims, the linked electronic health records platform CALIBER will be used. CALIBER is a platform that links primary and secondary care, disease registry and mortality data. Heart rate data for the exploration of my research questions will be provided by primary care and this is the first time that heart rate is assessed using general population data from a primary care source (**Chapter 3**). Each association will be individually approached, while major attention will be given to identification of effect heterogeneity (i.e. potential differential responses of cardiovascular mechanisms to the different levels of heart rate values). This will

be of utmost importance since potential heterogeneity in responses to heart rate levels might indicate dissimilar underlying mechanisms of action.

Heart rate associations with CVDs in various populations

One of the aims of this thesis is to identify potential correlations of heart rate with initial presentations of different cardiovascular diseases (**Chapter 4**). Intrinsically, the term "initial presentation" refers to the first manifestation of these diseases (first symptomatic presentation), hence the analysis will exclusively include population free of any cardiovascular disease, or prior manifestation or history. This thesis will attempt to estimate the prognostic ability of heart rate on people with established stable coronary artery disease using linked electronic health records data (EHR) from the general primary and secondary care in UK and will allow for more precise investigations with higher resolution not only among different CVDs but also between the two genders (**Chapter 5**). Another crucial outcome that obtained particular attention by this thesis is the rhythm disorder atrial fibrillation. Associations of resting heart rate with the incidence and prognosis of atrial fibrillation have been examined in **Chapter 6**.

In addition to heart rate, a variety of risk factors established or suspected to contribute to cardiovascular disease mechanisms will be investigated with an emphasis on markers and environmental factors that potentially modify the effect of heart rate on the different cardiovascular endpoints, (e.g. smoking). Moreover, by treating heart rate as a marker with distinctive levels and not simply as a continuous factor (i.e. effect varying according to where in the heart rate distribution one is), heart rate levels previously considered as "normal" will be approached as an independent entity that requires further investigation. Statistical approaches that were applied to explore these associations mainly entail Cox proportional hazard models and imputation techniques to account for the large missing values proportion.

Establishment of a consented clinical cohort of people with CAD(4C cohort)- Comparison with EHR

Due to the nature of the linked electronic health records data nature, data on quality of life or genetic information was not available. Therefore, to gather this type of information I recruited patients to assemble a clinical consented cohort of people with suspected or established coronary artery disease and chest pain. More specifically, I approached, consented and collected anthropometric measurements, biomarkers and blood samples from patients attending the chest pain clinic and angiography lab of Heart hospital in London (**Chapter 7**). Later on, the two different approaches (i.e. using linked electronic health records routinely recorded by primary and secondary settings and consented cohort data have been compared and contrasted and will be presented in **Chapter 8**.

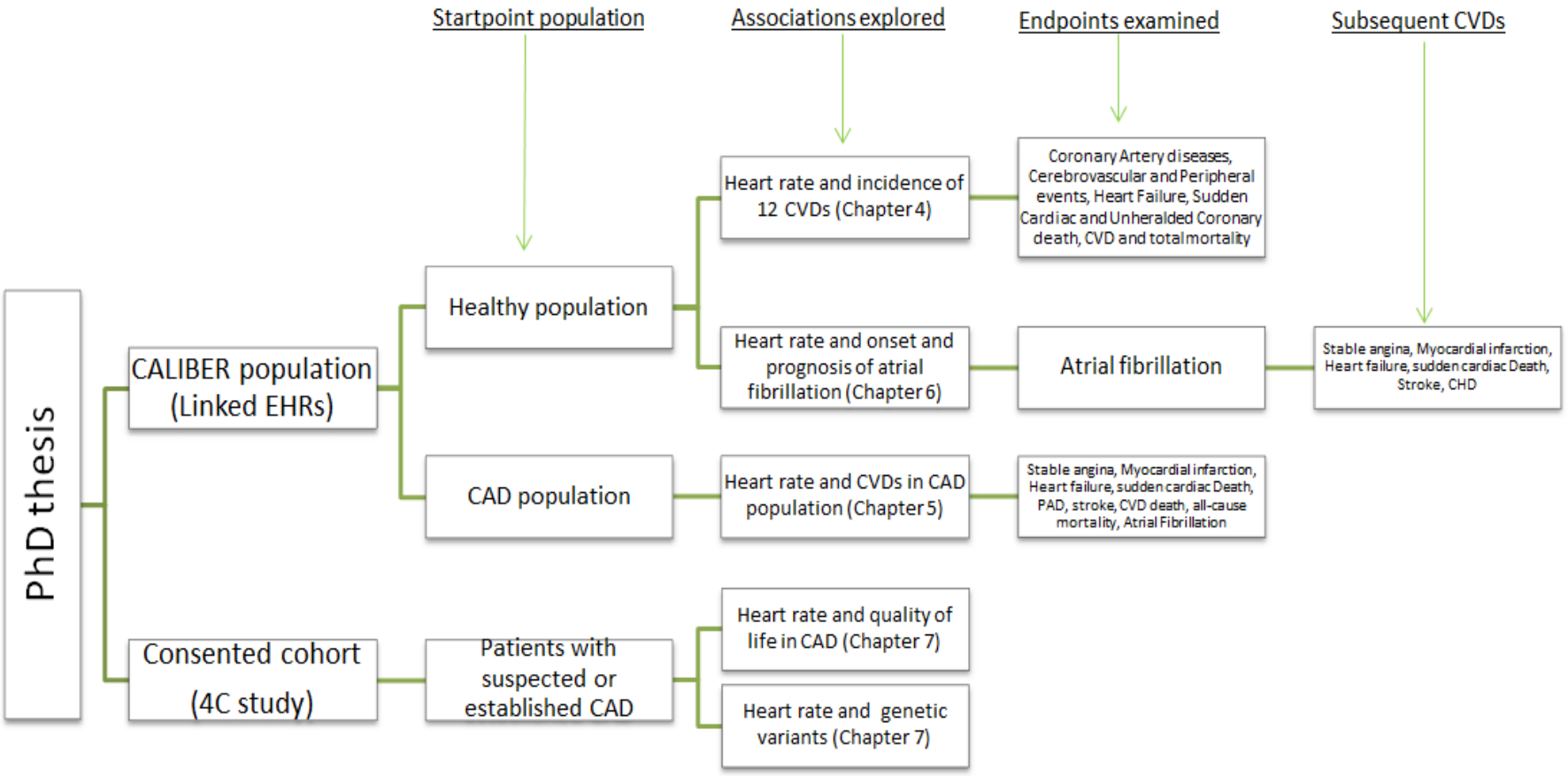


Figure 1. Flow chart of PhD individual studies examining associations of heart rate with CVDs

1. Heart rate measurement, physiology and trials of heart rate lowering

The purpose of this chapter is to describe the biomarker heart rate, from its definition, to the ways of measurement, normal limits and main mechanisms of effect on a cellular and pathophysiological level. Additionally, I will describe the main conditions and medications affecting heart rate with a focus on drug trials that aim at lowering heart rate and their implications in acute myocardial infarction, stable coronary artery diseased and heart failure populations after using beta-blockers, nondihydropyridine calcium antagonists and ivabradine.

1.1. Heart rate definition and normal values

1.1.1. Definition

Heart rate is the number of heartbeats per unit of time, typically expressed as beats per minute (bpm). Heart beats nearly 100,000 beats per day, or about 37 million beats per year and 3 billion in an average lifetime. Heart rate can vary as the body's need to absorb oxygen and excrete carbon dioxide changes, such as during physical exercise, sleep or illness. Because an individual has a constant blood volume, one of the physiological ways to deliver more oxygen to an organ is to increase heart rate to permit blood to pass by the organ more often. According to an interesting theory, yet to be proven, living beings are born with a predefined number of heart beats. Those with a particularly high heart rate use up their quota of energy more quickly and therefore have a lower life expectancy than those with a lower heart rate.[10, 11]

Heart rate in animals

Among mammals, it has been observed that the calculated number of heart beats in a lifetime is remarkably constant, despite a 40-fold difference in life expectancy. Life and energy available are equally important in evolution, and the intrinsic concept can be interpreted as the less energy needed, the longer the lifespan. Azbel stressed the concept that smaller animals have a higher heart rate and shorter lifespan than do larger animals, with a 35-fold difference in heart rate and a 20-fold difference in lifespan, and suggested that life expectancy is predetermined by the basic energetics of living cells and that the inverse relationship between longevity and heart rate reflects an epiphenomenon in which heart rate is a marker for or a determinant of metabolic rate and energetic needs [12].

1.1.2. Sinus rhythm and normal heart rate range

Sinus rhythm-definition and criteria

Sinus rhythm refers to any cardiac rhythm where depolarisation of the cardiac muscle begins at the sinus node[13] and is identified by the presence of correctly-oriented P waves on the

electrocardiogram (ECG). The term normal sinus rhythm (NSR) is sometimes used to denote a specific sinus rhythm where all other measurements on the ECG also fall within designated normal limits, giving rise to the characteristic appearance of the ECG when the electrical conduction system of the heart is functioning normally.[14] The ECG criteria used to define normal sinus rhythm are[14]:

- Normal heart rate (classically 60 to 100 beats per minute for an adult).
- Regular rhythm, with less than 0.16 second variation in the shortest and longest durations between successive P waves.
- The sinoatrial node should pace the heart – therefore, P waves must be round, all the same shape, and present before every QRS complex in a ratio of 1:1.
- Normal P wave axis (+15 to +75 degrees)
- Normal PR interval, QRS complex and QT interval.
- QRS complex positive in leads I, II, aVF and V3-V6, and negative in lead aVR

Abnormal sinus rhythm ranges

Other types of sinus rhythm include sinus tachycardia, sinus bradycardia.The current definition of sinus tachycardia is a heart rate >100 beats per minute (bpm), while sinus bradycardia is said to exist in the adult when the sinus node discharges at a rate <60 bpm.[15] In epidemiological studies in general populations or hypertensive cohorts, no increased risk of mortality was generally found for the lower extreme of heart rate. Only in the Chicago Heart Association Study were low heart rates (<60 bpm) related to an increase in sudden death.[16] However, in that study, subjects with bradyarrhythmias at ECG were not excluded, and, thus, the excess in mortality could be explained by subjects with bradycardia having important brady-arrhythmias. In the elderly subjects of the CASTEL study in which all individuals with brady-arrhythmias at standard ECG were excluded, a better prognosis in the subjects with heart rate <64 bpm than in those with heart rates between 64 and 80 bpm was found.[17] This suggests that there is not an increase in risk of mortality for the lower extreme of heart rate, provided the subject has been checked for possible sinoatrial dysfunction.

Is there a valid normal heart rate range?

The fundamental issue before examining the role of heart rate in the general population is to establish what we mean by "normal" heart rate values in humans. To begin with, resting heart rate (RHR) is defined as the heart rate when a person is awake, in a neutrally temperate environment, and has not undergone any recent exertion or stimulation, such as stress or even surprise. The heart rate in neonates is 130–140 bpm and falls throughout childhood to reach adult levels of 50–75 bpm, which is considered normal at the age of 20.[18]

Spodick et al[19] attempted to redefine the normal limits of heart rate on the basis of the results obtained in a population of subjects aged 50 to 80 years. By the addition of 2 SD to the mean

heart rate value, Spodick et al. found upper normal limits of 93 bpm for resting heart rate in the men and of 95 bpm in the women, which are above those found to be associated with an increased risk of mortality by most investigators.[20, 21] Moreover, the Spodick approach implies the existence of a normal distribution for heart rate in the general population and identified the level of 50 bpm as the lowest normal limit of heart rate, but there is no indication from the literature that a heart rate below that limit is really hazardous in the absence of sinoatrial dysfunction.

However, the normal range of a clinical variable can be established according to different criteria. For parameters such as most biochemical indexes, the standard deviation is calculated to identify the upper normal limit of the variable. This statistical approach does not appear suitable for clinical variables such as heart rate in which the relationship with the level of risk is a continuous one. Heart rate normal range was set arbitrarily when heart rate was not yet regarded as a risk factor for cardiovascular disease, probably with the main purpose of distinguishing between a disease state (fever, thyrotoxicosis, anemia, congestive heart failure, etc.) and a normal state.[22]

Heart rate variations

Heart rate is also supposed to continue to decrease with age, especially in the higher age groups, although there is a lack of consensus on this assumption. [23, 24]Some of the biological explanations for this phenomenon is fibrosis of the sinus atrial (SA) node, decreased adrenergic sensitivity and responsiveness to autonomic CV reflex. [25] It is widely accepted that resting heart rate is higher in women than in age matched men. [26] Of course, heart rate in humans changes in response to physiological conditions in order to maintain cardiac output and preserve perfusion to the vital organs. Other sources of variability will be described later on. Nevertheless, whether or not the aforementioned heart rate ranges are validated as normal and what are the acceptable heart rate above which the risk of adverse events increases, remains unclear.

Although there is no firm evidence that allow us to establish new normal limits for resting heart rate, it seems clear that the traditional 100 bpm value of tachycardia is not appropriate to define the threshold below which heart rate can be considered safe. The epidemiological studies that I will present in Chapter 2 clearly demonstrate that the association between heart rate and the cardiovascular mortality risk occurs for levels well below the 100 bpm value, while for specific cardiovascular endpoints this threshold has not been yet examined.

1.2. How to measure resting heart rate

1.2.1. Guidelines and standards

In view of the lack of evidence related to definition and standardised assessment of heart rate, a consensus meeting in Padova, Italy, sponsored by the European Society of Hypertension in 2005, reviewed and evaluated the available evidence to make recommendations for optimal methods of heart rate description. According to this Consensus Panel of the European Society of Hypertension, studies reporting heart rate data should also provide information related to a. resting period before measurement, b. environmental conditions, c. method of measurement, d. number of measurements, e. duration of measurement, f. body position, g. nature of the observer [27]. All the above parameters will be described in the present chapter.

1.2.2. Heart rate measurement in everyday life

The measurement of heart rate is used by medical professionals to assist in the diagnosis and tracking of medical conditions. It is also used by individuals, athletes or people trying to measure their fitness levels and are interested in monitoring their heart rate to gain maximum efficiency from their training, using various devices such as activity trackers (fitbits), smartphones, pedometers, accelerometers, etc. Wearable heart rate monitors for athletes were available in 1981.[28]Wearable fitness tracking devices, including wireless heart rate monitoring that integrated with commercial-grade fitness equipment found in gyms, were available in consumer-grade electronics by at least the early 2000s.

1.2.3. Preparation for heart rate measurement

Heart rate fluctuates during the day due to activity, stress, caffeine, medications, and other factors that might influence it. Heart rate at rest is the lowest that heart rate would go during the day. Ideally, one has to measure it when they first wake up in the morning, before any activity. In recent years, the international scientific societies have often focused on the methods of measurement of blood pressure, while no specific guidelines have been given for the assessment of heart rate. Whereas blood pressure is usually measured in the sitting position, there is no general agreement on the body position for heart rate measurement in the literature, with studies using sitting heart rate, and some other using supine heart rate. Venous pooling of the blood in the lower extremities while the patient is sitting decreases the sympatho-inhibition exerted by the cardiopulmonary baroreceptors.[29] Consequently, a higher heart rate is generally recorded in sitting than in supine patients with a 1–2bpm higher heart rate to be expected in the sitting posture. A period of 30 s appears to be sufficient to obtain a reliable estimate of heart rate because the duration of 30–40 cardiac cycles can be averaged out. In the majority of the studies available in the literature concerning heart rate measured in clinical settings and CVD risk, the heart rate was measured after a 5 min rest by the patient.[29] A period of rest is necessary for stabilization of the hemodynamic parameters. It is suggested that international guidelines should also be developed for the measurement of heart rate. This would allow a better between-

studies comparison and a stratification of the individual risk according to heart rate levels, giving a greater practical impact to this clinical parameter. [29]

In clinical practice, heart rate is measured using the palpation method, the more precise electrocardiogram (ECG) or automated blood pressure devices.

1.2.4. Methods of heart rate measurement

Palpation

One way for someone to determine heart rate is to manually take their pulse. Heart rate is measured by finding the pulse of the body and counting the number of times the heart beats in one minute. This pulse rate can be measured at any point on the body where an artery's pulsation is transmitted to the surface - often as it is compressed against an underlying structure like bone - by pressuring it with the index and middle finger.[29] The thumb should not be used for measuring another person's heart rate, as its strong pulse may interfere with discriminating the site of pulsation. The two most common locations used to take a pulse are at the radial artery in the wrist and the carotid artery in the neck. The radial artery is the easiest to use to check the heart rate. However, in emergency situations the most reliable arteries to measure heart rate are carotid arteries. This is important mainly in patients with atrial fibrillation, in whom heart beats are irregular and stroke volume is largely different from one beat to another. In those beats following a shorter diastolic interval left ventricle doesn't fill properly, stroke volume is lower and pulse wave is not strong enough to be detected by palpation on a distal artery like the radial artery.

Automated blood pressure device

Blood pressure devices (e.g. Omron device) help to monitor blood pressure and identify hypertension in everyday life and in clinical practice. It is an accurate technique in monitoring not only blood pressure but also heart rate and is able to detect irregular heartbeat. It is suggested by their manufacturers to carry out repeated home blood pressure readings throughout the day to obtain a representative picture of the blood pressure and heart rate in order to allow identification of average daytime measurements. An upper arm monitor is supposed to give more accurate readings. The alternative, the wrist monitor, needs more care as the cuff around the wrist has to be placed at the level of the heart to give an accurate reading. In that case, a computer chip changes the reading because heart rate and blood pressure measurements are different at the wrist compared to the upper arm.

ECG-RR interval

A more precise method of determining pulse involves the use of an electrocardiograph, or ECG (also abbreviated EKG). Continuous electrocardiograph monitoring of the heart is routinely done in many clinical settings, especially in critical care medicine. On an ECG the heart rate is measured using the R wave to R wave interval (RR interval). Additionally pulse oximeters

measure heart rate by pulse detection. Heart rate monitors allow measurements to be taken continuously and can be used during exercise when manual measurement would be difficult or impossible (such as when the hands are being used).[29] Various commercial heart rate monitors are also available. Some monitors, used during sport, consist of a chest strap with electrodes. The signal is transmitted to a wrist receiver for display. In several heart rate studies that will be presented in the next chapters of this PhD, the heart rate was measured from a standard electrocardiogram. Although this is an accurate method of computing the resting heart rate, it might be a further source of between study variability.[29] In the Chicago studies, the heart rate was higher in member of the Western Electric population, in whom it was measured by pulse, than it was in members of the Heart Association or the People Gas Company populations, in whom it was calculated from the electrocardiogram.[21] However, in the only study which compared the two methods, Erikssen et al.[30] found the same values (61.2bpm) for heart rates measured by cardiac auscultation for 1 min and calculated from the electrocardiogram (as the average of nine R–R intervals), and a good correlation between the data provided by the two methods ($r = 0.89$, $P < 0.001$).[29]

In this PhD, the assumption that blood pressure was measured using these devices will be also applied for heart rate measurements in the sense that heart rate measurements taken on the same day as blood pressure measurements, will be hypothesized to be recorded using automated blood pressure devices. This hypothesis will be also tested in Chapter 3.

1.2.5. Duration of measurements and clinical visits

There is scarce information on the duration of heart rate measurements in the vast majority of studies. However, the longer time of measurement, the greater the measurement precision. In a large majority of the studies, the reported heart rate values are based on a single measurement during one visit. Only a few authors calculated heart rate from more than one measurement[3, 31, 32] and only two performed more than one visit.[3, 31] The heart rate tends to decline progressively during a visit[33] and this decline is steeper during the second visit.[33]

In the present PhD, due to the nature of the data that comes from GP practices without reporting of the heart rate measurement method, I will not be able to give clear accounts related to the precise way that heart rate was recorded, the site of the palpation if this was the method used or details on any electronic device e.g. for blood pressure measurement that offered heart rate assessment as well.

1.3. Sources of heart rate variation

Despite the fact that resting heart rate is an easily measurable cardiovascular parameter, it is a highly variable physiologic phenomenon which can be influenced by a large variety of stimuli such as physical, psychological, and environmental factors. Methodological issues have often been neglected by the investigators even when heart rate was one of the major variables to measure.

Nature of the observer and technique

In most studies, heart rate was measured by a doctor, but in some it was measured by a technician[34], however the majority did not mention the observer. In some studies automatic instrumentation was used.[32] It is known that the alarm reaction at the time of measurement may vary according to the type of observer. Little or no reaction should be expected when the heart rate is measured with an automatic device.[29]

Ambulatory vs office measurements

In addition, the reproducibility of heart rate proved to be better for ambulatory than for office heart rate.[35] These findings suggest that heart rate measured out of the clinic might be a better prognostic indicator than traditional measurement in the hospital setting. Unfortunately, little data do exist on the clinical significance of heart rate recorded with ambulatory monitoring devices or collected at home. In a study performed with continuous electrocardiographic recording in a population of elderly participants, the risk of death increased by 14% for each 5 bpm increase in mean 24-h heart rate.[36] However, in that study no comparison with clinic heart rate was provided. The same limitation applies to the analysis by Hozawa et al.[37] These authors found a 17% increase in the risk of mortality for a 5 bpm increase in home heart rate, but, as mentioned above, also that study failed to compare the predictive power of out-of-office heart rate with that of clinic heart rate.[5] A simultaneous analysis of clinic heart rate and out of-office heart rate was provided in a subset of 807 participants enrolled in the Syst-Eur study [38]. In that study, 24-h ambulatory heart rate was recorded intermittently using ambulatory blood pressure monitoring devices. The positive relationship between clinic heart rate and the incidence of fatal end points found in the main study was confirmed in the ambulatory monitoring subgroup [38]. However, ambulatory heart rate failed to provide prognostic information over and above clinic heart rate.[5] On the other hand, in the PAMELA study neither in-office nor out-of-office heart rate were significant predictors of cardiovascular or all-cause mortality [39]. Overall, available data do not show that there is an advantage of heart rate measured out of the office over clinic heart rate, but the available evidence is still limited and more research is needed.[5]

Time of measurement

Other influences on the heart rate variability reflect the interaction with physiologic factors. With regard to these factors, it is known that the heart rate during sleep is substantially lower than that during daytime.[33] Whether and to what extent the heart rate varies during daytime hours remains controversial. With 24 h recordings in ambulant patients, some authors[40] found higher

heart rate levels during morning hours, whereas others[33] reported similar values during the morning and the afternoon, but in these studies the heart rate obviously was influenced by subjects activities. In 13 normotensive subjects confined to bed Casiglia et al[41] found heart rates 5 beats/min higher in the afternoon than in the morning. The clinic heart rate was also generally found to be higher when measured in the afternoon rather than in the morning[30, 42], indicating that, to obtain comparable results, heart rates should be measured at the same time of the day.

Hereditary parameters

Heredity also plays a substantial role in the inter-individual variation of resting heart rate, accounting for 26–32% of heart rate variation in prior studies. [43, 44] Large twin studies with electrocardiogram (ECG) data report even higher heritability estimates up to 55–63%. [45, 46] Candidate gene approaches have identified multiple loci associated with heart rate [44, 47, 48] but the results have been inconsistent and difficult to replicate. Genome-wide genotyping arrays of single-nucleotide polymorphisms (SNPs) assay common variation in the human genome and can identify genetic variants with modest influences on a complex trait such as heart rate, as shown by two recent genome-wide association studies (GWAS) that identified common variation at or near MYH6, GJA1 and CD34 associated with heart rate.[49, 50] These chromosomal loci identified in a genome-wide study may represent novel risk factors for cardiovascular disease outcomes. This knowledge may also have an impact on clinical care (i) by identifying novel factors that cause pathologic heart rate states (such as sick sinus syndrome or other arrhythmias), (ii) by identifying factors that influence cardiac structure or function (e.g. stroke volume) and thereby modulate heart rate (since cardiac output = heart rate × stroke volume) or (iii) by improving our understanding of the physiologic basis of heart rate regulation. Genetic determinants of heart rate could alter the function of the sinus node (the dominant pacemaker in the normal heart) either directly through altered pacemaking activity [51]or indirectly through sympathetic or parasympathetic inputs to the heart. Besides a direct effect on sinus node function, effects on cardiac structure, either developmental or through remodeling and function could underlie the observed associations.[52]

In this PhD I was unable to account for some variability sources such as physical activity, observer bias, time of the day since no heart rate variability measurements recorded by ambulatory devices have been reported in the data, nor specific details regarding the time and technicians/clinicians that recorded these data have been noted. Genetic variations and heart rate are out of this PhD scope.

1.4. Mechanistic considerations-Higher heart rate effects

1.4.1. Heart rate physiology

Initiation of heart rate and products

Heart rate could be described as a sort of language in which the centre is represented by the heart which communicates with the periphery (the body). The heart is in contact with virtually every cell of the body through the shear stress of the endothelium. The initiation of the heart rate by spontaneous sinoatrial node depolarization is determined by membrane currents, particularly the hyperpolarization-activated pacemaker current I(f), and by calcium release from the sarcoplasmic reticulum. In this I(f) current which was first described almost 30 years ago[53] "f" stands for "funny" because of the unusual properties of I(f) relative to other systems known at the time. Each time the heart beats, it expels around 90 mL of blood into the aorta, which creates a kind of shock wave (stress) which is propagated peripherally. Local shear stress (the tangential force in the direction of blood flow generated by flow velocity over the vascular surface.[54]) is sensed by endothelial receptors and induces endothelial gene expression and has multiple functions such as promotion of dilatation by stimulating constitutive nitric oxide (NO) synthase, which produces NO[55]. This mechanism, not only does the heart contract to drive the circulation, but it also sends out signals to keep the arteries open and relaxed, i.e. it contributes to the maintenance of vascular tone. If the heart rate increases then so does shear stress, along with the production of NO. This in turn produces vasodilatation, allowing more blood to reach peripheral tissue, accelerating metabolism and producing a relative increase in energy consumption and heat loss. It follows that heart rate is an indirect metabolic marker and hence of how much energy the body is consuming.

Heart rate and autonomic system

The central nervous system (CNS) controls the heart rate by varying impulse traffic in sympathetic and parasympathetic nerve fibers terminating in the sinoatrial node [56]. Heart rate is the result of the intrinsic automaticity of the sinoatrial node and the modulating influence of the autonomic nervous system (ANS).[57] The ANS is generally conceived to have two major branches—the sympathetic system, associated with energy mobilization, and the parasympathetic system, associated with vegetative and restorative functions.[56] Normally, the activity of these branches is in dynamic balance. There is a well-documented circadian rhythm such that sympathetic activity is higher during daytime hours and parasympathetic activity increases at night. In healthy individuals, average heart rate is greater during the day, when energy demands are higher, than at night, when energy demands are lower. Thus, the system has a local energy minimum or attractor for daytime and another for night time. Hence, the system always tries to minimize the energy requirements of the organism.[58]

Increase in heart rate is accompanied by autonomic imbalance (increase of sympathetic and a decrease of the parasympathetic activity). Empirically, there is a large body of evidence to suggest that autonomic imbalance, in which typically, the sympathetic system is hyperactive and the parasympathetic system is hypoactive, is associated with various pathological

conditions. Beside other effects stimulation of sympathetic nervous system can cause myocardial apoptosis as well as sudden cardiac death [59] [58].

Heart rate and energy consumption

In order to function, heart requires high availability of energy in the form of adenosine triphosphate (ATP) - the primary source of energy in the heart that is used for electrical excitation, contraction, relaxation, and recovery of the resting electrochemical gradients across membranes. It stores only small quantities of ATP, just sufficient to power a few beats[60] Heart rate might suddenly increase its output up to six-fold, thus requiring a huge amount of energy (hence ATP) and the low ATP levels are then counterbalanced by a higher level of creatine phosphate. In humans, the heart beats an average of 100,800 times per day, which corresponds to approximately 36.8×10^6 times per year, or 29×10^8 heart beats in a lifetime (average 80 years). The cost of each heart beat is approximately 300 mg of ATP.

Oxygen consumption

To produce ATP, the myocardium needs oxygen and it has been calculated that the basal oxygen consumption/body atom is approximately 10 molecules of oxygen/lifetime, which, referred to HR, corresponds to 10^{-8} molecules of oxygen per heart beat.[61] Hence, heart rate is among the factors that have important effect on myocardial oxygen consumption. It is the most easily measured of the variables and clearly has the most direct relationship to the rate of myocardial energy use.[12] It has been suggested that lowering heart rate may favorably increase the ischemic threshold and improve cardiac performance and this is of high significance, as a number of cardiovascular drugs alter heart rate as I will present in the following sections.[62] During each cardiac cycle the energy or work performed is converted into heat during relaxation of the heart. With increased heart rate more energy is wasted to perform internal work when more contractions are performed per unit time [63] [64]. These effects count tremendously more in the failing heart. The work is much decreased, whereas much more internal energy is generated which consecutively decreases efficiency. Therefore, when heart disease is present, in particular heart failure, heart rate becomes an important marker for inefficient myocardial oxygen consumption. These findings support the concept that lower energy consumption prolongs life. According to detailed calculations a heart rate reduction of 10 bpm can save about 5 kg of ATP per lifetime in humans. [65] Even though the above are crudely estimated, they point to the pivotal role of HR reduction at the cellular level.[66]

1.4.2. Heart rate and pathology

Oxygen delivery to the heart mainly occurs during diastole, and the fraction of the cardiac cycle occupied by diastole increases as HR decreases. Therefore, HR reduction improves diastolic perfusion time and myocardial perfusion. Any increase in HR could be deleterious, as it further reduces diastolic perfusion, increases stealing from the ischaemic zone, and impairs the flow at the ischaemic obstruction, which further compromises coronary flow, hence reduction in HR

under these circumstances is highly beneficial. Increasing HR by atrial pacing in patients with CAD produces coronary constriction, further impairs oxygen supply.[67] In patients with stable CAD, most episodes of ambulatory or exercise-induced myocardial ischaemia are preceded by an increase in HR.[68] Some epidemiologic studies have argued that he likelihood of developing ischemia is related to the baseline HR.[69] The frequency of ischaemic episodes in patients with CAD is related to their mean HR, in particular, patients with HR >80 bpm experience ischaemia almost twice as often as those with HR <70 bpm.[70] The main suggested pathological mechanisms are summarized in **Figure 1.1**.

Plaque disruption

Increased HR and haemodynamic forces may play a role in plaque disruption. Plaque rupture has been suggested as the main pathophysiological mechanism underlying acute coronary syndromes and the progression of coronary atherosclerosis[71] and in particular it was shown that elevated heart rate is associated with coronary plaque disruption in ACS patients.[72] The role of haemodynamic forces, i.e. HR, has been investigated in 106 patients who underwent two coronary angiographic procedures within 6 months.[73] This study identified positive associations between plaque rupture, left ventricular muscle mass >270 g, and a mean HR >80 bpm, and a negative association with HR-reducing medication.

Tensile stress

Elevated tensile stress (described above) is thought to induce direct endothelial injury and to increase endothelial permeability to LDL and to circulating inflammatory mediators. Very high HR (>120 bpm) by reducing the diastolic phase reduces the stroke volume and the cardiac output. Tachycardia (close to 100 bpm) increases the tensile stress and may promote endothelial injury and wall stiffness. In chapter 5, the effect of different levels of heart rate on adverse cardiovascular events in people with coronary artery disease will be thoroughly investigated.

1.4.2.1. Experimental evidence

Overall, there are several theories about what causes elevated heart rate and why high heart rate is associated with adverse events. As I mentioned above, heart rate may be a reflection of autonomic nervous system abnormalities[74]. It has also been suggested that heart rate plays a more direct role in the pathogenesis of certain disease states and progression of atherosclerosis.

Animal studies

More direct evidence of the importance of heart rate on the progression of coronary atherosclerosis comes from animal studies. In primates with similar blood pressure, serum lipid levels, and body weight profiles, atherosclerotic lesions in the group with low heart rates were

approximately one third the size of the lesions found in the group with high heart rates. [75]Beere et al [75] investigated the role of HR reduction in monkeys fed with an atherogenic high cholesterol diet for 6 months. These animals underwent sinus node ablation and compared with eight animals which had the same operation without sinus node ablation. The average lesion area in the low heart rate subgroup was one third that of the high heart rate subgroup, while the coronary arterial plaque area was found, on average, to be more than twice as large in monkeys with naturally high heart rates (mean 159 bpm) than in those with slower heart rates (mean 133 bpm). Kaplan et al.[76] have shown that monkeys with habitual high resting heart rate have twice as extensive lesions in the coronary arteries as animals with low resting heart rate. In a more recent study Kaplan et al. observed an attenuated progression of atherosclerosis through heart rate reduction by propranolol in primates. Heart rate was an important predictor of the size of coronary artery lesions in saturated- fat-fed monkeys with high resting heart rates versus those with low resting heart rates[77]. Moreover, decreasing the heart rate with propranolol in primates was associated with reduction in the progression of atherosclerosis, independent of total or high-density lipoprotein cholesterol concentration[77]. Further evidence for the link between heart rate and atherosclerosis has come from the measurement of changes in endothelial function and markers of inflammation. Increasing heart rate by 10% by electrical pacing in hypertensive rats significantly enhanced cardiac oxidative stress and activated pathways implicated in cardiac hypertrophy and cardiac remodeling, without any increase in blood pressure.[78] Guth et al.[22] evaluated the beneficial effect of intravenous atenolol on exercise-induced regional myocardial ischaemia and contractile dysfunction in dogs with single-vessel coronary stenosis. The regional dysfunction was reduced with atenolol but the improvement was prevented when HR was kept constant with atrial pacing. Evidence from heart rate reduction with ivabradine, a heart rate lowering medication that I will describe in the following sections, reduced oxidative stress, improved endothelial function, and prevented atherosclerosis in apolipoprotein E-deficient mice.[79] All the above evidence in animals, show towards the fact that HR reduction may play an important role in cardiovascular diseases.

Studies in humans

Experimental data have demonstrated that elevated heart rate has a role in the development of atherosclerosis and plaque disruption coronary artery endothelial dysfunction in experimental studies.[80, 81] It has been also speculated that heart-rate-induced alterations in the velocity and direction of blood flow may be a contributing factor in the pathogenesis of coronary artery atherosclerosis. A relatively high heart rate may indicate increased sympathetic activity, reduced vagal activity, or both. In experimental studies [82, 83] these factors have been shown to lower the threshold for ventricular fibrillation. In the presence of acute myocardial ischemia, a high heart rate produces a greater and more prolonged decrease in the ventricular fibrillation threshold[84]. High heart rate may also exert a negative effect on cardiac performance by increasing myocardial oxygen demand[85] as we previously described. In an epidemiological study, increased heart rate in patients with restricted coronary blood flow causes an increase

in myocardial ischemia and complications including pain, larger infarction, and arrhythmias[83]. An increase in myocardial oxygen demand may potentiate ischemia at a given level of coronary atherosclerosis[85]. Heart rate and double product (heart rate multiplied by systolic blood pressure) correlate well with myocardial oxygen consumption during exercise in patients with angina pectoris, while reduction of myocardial oxygen consumption raises the threshold for myocardial ischemia at a fixed level of coronary blood supply. [62]

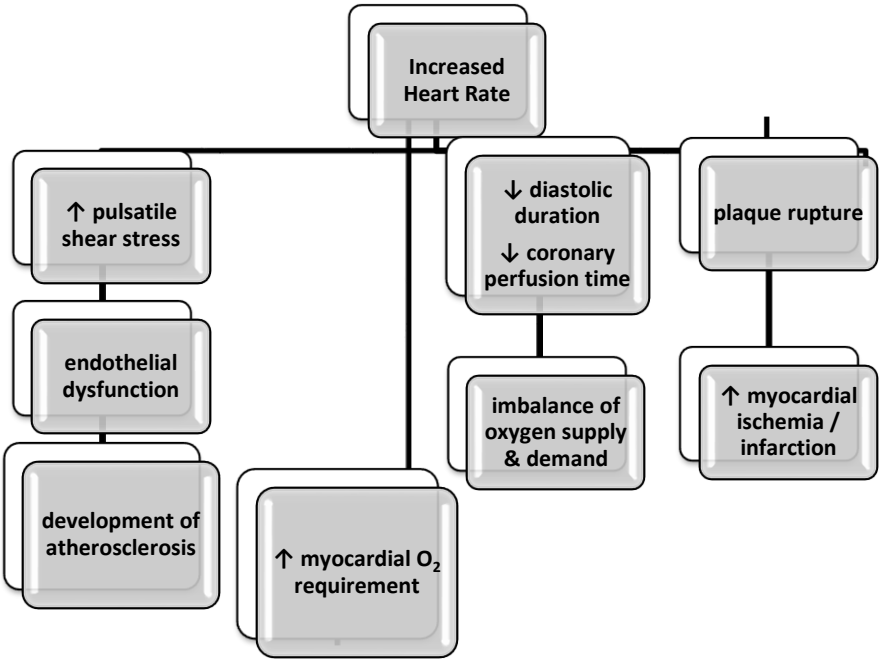
In summary, it has been experimentally suggested that high heart rate is of importance in the development and progression of atherosclerosis, myocardial ischemia, acute ischemic events, and sudden cardiac death, and that a reduction in heart rate has beneficial effects.[86] However, these suggestions have been largely derived by animal research and not by general, large scale population-based epidemiological studies. The present PhD will seek to explore associations of heart rate with coronary artery diseases and subsequent atherosclerotic events.

1.5. Factors affecting heart rate

1.5.1. Cardiac conditions affecting heart rate

This subchapter will present the most common cardiac conditions that affect the resting heart rate. Among the main conditions affecting heart rate are atrial fibrillation, thyroid diseases and anxiety. Abnormal heart rhythms (arrhythmias) are caused by problems with the electrical system that regulates the steady heartbeat and the heart rate can then be too slow or too fast. Finally structural disorders of the heart muscle such as cardiomyopathy and congenital abnormalities can damage the heart muscle or valves and influence the heart rate. The proportion of patients with structural or valve disorders in the CALIBER cohorts analyzed was small, hence they were not excluded from the final population.

Figure 1.1. Potential mechanisms between higher heart rate and cardiovascular diseases (adaptation from Fox et al.[87])



Some of the conditions that cause rhythm disorders are:

i. Atrial fibrillation

In atrial fibrillation, the heartbeat is irregular and rapid due to disorganized signals from the heart's electrical system. The atrium may beat as often as 300 times a minute, about four times faster than normal and has been linked with several adverse cardiovascular and cerebrovascular events. In large rate versus rhythm control trials in patients with atrial fibrillation, heart rate reduction tended toward improved survival when compared with a rhythm control strategy.[88] Atrial fibrillation is a pathological cardiac arrhythmia, and the optimal degree of heart rate reduction required for its treatment is unknown. [89]

ii. Ventricular fibrillation

In ventricular fibrillation, the heartbeat is fast causing the ventricles to spasm and heart rate is unable to pump the blood out of heart. Sometimes, a blockage of the heart arteries can lead to this type of arrhythmia and often leads to sudden cardiac arrest.

iii. Long QT Syndrome

This syndrome is a disorder of the electrical system, commonly genetically transmitted. People with long QT syndrome are at increased risk for ventricular fibrillation.

iv. Heart block

One of the disorders that decrease heart rate is heart block that happens when electrical signals from atria cannot travel to the ventricles. The heart then beats too slowly, decreasing the amount of oxygen that gets to the body and brain.

v. Sinus node disease

Sick sinus syndrome is not a disease, but a group of signs or symptoms that show the heart's natural electrical pacemaker, the sinus node, is not working properly. In this syndrome, the heart rate can alternate between slow (bradycardia) and fast (tachycardia). Severe sinus bradycardia may be a feature of sinus node disease, and in turn related to underlying cardiovascular disease and ageing.

vi. Heart Valve disorders

Finally, congenital diseases of the heart such as heart valve disorders affect the heart rate causing usually an increase of rhythm.

Associations of atrial fibrillation with heart rate and future cardiovascular events in healthy or CAD people have been also under-examined. This PhD will seek to examine these potential associations.

Experimental studies in lowering heart rate and arrhythmia events

Experimental studies suggest that heart rate modulation can reduce the risk of life-threatening arrhythmias during ischemic episodes; the beneficial effect of beta-blockade in this context may be mediated primarily by heart rate reduction.[90] Improvement of survival after reduction of heart rate has been shown in atrial fibrillation patients in the post-myocardial infarction or heart failure setting with some beta-blockers such as carvedilol.[91] More studies on heart rate lowering medication and its effect will be shortly presented in the next subsection.

1.5.2. Non-cardiac conditions affecting heart rate

Among the non-cardiac conditions that can result in heart rate changes is hypertension. Individuals with hypertensive disease, usually have higher values of heart rate than healthy controls. Furthermore, when the body's immune system becomes compromised for example, with injury, anemia, or infection, changes in heart rate although usually temporary, can occur. Particularly if septic shock sets in, the heart rate naturally gets more rapid to meet oxygen demands. In stressful situations such as panic episodes or generalized anxiety disorder, the body naturally responds with a faster pulse. The same applies for fear, another type of anxiety, which prompts the flight response and releases hormones that make the heart pump faster. Fever or a sudden increase in temperature also affects heart rate and quicken the pulse. In dehydration situations the heart naturally works harder to maintain the normal cardiac output and hence the heart rate increases.

Thyroid diseases

One of the differences between patients with hyperthyroidism and hypothyroidism is in the pulse-rate.

Experimental observations in the 1960s's suggest that this was a result from a direct effect of circulating thyroxine on the heart and not, as has been generally accepted, from an increase in sympathetic stimulation of the heart arising from potentiation of the cardiac actions of catecholamines by excess thyroxine.[92] Other thyroid disorders such as Hashimoto's disease also called chronic lymphocytic thyroiditis, is a form of chronic inflammation of the thyroid gland. These types of thyroid disorders decrease heart rate.[93]

Inflammatory syndromes

Systemic inflammatory response syndrome (SIRS) is an inflammatory syndrome that among its criteria for diagnosis established in 1992 as part of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference [94] is heart rate greater than 90 bpm. Other autoimmune diseases such as rheumatoid arthritis or infiltrative diseases such as amyloidosis might lead to a decrease of heart rate.

Stress

It has been also suggested that psychosocial stress associated with an increase in heart rate can trigger the onset of acute myocardial infarction, in addition to sudden cardiac death. This has been documented in the literature, and one example of an increase in attacks of sudden death occurred during the San Francisco earthquake in 1994.[95] During the earthquake, there was a seven-fold increase in the risk of sudden cardiac death reported by hospitals in the region. Elevated heart rate during mental stress may play a key role in the development of sudden cardiac death. It is well known that the incidence of sudden cardiac death among patients with hypertension, myocardial infarction, or congestive heart failure is reduced by beta-blockers[96]. These observations are supported by results from the Betablocker Cholesterol lowering Asymptomatic Plaque Study (BCAPS), a randomized trial that showed that administration of a beta-blocker reduces the rate of progression of carotid artery intima thickness in asymptomatic subjects[97].

1.5.3. Other factors affecting heart rate

Although it has been established that the maximal heart rate declines with age,[98] whether the resting heart rate increases or declines with advancing age remains controversial. The majority of studies[30] reported a slight decrease in heart rate with increasing age. Surprisingly, among multivariate analyses that removed all confounders, the decrease was the same (0.13 beats/year) in the study by Erikssen et al [30] in the Harvest study and in the Belgian population study. Some studies[21] found little or no change in heart rate related to age, whereas in one

study[85] a positive association was reported. Overall, these data indicate that age affects heart rate only to a slight extent.[29] A large body of evidence shows that the heart rate is higher in women than it is in men. This sex-related difference has been found both in economically advanced countries and in undeveloped countries.[29] According to the results of the Framingham study [85], the difference increases with advancing age, which was not observed in other studies[29, 34].

Other factors have also been found associated with heart rate. Smoking was correlated positively to heart rate in the Chicago studies [16] and the Paris Prospective study [23], but in other studies it was unrelated to (the Harvest study and the Belgian population study), or even correlated negatively to heart rate (the Tecumseh study and the Mirano study). Slight negative correlations were found between heart rate and alcohol consumption (in the Tecumseh, Harvest and Mirano studies) or coffee consumption (in the Tecumseh and Mirano studies), but they disappeared in multivariate analyses. A close inverse correlation between physical fitness and heart rate has long been recognized, and was demonstrated by experimental and epidemiologic studies[99, 100] at any age in both sexes. In Section 1.4 I will also present conditions and medications linked with heart rate and result to an increase or decrease of the marker.

1.6. Trials of drugs affecting heart rate and impact on CVD outcomes

As discussed before, myocardial ischemia results from an imbalance between myocardial perfusion and myocardial oxygen demand. Most episodes of myocardial ischemia, whether induced by exertion or detected during ambulatory monitoring, usually are found to be preceded by an increase in heart rate.[101, 102] Lowering heart rate, is a well-established strategy for management of stable angina pectoris.[103] The most common medications affecting heart rate are presented in **Table 1.4**. Two widely used types of antianginal drugs (b-blockers and non-dihydropyridine calcium channel blockers) have heart rate–lowering action[104]; much of the anti-ischemic benefit of b-blockade has been related to heart rate lowering.[22]

1.6.1. Beta-blockers and Nondihydropyridine calcium antagonists

It is well known that the incidence of sudden cardiac death among patients with myocardial infarction, stable coronary artery disease or congestive heart failure is reduced by beta-blockers,[96] extensively known for their heart rate lowering effects. These observations are supported by results from the Betablocker Cholesterol lowering Asymptomatic Plaque Study (BCAPS), a randomized trial that showed that administration of a beta-blocker reduces the rate of progression of carotid artery intima thickness in asymptomatic subjects.[97] Further evidence from clinical trials are presented below:

Table 1.4. Medications affecting heart rate

Drugs that increase heart rate	**Drugs that decrease heart rate**
Drug Category	
Sympathomimetics (BNF: 2.7)	**Sympatholytic drugs**
*Inotropic sympathomimetics (*BNF: 2.7.1)	*Beta-adrenoceptor blocking drugs (*BNF: 2.4)
*Vasoconstrictor Sympathomimetics (*BNF: 2.7.2)	**Vasodilators**
Bronchodilators	*Calcium Channel Blockers (*BNF: 2.6.2)
*Adrenoceptor Agonists (*BNF: 3.1.1)	*Long-acting nitrates (*BNF: 2.6.1)
*Antimuscarinic Bronchodilators (*BNF: 3.1.2)	**Cardiac Glycosides (**BNF: 2.1. (Positive Inotropic Drugs))
*Theophylline (*BNF: 3.1.3)	**Anti-Migraine drugs (**BNF: 4.7.4)
Thyroid Hormone Replacement (BNF: 6.2)	**Antiarrhythmics** (BNF: 2.3.2)
Antidepressant drugs (BNF: 4.3)	**Others**
*Tricyclic and related antidepressant drugs (*BNF: 4.3.1)	Ivabradine (BNF: 2.6.3 (Other anti-anginal drugs))
Selective serotonin re-uptake inhibitors (BNF: 4.3.3)	
Stimulants- Illicit Drugs (BNF: 4.4 (CNS Stimulants))	

Evidence from trials on post MI patients

- Beta-blockers

The majority of the information available on the effect of β-blockers on heart rate and mortality outcomes is obtained from old trials evidence on post myocardial infarction patients. A meta-analysis of 29 trials in which patients were assigned to early treatment with β-blockers revealed a 13% reduction in overall mortality.[105] The reduction in heart rate obtained with β-blockers ranged from 10.5% to 22.8%, and a benefit was obtained only if the heart rate was reduced by 14 bpm or more.[106] For a heart rate reduction of less than 8 bpm, no benefit at all could be achieved. In addition, this meta-analysis showed that if patients' heart rate was <55 bpm, only little effect was shown by beta-blocking therapy.[106] Data from 26 large trials in post myocardial infarction patients followed for long periods who received beta-blocker therapy on 5 through 28 days after the infarction showed a 23% mortality reduction among treated patients.[105] In particular, β-blockers proved effective in reducing sudden death and death due to pump failure.[105, 107, 108] Again, benefit from therapy in terms of both reinfarction and all-cause mortality was proportional to heart rate reduction.[106]

- Nondihydropyridine calcium antagonists

The way in which a drug slows the heart rate may be important in determining the outcome of heart rate slowing. If the disappointing effects of β-blockers in hypertension are due to their unfavorable effects on the lipid profile, the use of drugs that reduce blood pressure and heart rate without altering plasma lipids should provide better results in hypertensive patients with high heart rate. This could be obtained with nondihydropyridine calcium antagonists, which have shown to be neutral on the metabolic profile.[124,125] Phenylalkylamines for example, such as verapamil have a central action that decreases the sympathetic outflow and reduce heart rate.[128] Consequently, nondihydropyridine calcium antagonists reduced the risk of cardiac events and the death rate in post MI patients, but only in patients with no signs of heart failure.[109, 110]A meta-analysis of trials stratified according to whether calcium antagonists increased or decreased heart rate showed that for dihydropyridine calcium antagonists, there was a trend toward increased mortality, whereas for verapamil and diltiazem, the trend was toward a small decrease in mortality.[111] The Multicenter Diltiazem Postinfarction Trial and the Danish Verapamil Infarction Trial II showed a reduction in the combined end point of death or reinfarction in patients without clinical signs of congestive heart failure.[109, 110] Finally, a recent meta-regression analysis performed by Cucherat[112] to determine the extent to which heart rate reduction induced by the various beta-blockers and Nondihydropyridine channel blockers modifying heart rate affects the reduction of mortality and morbidity observed in randomized placebo-controlled trials in patients with myocardial infarction.[106] A significant relationship was found between resting heart rate reduction and the clinical benefit caused by these drugs, including reduction in cardiac death, all-cause mortality, sudden death and nonfatal MI recurrence. A 30% reduction in the relative risk of cardiac death was observed for each 10 bpm reduction in the heart rate.

The findings of these trials confirm that the beneficial effect of beta-blockers and calcium channel blockers in post MI patients is proportionally related to the reduction of resting heart rate.

Evidence from trials on CAD patients

In patients with stable coronary artery disease, it has been shown that reduction of angina and of the underlying ischemia determined by heart rate–lowering drugs is related to reduction of heart rate.[113, 114]In the ASIS study, propranolol caused a greater reduction of heart rate than diltiazem and was more effective in relieving both symptomatic and asymptomatic ischemic episodes.[115] Beta-blockers and nondihydropyridine calcium antagonists however, might have negative effects especially presented in patients with left ventricular dysfunction (heart failure). Therefore, a pure heart rate lowering drug, ivabradine, has been developed and will be described later on in this section.

Trials on heart failure patients

Beta-blockers, have been shown to be effective also in patients with congestive heart failure.[116, 117] Pooled results from carvedilol trials in subjects with congestive heart failure reported a marked reduction in mortality with the use of this β-blocker.[118] Mortality reduction was higher in patients with a high heart rate. The mechanism by which β-blockers improve left ventricular function is still uncertain. Several mechanisms have been proposed including improved cardiac myocyte metabolism and reduction in apoptosis, a reduction in heart rate, a reduction in atrial and ventricular arrhythmias, or a reduction in myocardial ischemia and/or hibernation.[119] The Metoprolol CR/XL Randomized Intervention Trial in Chronic Heart Failure demonstrated similar heart rate reductions at doses of extended-release metoprolol above and below the median.[120] Importantly, similar relative risk reductions in all-cause mortality were observed in that study between patients receiving high and low doses, supporting the concept that it is heart rate reduction that may be more important than absolute dose in maximizing clinical benefit.[106] Finally, an analysis of the CIBIS II trial showed that both low baseline heart rate and a marked heart rate reduction caused by β-blocker administration were significantly associated with a better prognosis in patients with heart failure.[121] The hypothesis that heart rate reduction was the main mechanism by which β-blockers improve outcome in congestive heart failure was tested in a randomized, double-blind, parallel group study comparing chronic higher-rate (80 bpm) with lower-rate (60 bpm) pacing in pacemaker-dependent patients with symptomatic left ventricular systolic dysfunction receiving β-blockers. [73] Mean left ventricular end-diastolic (P = .03) and systolic (P =.006) volumes increased with higher-rate vs lower-rate pacing, whereas left ventricular ejection fraction declined with the former compared to the latter. These findings suggest that heart rate reduction is the main mechanism of beta-blockers' effect in patients with congestive heart failure.[106]

Prescribed beta-blocker medication has been considered in my analyses of heart rate associations with CVDs in healthy, CAD and atrial fibrillation populations, as a potential confounding factor and in sensitivity analyses restricted to people who did not had prescribed beta-blockers.

1.6.2. Ivabradine

So far I described the most common medications that have an effect on heart rate and are quite commonly prescribed in clinical practice. However, lowering agents may have multiple other actions on the heart and on other organs and tissues.[103] Some of these may cause undesirable adverse effects in some patients, for instance beta-blockers and non-dihydropyridine calcium channel blockers have negative inotropic effects, can, affect intracardiac conduction, and may cause hypotension.[103, 104]

Mechanisms of action

Ivabradine, is the first specific heart rate lowering agent and acts by inhibiting *I*f, an ionic current involved in pacemaking activity in the sinoatrial node. *I*f contributes a depolarizing current that drives spontaneous diastolic depolarization to trigger a subsequent action potential, and modulation of *I*f is important in physiological regulation of heart rate. [122] Ivabradine has no appreciable action at other receptors or channels in the cardiovascular system. The heart-rate-lowering action of ivabradine has been compared directly with β-blockers in experimental studies in healthy animals and in models of CAD and heart failure. Ivabradine reduces myocardial oxygen demand and simultaneously improves oxygen supply, by prolonging diastole and thus allowing increased coronary flow and myocardial perfusion.[123] As beta-blockers additionally reduce myocardial contractility, it might be predicted that β-blocking treatment would reduce myocardial oxygen demand more than ivabradine.[106] However, it has been experimentally shown (in animals) that for all parameters of regional myocardial ischemia measured, the effect of ivabradine was as great or greater than that of propranolol.[124]

Overall, compared with β-blockade, ivabradine produces a form of heart rate lowering that more closely resembles the physiological situation and that does not perturb a series of mechanisms involved in ensuring efficient myocardial performance at different beating rates. However, it should be emphasized that β-blockade has effects other than heart rate reduction, which might be beneficial in some clinical situations. For example, elevated heart rate can reflect a generalized increase in sympathetic tone, which can induce adverse effects unrelated to heart rate. In this case, heart rate lowering with ivabradine is unlikely to produce the full range of benefits potentially achievable with β-blockade. On the other hand, ivabradine can be appropriate in some patients with contraindications to β-blockers resulting from such additional effects.

Evidence from trials in people with CAD

The evidence available on associations of heart rate reduction with ivabradine and cardiovascular diseases have been exclusively provided by trials on coronary artery diseased populations. The most important and up-to date findings on ivabradine in a CAD population with heart failure (left ventricular ejection fraction <40% have been showed by a large clinical trial (BEAUTIFUL trial).[125] The BEAUTIFUL study [125] randomized 10,917 patients with coronary disease and left ventricular dysfunction to receive ivabradine or a placebo, to test whether reducing the heart rate would reduce cardiovascular mortality and morbidity. A subgroup of patients with a heart rate >70 bpm was shown to have a 46% increased risk of MI and 38% increased risk of coronary revascularization. Further analysis showed that for every 5 bpm increase in heart rate, there were increases in cardiovascular death (8%, P=0.0005), admission to hospital with heart failure (16%), admission to hospital with MI (7%), and coronary revascularization (8%).These findings suggest that addition of ivabradine to standard treatment including β-blockers can improve outcome in CAD patients with heart failure. The effects of ivabradine were analysed in a subgroup of patients with a heart rate of >70bpm. Ivabradine

treatment did not affect the primary composite outcome, cardiovascular death, or admission to hospital for new-onset or worsening heart failure, but reduced secondary end points: admission to hospital for fatal and nonfatal myocardial infarction and coronary revascularization. All the available clinical trials using ivabradine and examining associations of heart rate reduction with cardiovascular diseases are presented in **Table 1.5.** Ivabradine was not available in CALIBER dataset, hence it has not been used in the analytic process.

Table 1.5 Trials examining associations of ivabradine and other heart rate lowering medications with CVD prognosis in people with sCAD

Author/year	number of patients	Trial arms		Population	Duration of follow-up	Primary endpoint	Main results
		Intervention	Controls				
The International Collaborative Study Group 1984[108]	144	Intravenous timolol	Placebo	MI	-	Infarct size	The timolol group had reduced infarct size
The Multicentre Diltiazem Postinfarction Trial Research Group 1988[110]	2466	Diltiazem	Placebo	Past MI	25 months	Mortality, reinfarction	The Diltiazem group had 11% reduction in cardiac death or nonfatal reinfarction, but no difference in overall mortality.
Stone 1990[115]	50	Propranolol, or diltiazem, or nifedipine	Placebo	Stable angina and a high frequency of asymptomatic ischemic episodes	1.5 months	Ischaemia episodes	The propranolol group had fewer ischemia episodes .
Danish Study Group 1990[109]	1775	Verapamil	Placebo	MI without heart failure	18 months	Death, composite of death or reinfarction	The verapamil group had 4.1% lower mortality and 5.1% lower composite rate
Packer 1996[118]	1094	Carvedilol	Placebo	Chronic heart failure	6 months	Death or hospitalization for cardiovascular reasons	The carvedilol group had27%reduction in risk of hospitalization for cardiovascular causes and a 38% reduction in the

							hospitalization/ death composite
Van Der Vring 1999[114]	335	3 arms: Mibefradil, Diltiazem or amlodipine	Placebo or one of the other arms	Stable angina with myocardial ischaemia produced at ETT under b-blocker medication	14 days	Duration of exercise, onset of ischaemia, time to onset of angina, time to onset of ischaemia	The mibefradil group had the largest anti-ischaemic effect and improved time to ischaemia by 29.8s than amlodipine. No difference between diltiazem and amlodipine. Further reduction of heart rate was associated with better anti-ischaemic effects
Lechat 2001[121]	2539	Bisoprolol	Placebo	Chronic heart failure	2 months	Mortality and hospitalization for heart failure	The bisoprolol group had reduced mortality in patients with sinus rhythm (RR= 0.58) but not in patients with atrial fibrillation (RR=1.16). Reductions were also observed for cardiovascular mortality and hospitalization for heart failure.
Wikstrand 2002[120]	3991	-Metoprolol CR/XL	Placebo	Heart failure	3 months	Total mortality, composite of all-cause mortality and all-cause hospitalization (time to first event)	The metoprolol group had reduction risks of 38% for total mortality, 45% for sudden death and 54% for hospitalizations for heart failure.
Borer[126] **2003**	360	Ivabradine	Placebo	Chronic stable angina	-	Time to 1-mm ST-segment depression and	Angina attacks decreased from 4.14±5.59 attacks per

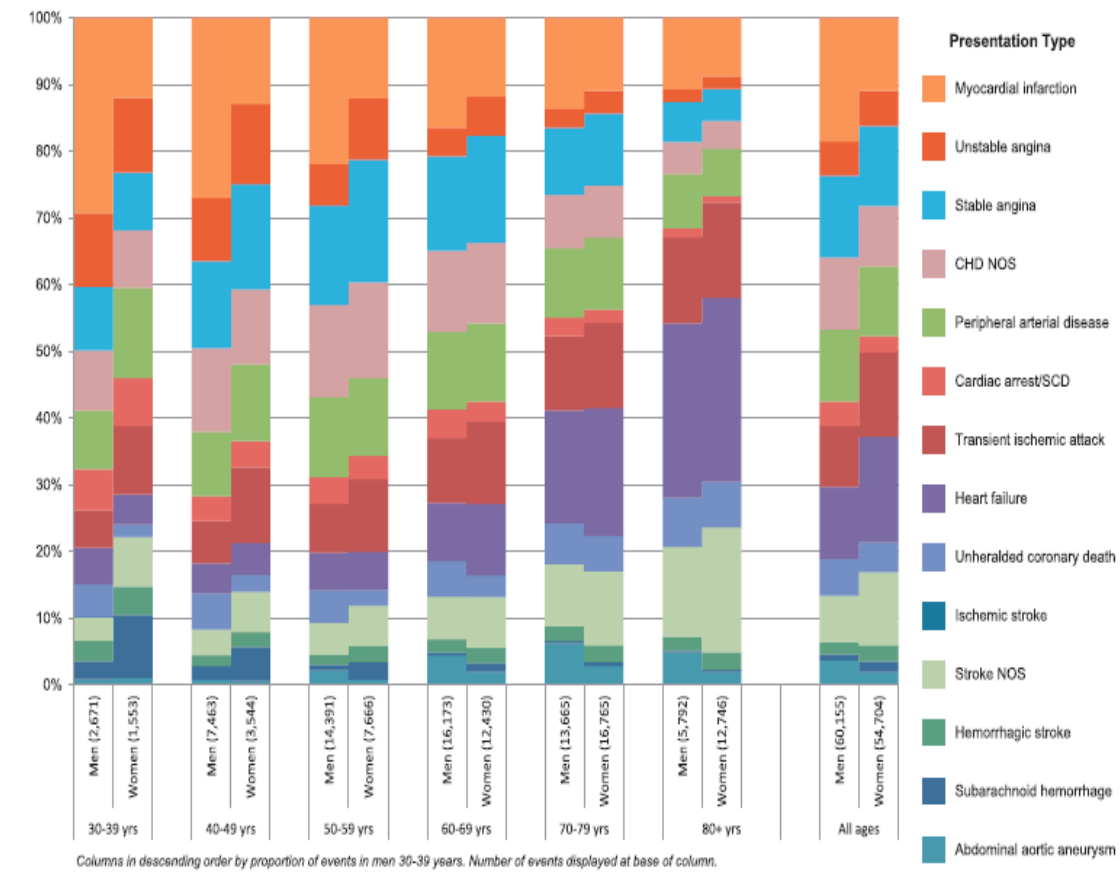
						time to limiting angina during ETT	week at baseline to 0.95±2.24 attacks per week
Fox 2008[127] (BEAUTIFUL)*	5,438	Ivabradine	Placebo	Coronary Artery Disease and Heart Failure	19 months (median)	Composite of cardiovascular death, admission to hospital for acute myocardial infarction, and admission to hospital for new onset or worsening heart failure.	Heart rate reference level: <70bpm Increased risk of MI, HF, revascularization and CV death for <70 vs. >70bpm heart rate.
Fox[128] 2014 (SIGNIFY)*	19,102	Ivabradine	Placebo	Coronary Artery Disease (activity-limiting angina)	27.8 months (median)	Composite of death from cardiovascular causes or nonfatal myocardial infarction.	No effect difference on the primary endpoint between >75 vs. <75bpm heart rate

*** Studies that used specific heart rate values for comparisons of hazards; ETT, Exercise Tolerance Test; MI, Myocardial Infarction**

1.7. Cardiovascular diseases

In this section I will describe the main outcomes explored in this PhD in relation to resting heart rate. These outcomes include diseases that affect the coronary, cerebral and peripheral arterial beds. The incidence of specific cardiovascular diseases in the CALIBER population by age and sex is illustrated in **Figure 1.2**.[129]

Figure 1.2 Age and sex distribution of 60 155 events in men and 54 704 in women representing the initial presentation of a wide range of CVDs. CHD indicates coronary heart disease; CVD, cardiovascular disease; NOS, not otherwise specified; and SCD, sudden cardiac death.



1.7.1. Coronary diseases (stable angina/myocardial infarction)

Definition

The term "coronary artery disease" (CAD) or “coronary heart disease” (CHD) encompasses a range of diseases that result from atheromatous changes in coronary vessels. In the past, CHD was thought to be a simple, inexorable process of artery narrowing, eventually resulting in complete vessel blockage (and MI). However, in recent years the explanatory paradigm has changed because it was realized that a whole spectrum of coronary plaques exists – from stable

(lipid-poor, thick fibrous cap) to unstable (lipid-rich, thin fibrous cap) [130] Angina results when myocardial perfusion is insufficient to meet the myocardial metabolic demand.

Clinical evidence

Framingham estimates traditionally predict total CHD, which includes angina pectoris, recognized and unrecognized myocardial infarction, coronary insufficiency (unstable angina), and CHD deaths.[131] The inclusion of unstable angina and unrecognized myocardial infarction (defined by electrocardiography) probably gives estimates of hard CHD that are somewhat higher than combined end points reported in several clinical trials.[132, 133] Another clinical trial[134] specified acute coronary events, including unstable angina, acute myocardial infarction, and coronary death, as the primary end point. This combined end point probably corresponds closely to the Framingham study's definition of hard CHD. Definitions of coronary end points assume critical importance when risk cut points are defined to select patients for specific therapies.[131]

Clinical evidence exists from ambulatory electrocardiographic (ECG) monitoring in patients with stable CAD that increases in heart rate are associated with episodes of myocardial ischemia.[87] For example, in one study, 89% of participants were preceded by an increase in heart rate of ≥10 bpm.[135] In another trial described before, the BEAUTIFUL trial,[125] the relative risk of cardiovascular death was increased by 34% in patients with heart rate ≥70 bpm compared with those whose heart rate was <70 bpm, and the rate of cardiovascular death increased progressively with baseline heart rate. The effect of heart rate on myocardial ischemia underlies the use of heart-rate-reducing drugs, such as β-blockers, in the treatment of stable angina pectoris. In US guidelines, a target resting heart rate of 55–60 bpm is recommended in patients with stable angina.[22] In experimental animals[23] and in patients[24] the anti-ischemic benefits of beta-blockers were eliminated if the heart rate reduction was prevented by electrical pacing. On the other hand, studies of placebo and active control treatment studies using a prototype agent of ivabradine (zatebradine) in angina patients has revealed no antianginal or anti-ischemic activities of the drug in spite of reductions in both rest and exercise heart rate.[136, 137] The implication of these findings is that HR reduction alone may play a small role, if any, in the antianginal actions of drugs such as beta-blockers and calcium blockers.[138] In a recent clinical trial of people with angina and ejection fraction >40%, the addition of ivabradine to standard background therapy to reduce the heart rate did not improve the primary outcome which was composite of death from cardiovascular causes or nonfatal myocardial infarction. Beta-blockers are effective at reducing angina and are usually preferred as initial therapy. The non-inferiority of ivabradine compared with atenolol was demonstrated when ivabradine induced a similar or greater improvement in exercise capacity than beta-blockers for a comparatively smaller reduction in HR.[139]

Evidence from Genome-Wide association studies

In contrast to the above trial findings, genome-Wide association studies (GWAS) failed to identify associations of heart rate loci with coronary artery disease (CAD) or MI. However, a 2-stage meta-analysis of GWAS in up to 181,171 individuals showed that heart rate–increasing alleles were associated with prolonged PR duration and reduced QT duration independent of heart rate, as well as with both reduced and prolonged QRS duration. None of the heart rate loci showed evidence of association with the risk of coronary artery disease or myocardial infarction.[140]

In this PhD, associations of stable angina and myocardial associations with heart rate will be examined in healthy, CAD and atrial fibrillation populations.

1.7.2. Cardiac diseases

1.7.2.1. Heart failure

Definition

Heart failure is defined as the inability of the myocardium to adequately supply circulation with blood at normal enddiastolic filling pressures provided that normal venous return exists. Neuroendocrine mechanisms like an increase of the sympathetic activity and increased activity of the renin-angiotensin-aldosterone (RAA) system are activated and contribute to a progression of ventricular dysfunction. [4]

Clinical importance

Heart failure is a frequent cause of hospitalization, and it is estimated in Europe to be responsible for 1 million hospitalizations per year. Increased resting heart rate has recently received attention regarding its ability to be an independent prognostic factor in paints with heart failure.[141] As the natural history of patients with CAD includes the possible occurrence of acute myocardial infarction, progression towards heart failure, and death from a cardiovascular origin, heart rate reduction represents a potential approach to improving the prognosis of patients with heart failure.[142] A number of factors support the benefit that may be derived from heart rate reduction in heart failure. It is well established that heart rate is a regulating factor in myocardial oxygen demand. Factors that can affect myocardial oxygen demand include wall stress, which is dependent on preload and afterload, myocardial contractility, and heart rate.[142] As reported many years ago by Holmberg and Varnauskas,[143] myocardial oxygen uptake increases as a product of heart rate and systolic blood pressure in a linear fashion. On the other hand, the level of heart rate reflects the interactions of the adrenergic drive and vagal tone. The autonomic nervous system plays an important role in the development of atherosclerosis and is known to be an acute trigger of sudden cardiac death that accounts for a high proportion of heart failure-related mortality[142].

1.7.3. Stroke, peripheral vascular disease

Definition

Stroke is a result of restricted blood flow to an area of brain tissue, e.g. due to a blood clot or a bleed. The blood deprivation causes a cell death. The most common types of stroke are the ischaemic (when the artery that supplies blood to the brain is blocked) and haemorrhagic (when a blood vessel bursts and bleeds into your brain, damaging brain tissue and starving some of your brain cells of blood and oxygen). An additional form of stroke is the transient ischaemic attack (TIA) that occurs when there is a temporary blockage in the blood supply to the brain.

All the aforementioned types of strokes will be individually explored in relation to heart rate in the present PhD.

Clinical importance

As heart rate is a parameter reflecting heart function, and adverse effects of resting heart rate include an increased susceptibility to cardiac events, the adverse cardiovascular events such as heart failure of increased heart rate could be predominantly present in CAD and general populations.[144] However, as elevated sympathetic nervous activity is also present in patients with vascular diseases at other locations and other adverse effects of heart rate such as atherosclerotic plaque rupture and endothelial dysfunction are systemic, it is possible that the detrimental effects of an elevated heart rate could affect patients with clinical manifest vascular disease. In a post hoc analysis of the ONTARGET/TRANSCEND trials, associations between baseline and average heart rate in trial with stroke were evaluated. They found that associations between baseline heart rate and stroke were significant in crude analyses and after adjusting for age and sex alone, but not after adjusting for other prognostic factors, while in-trial heart rate was significantly associated with stroke even after multivariate adjustment.[145] Associations between heart rate and other vascular diseases such as peripheral arterial disease or abdominal aortic aneurysm have not yet been explored and the question whether there is a differential effect of heart rate on specific separate vascular or (cerebro)vascular diseases. This PhD seeks to explore these cerebral and peripheral vascular phenotypes individually and with higher resolution among genders.

1.8. Conclusions

Heart rate is the number of heartbeats per unit of time, typically expressed as beats per minute (bpm). Heart rate limit was set arbitrarily when heart rate was not yet regarded as a risk factor for cardiovascular disease, probably with the main purpose of distinguishing between a disease state. In clinical practice, heart rate is measured using the palpation method, the more precise electrocardiogram (ECG) or automated blood pressure devices. HR reduction plays a pivotal

role at the cellular level. Heart rate is affected by specific medication types such as sympathomimetics, bronchodilators and anti-depressives that increase heart rate and sympatholytics, vasodilators and glycosides that decrease it. Among the heart rate lowering medications, ivabradine acts by inhibiting *I*f, an ionic current involved in pacemaking activity in the sinoatrial node. The findings of clinical trials confirm that the beneficial effect of beta-blockers, calcium channel blockers and ivabradine in post MI patients or heart failure patients is proportionally related to the reduction of resting heart rate. The most commonly investigated cardiovascular diseases (besides fatal cardiovascular events) examined by literature as having affected by increased heart rate are coronary diseases (stable angina, myocardial infarction), cardiac diseases such as heart failure, and vascular diseases particularly stroke. This PhD will expand the range of cardiovascular diseases assessed by published epidemiological studies and will further explore associations of heart rate with coronary, cerebral and vascular endpoints individually examined.

2. Associations of heart rate and cardiovascular diseases: literature findings

In this chapter I summarize the main findings of published cohort studies concerning the association of resting heart rate with cardiovascular diseases in three different populations: healthy, patients with coronary artery disease and patients diagnosed with atrial fibrillation. The main objectives of this literature review are:

- To identify cohort studies on resting heart rate and incidence of CVDs (fatal or non fatal) in healthy populations (free from initial atherosclerotic disease at the time of entry in the study)
- To identify cohort studies on resting heart rate and CVDs experience (fatal or non fatal) in populations with stable coronary artery disease
- To detect cohort studies on resting heart rate and a)the onset of atrial fibrillation in general poulations and b) the experience of subsequent CVD events in atrial fibrillation populations.

The start of follow-up in these studies should be designated by the heart rate measurement at baseline and the end by the experience of one of fatal or non fatal cardiovascular outcome or all-cause mortality. In each section I start describing the search strategy that I conceived and implemented to retrieve relevant studies. I used the PICO tool, a helpful structured approach for developing questions about interventions (population, intervention (or risk factor of interest), comparison and outcome), adjusted to the form of questions at the present PhD. This approach divides each question into four components: 1) population (the population under study, in this case healthy, CAD or atrial fibrillation), 2) intervention (heart rate), 3) comparators (different levels of heart rate), 4) outcome (risk of cardiovascular diseases)[146]. I then list the main studies found and analyze the knowledge gaps in the field of interest and the methodological limitations of previous studies. I finish by summarizing key issues that need to be addressed to advance knowledge in order to answer the research questions of interest.

2.1. Heart rate and onset of CVDs in initially healthy populations

2.1.1. Search strategy

Eligibilty criteria

Studies with subjects who had history of prior cardiovascular disease were excluded. Populations not in sinus rhythm, or populations contained children or adolescent subjects were also excluded. Studies examining heart rate measurements not taken at a resting state (during

exercise or from ambulatory devices) were also excluded, as well as studies that were using heart rate variability, or fetal heart rate or infant heart rate in their titles or abstracts.

Literature search

To identify all the appropriate published literature, I initially focused on the PICO componentsof each individual research question and determined which were searchable and which could be spread out into multiple terms (e.g. for the exposure-heart rate split into: heart rate/classification, heart rate/drug effects, heart rate/etiology, etc.). Once I had determined all of the specific concepts (the main term was heart rate (pulse rate as synonym)) and to the study outcomes I combined the terms with the Boolean operators, AND, OR or NOT to optimize my search in Pubmed, Medline and google scholar. I used both a comprehensive list of relevant terms and Medical Subject Heading (MeSH) terms to construct my search. I also used truncation (wildcards) in the form of the symbol "*" to identify terms of similar syntax (e.g. "ischaem*). Finally, I used free text to search studies in google scholar. This type of search has limited specificity but high sensitivity. The detailed step-by-step research strategy that I used to identify all relevant studies on resting heart rate and CVDs in healthy populations is presented in **Table 2.1**. The final query used in search strategy yielded 1,209 studies. The abstracts of these studies then were retrieved and of the ones that were relevant, the whole paper was downloaded. I identified 19 cohort studies that met my search criteria. These are listed in **Table 2.2**.

Table 2.1 Search strategy used to identify studies on association between heart rate and onset of CVD

Concepts	**Boolean operator**	**# search**	**Terms and queries used**	**No. of studies found**
Risk factor (Heart rate)	OR	#1	((((((“heart rate"[MeSH Terms] OR pulse rate[Title]) NOT variability[Title]) NOT infant*[Title]) NOT fet*[Title])) NOT exercise[Title]	10,520
		#2	(("pulse"[MeSH Terms] OR pulse rate[Title]))	599
Population	OR	#3	Search incidence of cardiovascular disease*[Title/Abstract]	9274
		#4	Search (cardiovascular disease NEXT onset[Title/Abstract]) OR CVD NEXT onset[Title/Abstract] Schema: all	0
Endpoints	AND	#5	(((((“coronary artery disease”[MeSH Terms] OR coronary heart disease[Title/Abstract]) OR angina pectoris[Title/Abstract]) OR stable angina[Title/Abstract]) OR unstable angina[Title/Abstract]) OR angina[Title/Abstract]	127,207
	OR	#6	(((((((("myocardial infarction"[MeSH Terms]] OR Ischaem* OR STEMI[Title/Abstract]) OR non STEMI[Title/Abstract]) OR nSTEMI[Title/Abstract]) OR acute coronary syndrome[Title/Abstract]) OR heart attack[Title/Abstract]) OR heart failure[Title/Abstract]) OR syncope[Title/Abstract] OR syncope/cardiac[Title/Abstract] OR syncopy[Title/Abstract])	232,803
	OR	#7	("stroke"[MeSH Terms] OR "stroke"[All Fields]) OR cerebrovascular disease[Title/Abstract]	205,117
	OR	#8	(((abdominal aortic aneurysm) OR peripheral arterial disease) OR peripheral ischaemia) OR peripheral vascular disease	92,979
		#9	((cardiac arrest) OR sudden cardiac death) OR death	592,057

Final Query used		#1 OR #2 AND #3 OR #4 AND #5 OR #6 OR #7 OR #8 OR #9	(((((((heart rate[Title]) OR pulse rate[Title]) NOT variability[Title]) NOT infant*[Title]) NOT fet*[Title])) NOT exercise[Title]) AND ((((((coronary artery disease[Title/Abstract]) OR coronary heart disease[Title/Abstract]) OR angina pectoris[Title/Abstract]) OR stable angina[Title/Abstract]) OR unstable angina[Title/Abstract]) OR angina[Title/Abstract])) OR (((((((myocardial infarction[Title/Abstract] OR STEMI[Title/Abstract]) OR non STEMI[Title/Abstract]) OR nSTEMI[Title/Abstract]) OR acute coronary syndrome[Title/Abstract]) OR heart attack[Title/Abstract]) OR heart failure[Title/Abstract]) OR syncope[Title/Abstract] OR syncope/cardiac[Title/Abstract] OR syncopy[Title/Abstract]))) OR ((stroke) OR cerebrovascular disease[Title/Abstract])) OR ((((abdominal aortic aneurysm) OR peripheral arterial disease) OR peripheral ischaemia) OR peripheral vascular disease)) OR (((cardiac arrest) OR sudden cardiac death) OR death OR mortality)	1,209

2.1.2. Studies of heart rate and onset of CVDs

Zero out of nineteen of the cohort studies identified were based on the use of linked electronic health records to define heart rate.Twelve studies were conducted used data collected in 1960's, 1970's or 1980's, one in 1940's and two in 1990's and the study periods terminated around ten or twenty years ago. The sample size varied, with only two being of a 10^5 size (Tverdal, Hsia). The majority of the studies were conducted in USA (5 studies) and the rest in Europe (apart from 3 in Asia) and only one in UK included 7,735 subjects.

The majority of studies focused on all-cause mortality, cardiovascular and non-cardiovascular death, with one reporting on sudden cardiac death and myocardial infarction.[147] None disaggregated the composite endpoints (e.g. disagreggate CHD into stable and unstable angina and myocardial infarction). Studies were restricted to the investigation of coronary diseases. None specifically reported on cerebral, abdominal or peripheral arterial disease associations with heart rate.

In terms of the heart rate levels used to analyse their research questions, only 3 studies used the 70-79bpm level which represents average heart rate values in the population.[148-150]

The studies found did not explore potential differences between genders. One of the two largest studies, including 129,000 patients was restricted to post-menopausal women (Hsia)[151] and only four reported a sex related comparison in heart rate associations[152-155] with cardiovascular mortality and all-cause mortality outcomes that showed positive and graded relationship between heart rate and mortality from CVD, IHD, stroke, and death from any cause both in men and women. The shape of the associations that could provide information on thresholds above or below which the risk of cardiovascular events is increased or decreased was described only by the same study of mortality outcomes.[152]

Overall, I identified 19 cohort studies (no trials identified), the majority characterized by limited sample size in the majority that did not allow for further subgroup analyses, or specific cardiovascular endpoints examination. None of the studies used primary care data to collect heart rate or linked electronic health records in the data collection process. A clear need for a study of large sample size and high resolution that will explore specific cardiovascular phenotypes with sufficient power for gender comparisons is apparent.

Table 2.2 Summary of cohort studies examining associations of resting heart rate with the onset of CVDs in healthy populations

Design and methods								Endpoints		Results			
Author	**Country**	Data sources		Year of study initiation	Sample size	Age	Gender	Mortality only outcomes	N of non-fatal specific diseases	Description of shape of association	Estimates reported for 70-79bpm	Test for sex interaction	Reported comparison and main findings
		Population survey	EHR										
Kannel et al.(1987)[85]	USA	●	○	1948	5,209	35-95	Both	●	0	○	○	ɵ	Per 1bpm increase Finding: No evidence of threshold or association was found.
Gillum et al. (1991)[153]	USA	●	○	1971	5,995	45-74	Both	●	0	○	○	●	Reference level: <74bpm. Finding: High risk of all-cause and CVD death for HR>84bpm for both sexes (in white people), risk for CHD only present in men
Shaper et al (1993)[148]	UK	●	○	1969	7,735	40-59	Males	●	0	○	●	○	Reference level: <90 Findings: high statistically significant risk of IHD morbidity and mortality and SCD for ≥90bpm but not for 70-to -89
Mensink et al. (1997)[19]	Germany	●	○	1982	4,756	40-80	Both	●	0	○	○	ɵ	Per 20bpm increase Findings: Men: all-cause and CVD mortality HazR=1.7 and 1.7 Women: HazR=1.4 and HazR=1.3 respectively
Benetos et al.[154] (1999)	France	●	○	1970	19,386	40-69	Both	●	0	○	○	●	Reference level: 60-80bpm In men increased risk for CV, all-cause and non-CV death and CAD events for HR>100bpm. No stroke risk *Women: insignificant increased risk for CVD & stroke.*
Greenland et al. (1999)	USA	●	○	1967	33,781	18-74	Both	●	0	○	○	○	Per 12 bpm increase associated with increased risk of CHD, CVD mortality in men but *not consistently in all ages for women*
Palatini et al. (1999)[156]	Italy	●	○	1983	1,938	>65	Both	●	0	○	○	○	**Reference level 1st quintile (non-specific values)** **Elder** Men/women (for all-cause mortality, 5th quintile: RR=1.21/1.13), Cardiovascular mortality: RR=1.55/1.08
Kristal-Boneh et al. (2000)[157]	Israel	●	○	1985	3,527	43	Males	●	0	○	○	○	Reference level: 70-79bpm For >90bpm: All-cause mortality RR=2.23 CVD mortality: RR=2·02. *For 80-89bpm no effect was found*

Seccarecci a et al. (2001)[149]	Italy	●	○	1984	2,533	40-69	Males	●	0	○	●	○	Reference level: <60bpm For≥90 bpm: All-cause HazR = 2.67 CVD mortality: HazR=2.54 Non-CVD mortality :HazR=2.87
Jouven et al. (2001)[147]	France	●	○	1967	7,746	42-53	Males	MI fatal, SCD	2	○	○	○	For 1 SD increase of HR: Sudden death: HazR=1.28 (1.06-1.61) Fatal MI: HazR=1.05 (0.95-1.16) (multivariable)
Fujiura et al (2001)	Japan	●	○	1977	573	40-64	Males	●	0	○	●	○	Reference level: 60-69bpm For>90bpm: mortality risk :RR=2.68
Okamura et al. (2004)	Japan	●	○	1981	8,800	30	Both	stroke	1	○	○	○	For 11bpm increase: CHD+HF, non-CV and all-cause death: insignificant for both men/women. For highest quartile (HR>74bpm vs <60bpm), CHD+HF HazR=3.99 in younger men. HR not associated with cerebral infarction, cerebral haemorrhage
Tverdal et al. (2008)[152]	Norway	●	○	1985	379,843	40-45	Both	●	0	●	○	●	In HR>95bpm vs <80bpm and every 10bpm: SCD insignificant In HR >95bpm vs <65bpm: Stroke death insignificant in both sexes, CVD and IHD death significant only in men
Hsia et al. (2009)[151]	USA	●	○	1993	129,135	50-79	Women	stroke	1	○	○	○	Reference level 1st quintile (<62bpm) For HR>76bpm: MI or coronary death: HazR=1.68 Stroke: HazR=1.23 For HR 71-76bpm (4th quintile), HazR=1.21
Cooney et al. (2010)	Finland	●	○	1972	21,853	25-74	Both	●	0	○	○	ɵ	*For each 15 bpm*: CVD, CHD and total mortality significant in men/women, MI (non-fatal)+CHD death insignificant for men *>90bpm vs <60bpm* was associated with a 2-fold increased risk of CVD mortality in men and 3-fold increased risk in women
Jensen et al. (2012)	Denmark	●	○	1976	6,518	56.2	Males	●	0	○	○	○	For every 10bpm HR: CVD mortality: HazR=1.21. All-cause HazR=1.15
Jensen et al. (2013)[158]	Denmark	●	○	1970	2,798	63	No	●	0	○	○	○	Reference level: <50bpm 5th quintile(>90bpm):All-cause mortality risk: HazR=3.06
Nanchen et al. (2013)[159]	Netherlands	●	○	1993	4,768	≥55	Both	HF	1	○	○	ɵ	Per 10 bpm in men, risk of HF: HazR=1.14 (1.03–1.27) ***No association found in women***
Opdahl et al. (2014)	USA	●	○	2000	6,814	45-84	Both	HF	1	○	○	●	Per 1bpm: Heart failure incidence: HR=1.04(1.02-1.06), Quartile analysis reference level: <57bpm For >69bpm (4th quartile): HR=3.76 (2.00–7.07).

												Risk consistent for 2nd, 3rdquartiles.
CALIBER study	**UK**		●	**1997**	**196,508**	**>30**	Both	●	11	●	●	In UCD no association with women was found	Reference level: <60bpmHeart rates >80bpm have an increased risk of heart failure and unheralded coronary death and a risk of sudden cardiac death for heart rate >90bpm. No association with CAD endpoints, cerebrovascular, or peripheral vascular diseases. Apparent threshold for effect on SCD with the linear association confined to heart rate values >85bpm.

Abbreviations: HER, electronic health records; HazR, Hazard Ratio; HR, heart rate; Q, quintile; CAD, coronary artery disease; CVD, cardiovascular disease; MI, myocardial infarction; HF, heart failure; AF, atrial fibrillation; SCD, sudden cardiac death; In test sex interaction: ● denotes tested and women had similar results as men; ɵ denotes weaker associations in women; ○ denotes no testing

2.2. Heart rate and cardiovascular diseases in populations with CHD

In this sub-chapter I present the search strategy and findings of studies looking at the association of resting heart rate with cardiovascular diseases in patients with coronary artery disease. The start of follow-up in these studies should be designated by the heart rate measurement after a diagnosis of stable coronary heart disease and the end by the experience of one of fatal or non fatal cardiovascular outcome or all-cause mortality. Eligibility of studies was based on whether their population did not suffer from stable coronary artery disease (alone or with co-morbidities), or if they exclusively had an acute coronary event in less than a month. Systematic reviews or meta-analytic studies, as well as studies that examined heart rate variability associations with CVDs since these studies do not explore associations of a resting heart rate at baseline but the change in heart rate values over time, or finally their populations contained children or adolescent subjects (or fetal subjects) were also excluded.

2.2.1. Search strategy

Eligibility criteria

Studies with healthy subjects or studies with an acute ischaemic event at baseline or less than a month before the study entry and initiation of follow-up were excluded. Populations not in sinus rhythm, or populations contained children or adolescent subjects were also excluded. Studies examining heart rate measurements not taken at a resting state (during exercise or from ambulatory devices) were also excluded, as well as studies that were using heart rate variability, or fetal heart rate or infant heart rate in their titles or abstracts. No restriction criteria were set regarding language or date of publication.

Literature search

Similarly as in the first section, to identify all the appropriate published literature, I initially focused on the PICO componentsof each individual research question and determined which were searchable and which could be spread out into multiple terms and I combined them with the Boolean operators, AND, OR or NOT to optimize my search in Pubmed, Medline and google scholar. The search for the exposure heart rate was identical in all literature searches. I used both a comprehensive list of relevant terms and Medical Subject Heading (MeSH) terms to construct my search. I also used truncation (wildcards) in the form of the symbol "*" to identify terms of similar syntax (e.g. "ischaem*). Finally, I used free text to search studies in google scholar. Web crawling was implemented, cross references from original articles (backward and forward citations) and systematic reviews were also searched and assessed, whereas grey literature (conference proceedings and symposiums') was handsearched. The strategy used is presented in **Table 2.3**. The final query used in search strategy yielded 1,209 studies. The abstracts of these studies then were retrieved and of the ones that were relevant, the whole

paper was downloaded. I identified 19 cohort studies that met my search criteria. These are listed in **Table 2.4**.

Table 2.3 Search strategy used to identify studies on association between heart rate and prognosis of CVDs in people with CAD

Concepts	Boolean operator	Search	Query	Items found
Risk factor		#1	((((((“heart rate"[MeSH Terms] OR pulse rate[Title]) NOT variability[Title]) NOT infant*[Title]) NOT fet*[Title])) NOT exercise[Title]	10,520
Population	AND	#2	coronary artery disease	129031
	OR	#3	Search (((stable[Title]) AND coronary artery disease[Title]) OR coronary heart disease[Title]) OR coronary artery disease[MeSH Terms]	55112
		#4	Search coronary heart disease[MeSH Terms]	507623
Endpoints		#5	Search (((cardiovascular diseases[Title]) OR coronary artery disease[Title/Abstract]) OR coronary heart disease[Title/Abstract]) OR ischaemic disease[Title/Abstract]	2872
	OR	#6	Search (heart failure[Title/Abstract]) OR heart attack[Title/Abstract]	108486
	OR	#7	Search mortality[Title/Abstract]	118582
	OR	#8	Search sudden cardiac death[Title/Abstract]	10195
	OR	#9	Search atrial fibrillation[Title/Abstract]	43259
	OR	#10	Search (stable angina[Title/Abstract]) OR angina pectoris[Title/Abstract]	21014
		#11	Search ((myocardial infarction[Title/Abstract]) OR ischaemic[Title/Abstract]) OR ischaemi*[Title/Abstract]	181708
		#12	Search (#1 AND #2 or #3 AND #4 AND #5 OR #6 OR #7 OR #8 #9 OR #10 OR (#11 OR #12))	237689
Final Query used		#13	Search ((((((((((#1) AND #2) OR #3)) OR #4) AND #5)) OR (#6 OR #7 OR #8 OR #9 OR #10 OR #11)	8583

2.3. Studies on heart rate and prognosis of CAD

Of the 8,583 studies identified, 12 were eligible and are presented in **Table 2.4.** Among the cohort studies identified that assessed resting heart rate association with CVDs, a multicentre cohort of Bangalore et al.[160] examines the association of heart rate lowering medication (beta-blockers) with the prognosis of cardiovascular events in CAD populations. In chapter 1 we also observed 3 RCTs that examined associations of resting heart rate lowering via ivabradine intake with CVDs (**Table 1.4**). One of them, BEAUTIFUL study by Fox et al.[125] uses data from this RCT to assess in a subgroup of patients with CAD and left ventricular systolic dysfunction the impact of the effect of heart rate on cardiovascular outcomes directly and not through the use of ivabradine as proxy of heart rate lowring. This study is also included in **Table 2.4**.

None of the studies was based on the analysis of linked (or non-linked) electronic health records collected from baseline to follow-up. Contemporary studies were exclusively conducted in populations included in angiography registries [161-165] and clinical trials.[125, 145, 166-168] None explored associations in the general population (most severe cases admitted in hospitals or recorded in registries) or a systematic level (ascertainment bias/Berkson's fallacy). The latter might result in a spurious negative correlation between specific characteristics of the CAD (e.g. people that have more severe chest pains or lower LVEF tend to get admitted for coronary procedures that people with CAD in the general population). As a result, angiography registries contain data exclusively colected for research purposes and is confined to high risk patients or patients admitted for acute coronary syndromes or referred for specific cardiovascular procedures. Consequently, the external validity of their findings is potentially compromised, while the applicability and generalizability of this data on the general population is under question.

Apart from the latent differential effects in clinical trials and research-selective populations, limitations stemming from their inclusion criteria confinining their population generalisability. To be more specific, approximately half of the studieswere conducted among patients who had specific comorbidities. In BEAUTIFUL study by Fox et. al. in 2008[125], included people with signs of heart failure (reduced left ventricular ejection fraction). Kolloch in 2008[166] studied people with CAD and hypertension, Anselmino in 2010[163] people with CAD and diabetes, and Jensen in 2013[168] patients with stable and unstable coronary disease after PCI. Only Diaz et al. explored heart rate associations with CVDs in CAD patients without other comorbidities[161].

Only three studies assessed specific cardiovascular endpoints (Kolloch (N=22,192), Diaz (N=24,959), Lonn (N=31,531)). Composite cardiovascular endpoints have been extensively studied. None investigated atrial fibrillation as an incident event in people with CAD.

No study described the shape of the association between heart rate and CVDs to identify risk thresholds. Gender differences in heart rate associations with cardiovascular events have not been sufficiently explored. Specifically, only one study investigated interactions with sex [166] since its sample size allowed to, however not at a baseline heart rate analysis. Finally, current evidence is largely indirectly derived from evaluations of heart rate lowering medication on cardiovascular endpoints and not on the study of associations with heart rate measurements [126, 128, 160]. Table 2.2.2 (b) lists these studies.

Two of the largest published studies conducted in populations with CAD show conflicting results. The BEAUTIFUL study that analysed patients' outcomes based on a heart rate division of >70bpm vs <70bpm found that heart rate >70bpm resulted in statistically significant higher risk of cardiovascular death, heart failure, MI and coronary revascularisation in people with reduced LVSF[125]. Although the risk for coronary outcomes was higher in the groups with heart rate above 70 bpm, they found no evidence of a strong gradient for risk for higher heart rates. The SIGNIFY trial conducted in 2014 by Fox et. al. assessed ivabradine (a pure heart rate lowering agent) efficacy and effectiveness in people with CAD and a normal LVSF[128]. The investigators found that there was no significant difference between the ivabradine group and the placebo group in the incidence of death from cardiovascular causes and nonfatal myocardial infarction. Ivabradine was associated with an increase in the incidence of the primary end point among patients with more severe angina but not among those with less severe.

Table 2.4 Literature review of studies examining resting HR and prognosis in people with stable coronary artery disease.

Author/year	Country	Year of data collection	No of patients	Clinical trial	(Angiography) Registry	EHR	Comorbidities in addition to CAD at baseline	Heart rate classifications	Gender comparison	>1 disease outcomes	Atrial Fibrillation	Shape of association	Findings
Cohort studies													
Diaz[169]	Canada	1975-1979	24,959	○	●	○	○	5th Quintile (>83bpm) vs 1st (<62bpm):	○	Hospitalization for: HF, MI, SA, stroke	○	○	Reference level: <62bpm (1st quintile) For 5th Q (>83bpm): **No significant association with HF, MI, SA, stroke**
Aboyans[162]	France	1998-2002	1,022	○	●	○	○	10bpm HR increase	○	Stroke/death/ MI/stroke/TIA composite	○	○	For 10bpm HR increase, no association with stroke/death endpoint and mild with MI/stroke/death
Anselmino[163]	Multicentre (25 European countries)	2003-2004	2,608	○	●	○	Diabetes	10bpm RHR increase	○	Composite of all-cause mortality, MI, and stroke	○	○	10bpm RHR increase mildly associated with all-cause mortality/MI/stroke
Ruiz Ortiz[164] **2010**	Spain	2000-2004	1,264	○	●	○	○	1bpm HR increase, or >70bpm vs <70bpm or highest quartile (>74bpm vs <60bpm)	○	Composite of mortality, ACS, need for coronary revascularization, stroke, or admission for HF	○	○	For 1bpm HR increase, or >70bpm vs <70bpm or highest quartile (>74bpm vs <60bpm) no association of RHR with the rate of major or coronary events or total mortality

ó Hartaigh[165]	Germany	1997-2000	3,316	○	●	○	○	Quartiles (4th >84bpm vs 1st <64bpm) and 10bpm increase	○	All-cause and CVD mortality	○	●	Reference level: <64bpm (1st quartile) >84 bpm or 10bpm increase in HR associated with overall and CVD mortality
Bangalore[160] **2012**	44 countries across 6 major regions (Latin/North America, Europe, Asia, the Middle East, and Australia)	2003-2004	16,315	○	●	○	Hypertension	-	○	Stroke, MI	○	○	Heart rate lowering medication (ß-blocker) use associated with increased risk of CV events and death
Bemelmans[170]	Netherland	1996-2009	4,272	○	●	○	PAD, AAA	Quartiles (Q5 >82bpm vs Q1 <51bpm), 10 bpm increase	○	MI, stroke, vascular death, all-cause mortality	○	○	Reference level: <51bpm (1st quartile) No association between an increase of 10 bpm RHR or Q5 in MI or stroke risk, associations with all-vascular events and death
Clinical trials													

Fox[125] 2008 (BEAUTIFUL)	International, multicentre	2004-2006	5,438	●	○	○	LVSD	>70bpm vs <70bpm	○	Hospitalization for: MI, HF, revascularization, death	○	○	Reference level: <70bpm For heart rate >70bpm, increased risk of MI, HF, revascularization and CV death
Kolloch[166]	Multicentre (United States, Australia, New Zealand Germany, Canada,	1998-	22,192	●	○	○	Hypertension	-	○	Composite of all-cause death, non-fatal MI, or non-fatal stroke	○	●	Baseline heart rate associated with adverse outcomes with a linear relationship (Not specified HR values)
Ho[167] J.E	multicentre	1998-1999	9,580	●	○	○	○	>70bpm vs <70bpm	○	Composite of CHD death, nonfatal MI, resuscitated cardiac arrest, or stroke.	○	○	Reference level: <70bpm For >70bpm, **HF risk**: HR=2.30 Mild association with MI and stroke

Jensen	Switzerland, Denmark, Austria, Italy	2007-2008	2,029	●	○	○	Stable/ unstable population after PCI	<60, 60-69, 70-79, 80-89, >90bpm	○	Composite of CVD death/MI	○	○	Reference level: <60bpm For HR >90bpm the risk of CVD death and MI composite: HR=6.2
Lonn[145]	multicentre	-	31,531	●	○	○	Peripheral or CBV disease with diabetes and end organ damage	Quintiles, HR ranges:<50, 50–59, 60–69, 70–79, 80–89, 90–99 and >100bpm, also <70bpm	○	Composite of: death from CV causes, MI, stroke, or hospitalization for HF and all-cause mortality	○	○	Reference levels: <50bpm and <70bpm Continuous relationship between MVE and HR with no observed threshold. MVE, CV death, stroke, CHF, and all-cause death
Present PhD													
CALIBER	UK	1997-2010	51,703	○	○	●	○	<60, 60-69, 70-79, 80-89, >90bpm, per 10 continuous, quintiles	●	SA, MI, AF, HF, SCD, PAD, Stroke CVD death, All-cause mortality	●	●	Reference level: <60bpm For >90bpm increased risk for HF (HazR=2.96), SCD (HazR=1.30) and AF (HazR=2.04)

Abbreviations: HER, electronic health records; HazR, Hazard Ratio; HR, heart rate; Q, quintile; CAD, coronary artery disease; CVD, cardiovascular disease; MI, myocardial infarction; HF, heart failure; AF, atrial fibrillation; SCD, sudden cardiac death;PAD, peripheral arterial disease; SA, stable angina

In summary, available literature findings come from trials and registries and are conducted for research specific purposes, are confounded by comorbidities, with insufficient sample sizes and underreporting of potential differential effects among subgroups. Opposing findings of trials conducted in research-recruited populations or through drug treatment administration analysis, complex the mechanistic inferences that were established so far pointing out the endothelial dysfunction pathway. The criteria set at the search strategy stage and the findings of **Table 2.4** enhance the contribution of our study in the sense that this is the first attempt to assess CVD prognosis in a general sample of CAD people that includes less severe cases of coronary disease that ranges from mild symptoms to severe cases that undergo procedures and is highly representative and potentially avoid overestimation of effects. The need for use of clinically relevant heart rate levels, collected from a primary care seeting of GP practices with sufficient indivual sizes that allow risk assessment for heart rate values previously regarded as normal and were so far dismissed from inclusion in the alarming categories, is apparent. An additional benefit of the use of Linked electronic health records, is the provision of insights into the pathophysiological mechanisms of disease progression in a stable CAD population.

2.4. Heart rate and atrial fibrillation incidence in healthy populations

Similar search process and tools as in the revious sections were followed to retrieve studies exploring ithe association of resting heart rate with i) the incidence of atrial fibrillation and ii)the risk assessment of patients with atrial fibrillation (AF) for subsequent cardiovascular and coronary diseases. Specifically, exposure (heart rate) search was identical to the two previous searches. Additional search terms for outcomes (atrial fibrillation) were added. The start of follow-up should be the date of heart rate measurement and the end the date of atrial fibrillation experience (regardless of cardiovascular events prior to the atrial fibrillation event) in order to explore heart rate associations and AF onset. To assess heart rate associations with CVD prognosis of patients with AF, the initiation of follow-up should coincide with a heart rate measurement in people with AF and the end of follow-up with the first experience of a cardiovascular event (fatal or non-fatal). The detailed research strategy I used to identify all relevant studies is presented below in **Table 2.5**.

2.4.1. Search strategy

Eligibility criteria

For the objective (i) studies with subjects who had history of prior cardiovascular disease were excluded. Populations not in sinus rhythm, or populations contained children or adolescent subjects were also excluded. Studies examining heart rate measurements not taken at a resting state (during exercise or from ambulatory devices) were also excluded, as well as studies that were using heart rate variability, or fetal heart rate or infant heart rate in their titles or abstracts.

For the objective (ii) similar criteria were set with the difference that patients should have been diagnosed with AF before the time of heart rate measurement.

Literature search

In this sub-chapter I present the search strategy and findings of cohort studies looking at the association of resting heart rate with incidence of atrial fibrillation in healthy population and subsequent cardiovascular events in the atrial fibrillation patients. The inclusion of studies was based on whether their population was free from a previous atrial fibrillation event, or atrial fibrillation population followed-up for cardiovascular risk and their populations provided heart rate information. Systematic reviews or meta-analytic studies, as well as studies that examined heart rate variability associations with atrial fibrillation or CVDs, or their populations contained children or adolescent subjects (or fetal subjects) were excluded.

Table 2.5 Search strategy used to identify studies on association between heart rate, incidence of atrial fibrillation and the risk for future CVDs

Concepts	Boolean operator	Search	Query	Items found
Risk factor		#1	((((((“heart rate"[MeSH Terms] OR pulse rate[Title]) NOT variability[Title]) NOT infant*[Title]) NOT fet*[Title])) NOT exercise[Title]	10,520
Endpoint Atrial Fibrillation	AND	#2	Search atrial fibrillation[Title]	24890
	OR	#3	Search atrial fibrillation[MeSH Terms]	36751
	OR	#4	Search "atrial fibrillation/epidemiology"[MeSH Major Topic]	2139
	OR	#5	Search (onset) AND atrial fibrillation[Title/Abstract]	448
	OR	#6	(incidence[Title]) AND atrial fibrillation[Title]	448
Cardiovascular Outcomes		#7	(((prognosis[Title/Abstract]) AND coronary artery disease[Title/Abstract]) OR cardiovascular disease*[Title/Abstract]) OR CVD[Title/Abstract]	116915
	OR	#2	(cardiovascular disease[Title/Abstract]) OR CVD[Title/Abstract]	89365
	OR	#3	incidence of cardiovascular disease*[Title/Abstract]	40075
	OR	#6	((onset) AND cardiovascular) AND CVD	539
	OR	#7	(incidence of cardiovascular disease*) OR incidence of CVD	9274
	OR	#8	((myocardial infarction[Title]) OR stable angina[Title/Abstract]) OR heart	178839
		#9	((adverse[Title/Abstract]) AND cardiovascular outcomes[Title/Abstract]) OR cardiovascular*[Title/Abstract]	301501
		#10	(((((#2) OR #3) OR #4) OR #5) OR #6)	38045
		#11	(((#7) OR #8) OR #9)	462898
Final Query used		#12	(((#1) AND #10)OR#11)	4921

2.4.2. Existing studies on heart rate and incidence of atrial fibrillation

From the literature search, 4,921 studies were found relevant and their abstracts were downloaded. Only 7 of them fulfilled the eligibility criteria. **Table 2.6** below shows that information on heart rate and atrial fibrillation incidence from observational or experimental studies is limited. Recent epidemiological studies are few and have been extensively conducted in populations with specific comorbidities already, namely established cardiovascular diseases [171-175], or hypertensive populations[173]. None examined sex differences in associations or described shapes of associations, potentially due to their limited sample sizes. Additionally no study used clinically relevant or sensitive heart rate levels to yield information on "normal" heart rate values associations with AF applicable to general practice. No study has previously assessed the risk of subsequent non-fatal cardiovascular events risk in patients with atrial fibrillation and only two assessed subsequent mortality but with limited sample sizes (**Table 2.7**). There is a clear literature gap that would render a new study exploring associations of resting heart rate with the incidence of atrial fibrillation and subsequent risk of CVDs, necessary.

Table 2.6 Cohort studies reporting association between resting heart rate and incidence of atrial fibrillation

Author/year	Year of data collection	# of patients	Population based cohort		Baseline CVDs excluded	Gender comparison	Heart rate levels	N of AF events	Shape of association	Findings
			EHR	survey/registry/ trial						
Krahn[171]	1948-1992	3,983	o	●	o	o	<100bpm, >100bpm	299	o	Reference level: <100bpm Findings: For HR>100bpm: RR=1.81 (1.40-2.34)
Wilhelmsen[172]	1970-1997	7,495	o	●	o	o	<65bpm, 66-80bpm, >89bpm	754	o	Reference level: <65bpm Findings: For HR>89bpm: RR=0.89
Okin[173]	1995-1997	8,828	o	●	o	●	Quintiles (>84bpm), per 10bpm	701	o	For every 10bpm increase, HazR of AF=1.19 (1.13 for men, 1.22 for women)
Perez[176]	1987-2000	42,751	o	●	N/N	o	Per 10bpm	1,050	o	Per 1bpm HR, RR=1.00 (1.0-1.01)
Schnabel[174]	1968-1987	4,764	o	●	o	o	Per 1 bpm	457	o	Per 1bpm, RR=0.98 (0.89-1.08)
Chamberlain[175]	1987-1989	14,546	o	●	o	o	<60bpm, 60-90 bpm, >90bpm	515	o	Reference level: 60-90bpm Findings: HR>90bpm, RR=2.03 (1.34-3.06)
Grundvold[177]	1972-1975	2,014	o	●	●	o	Per 1SD of HR increase	270	o	HR per 1SD: RR=0.98 (0.86-1.11)
CALIBER study (Present PhD)	1997-2010	196,436	●	o	●	●	<60bpm, 60-70bpm, 70-80bpm, 80-90 bpm, >90bpm	6,983	●	Reference level: 70-79 bpm Findings: For HR>90bpm, AF HazR=1.43 (1.33-1.54) For HR<60bpm, HazR=1.22 (1.11-1.34)

Table 2.7 Cohort studies reporting association between resting heart rate and CVDs prognosis in people with atrial fibrillation

Author/year	Year of data collection	# of patients	Population based cohort: EHR	Population based cohort: survey/register/ trial	Heart rate levels	Outcomes	Shape of association	Findings
Andrade et.al. (AFFIRM)[178] (pre-pub)	-	5,164	o	●	90-114bpm, >114bpm	Hospitalizations and mortality	o	Reference 90-114bpm Findings: For >114bpm, HR for hospitalization=1.18. No association with mortality
Li et. al.[179] (pre-pub)	-	7,392	o	●	<60bpm, 61-70, 71-80, 81-90, 91-100, >100bpm	All-cause mortality	o	Reference level <60bpm For heart rate>100bpm, HR for all-cause mortality=1.29 (p=0.003)
CALIBER study (Present PhD)	1997-2010	196,436	●	o	<60bpm, 60-70bpm, 70-80bpm, 80-90 bpm, >90bpm	HF, SCD, SA, STROKE, MI, PAD, CVD & all-cause mortality	●	Reference level: <60bpm Findings: For HR>90bpm, risk of heart failure for HR>90, HazR=1.89 (1.30-2.75)

2.5. Discussion

During the literature search, no meta-analysis was identified related to studies (cohorts or trials) assessing the impact of heart rate on cardiovascular outcomes, neither on general healthy populations, nor coronary heart disease patients. This is not surprising as the majority of cohort studies (and the three trials) showed strong associations of heart rate with mortality outcomes, hence there were no controversial findings related to whether or not an established link was present. Additionally, studies assessing specific cardiovascular events were scarce so the contribution of a meta-analysis would be quite limited. I conducted the literature search without language restrictions, with a combination of free text and controlled vocabulary, used and assessed cross references from original articles and systematic reviews to identify any grey literature evidence. The lack of findings contrasting the strong evidence of heart rate associations with mortality outcomes might imply a "file drawer problem"[180], in other words a sort of publication bias that affects the probability of a study to be published based on whether or not the results are statistically significant, practically significant, or agree with the expectations of the researcher, editor or funder. In the following chapters I will explore associations of heart rate with specific cardiovascular endpoints as well as mortality outcomes (cardiovascular and all-cause) that will enable me to make comparisons with existing literature findings.

2.6. Conclusions

In this chapter, I present the findings of a thorough literature search concerning resting heart rate and its impact on cardiovascular diseases in various populations. We observed that the whole literature body is derived by population surveys, clinical trials or registries, that their common characteristic is the research specific purpose of their data collection. The disadvantages stemming from that are identified in various aspects such as the limited sample sizes, the questionable generalizability of the findings or the representativeness. We also saw that their findings are mostly related to mortality endpoints or composite phenotypes. Furthermore, different trials showed conflicting results in respect to the nature of endpoints affected by heart rate increase that triggers mechanistic considerations regarding the underlying risk pathways of cardiovascular diseases. Finally, clinically relevant heart rate ranges are often ignored from an analytical perspective. Of particular importance is the use of linked electronic records to assess these associations, since the large sample size and resolution they offer, enable the design and perform of large scale analyses allowing for investigation of heart rate associations across a wide range of individual phenotypes.

3. CALIBER: A research platform of linked electronic health records

In the present chapter I will describe the CALIBER research platform of linked electronic health records (EHRs) that I analysed to answer the main research questions that form part of my PhD. The central focus of this chapter is to describe in detail heart rate data available in CALIBER, from the source of recording and the marker's initial form to the research ready values of heart rate and their characteristics, parameters important for the exploration of the marker's association with CVDs in the following chapters. Additional aims of this chapter are i) to describe the raw data that I used to define the populations, risk factors and cardiovascular diseases studied in this PhD, ii) to explain how the process of generation of research ready data that I used can be applied to the design of my and similar studies and iii) Discuss the strengths and weaknesses of CALIBER.

3.1. Introduction

3.1.1. The importance of HER

EHR systems are revolutionizing health research since they have the potential to transform health care from a mostly paper-based system to one that utilizes clinical and other pieces of information to assist providers in delivering higher quality of care to their patients. Some of the basic benefits associated with the use of EHRs include being able to easily access computerized records and the elimination of manual processes, which has historically plagued the medical chart [181, 182]. In 2011 the government published a Strategy for UK Life Sciences[183] which placed EHR research as a central part of the strategy to accelerate health research in the UK. The UK is unique in being the only country with national cardiovascular disease (CVD) registries and primary care data (including important information on cardiovascular risk factors and their management in the community) as well as more standard sources such as cause-specific hospitalization and mortality records and census data available at scale for research. Patients' interactions with the healthcare system generate unprecedented amounts of structured and unstructured EHR data that are stored in disparate clinical information systems. The rich national EHR data sources are increasingly being linked for translational research in the US and Europe with the potential to have a positive impact upon medical care and research. In the UK, a unique ten digit identifier is assigned to each patient and used at each interaction with the NHS allowing the complete patient journey to be traced through EHRs spanning primary care, hospitals, disease registries and ultimately death registries.[184]

3.1.2. The CALIBER platform

CALIBER is a research platform of linked electronic health records (EHR) and administrative health data from primary, secondary and tertiary care, that is GP practices, hospital and disease

registries that is held and developed at the Farr Institute of Health Informatics Research at UCL. Its aim is to provide evidence to inform health care and public health policy for CVDs across different stages of translation, from discovery, through evaluation in trials to implementation, where linkages to electronic health records provide new scientific opportunities. In England the vast majority of the population are registered with a general practice. The majority of symptoms and a large part of diseases first present and captured by primary care in GP practices.

Whereas UK general practices have, via the Clinical Practice Research Datalink (CPRD) and other initiatives, contributed EHR data that led to a substantial number of publications, use of data within hospitals beyond the Hospital Episode Statistics (HES) has led to very limited research. One of the reasons for this is that UK hospitals, similarly to Europe's hospitals, have been at a low level of digital maturity, for example according the Healthcare Information Management Systems Society classification.[185]

3.1.3. EHR and heart rate literature

As I showed in Chapter 2, there is a lack of epidemiological studies examining the associations between heart rate and CVDs. The wealth of data recorded in primary and hospital care remains unexploited. Heart rate is a clinical finding often collected by GPs in daily medical practice. These data generated by those frequent measurements, are population-derived and largely representative and could potentially contribute majorly to the validation and improvement of clinical practice through heart rate examination and the assessment of its place in cardiovascular research. EHRs collected within primary and secondary care settings and processed and generated by researchers at Farr Institute however, have substantially contributed to cardiovascular research, from the onset of cardiovascular diseases [186-190], to the progression of CVDs as showed by CALIBER literature (**Table 3.1**).[191]

Table 3.1. CALIBER studies

CALIBER studies	Study	Exposure and initial presentation of CVDs	Prognosis of CVDs in CAD	Models adjusted for heart rate	Heart rate as main exposure	Associations of an exposure with atrial fibrillation
Rapsomaniki et. al.[188] 2014	BP & incidence of 12 CVDs	●	o	o	o	o
Rapsomaniki et al.[191]	Prognostic models for CAD	o	●	●	o	o

Pujades-Rodriguez et. al.[190] 2014	Socioeconomic Deprivation and the Incidence of 12 CVDs	●	o	o	o	o
Pujades-Rodriguez et. al.[189] 2015	Heterogeneous associations between smoking and a wide range of initial presentations of CVDs	●	o	o	o	o
Shah et al.[187] 2015	Type 2 diabetes and incidence of CVDs	●	o	o	o	o
George et. al.[186] 2015	How does CVD first present in women and men?	●	o	o	o	o
Present PhD	●	●	●	●	●	●

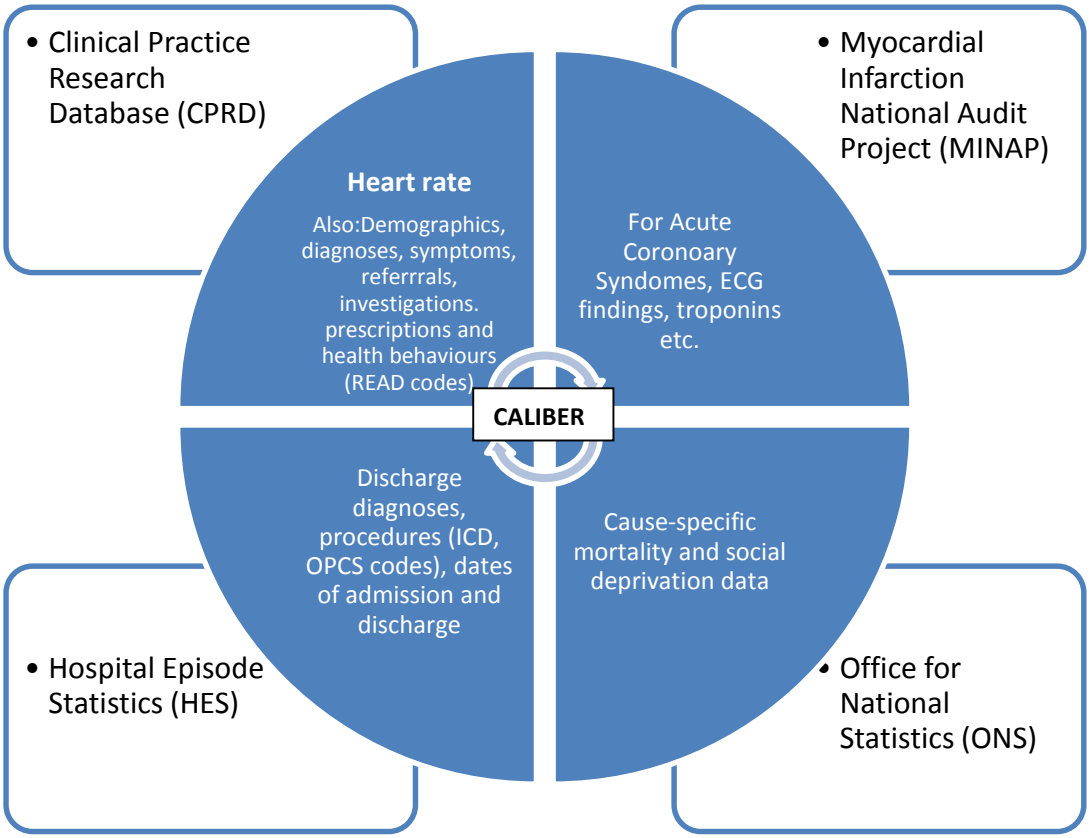
This wealth of information provides a significant source of data towards the assessment of important research questions posed by this PhD on heart rate associations with cardiovascular diseases onset (chapter 4), prognosis (chapter 5) and rhythm disorders (chapter 6).

3.2. CALIBER data sources

Four sources of electronic health data have been linked to form the CALIBER dataset. These data sources spanning primary care records from i) General Practitioner practices (Clinical Practice Research Datalink) and secondary care (ii)myocardial infarction registry (MINAP project), iii) hospital episode statistics (HES) and iv) Office of National Statistics (ONS) mortality

and social deprivation data) (**Figure 3.1**). I used these records linked and processed by researchers at Farr [ł] to address and explore the three main research questions posed by this PhD. The CALIBER dataset was used to assess the associations of resting heart rate with CVD incidence (Chapter 4), CVD progression (Chapter 5) and incidence and progression of atrial fibrillation events (Chapter 6).

Figure 3.1. CALIBER platform data sources



3.2.1. CPRD data

General practices linkage

The CPRD database is a primary care data source containing anonymised patient records for approximately 8% of the UK population (5.2 million patients)[192] and is the only source of heart rate information available in CALIBER. General practitioners routinely collect heart rate as part of their clinical practice. Patients registered with these practices are informed about the data extraction and offered the opportunity to opt out of having their personal data extracted.[193] Forty per cent of the 636 general practices participating in CPRD permit additional data to be extracted to allow linkage of individual patient records with other data sources.[194] For the

studies included in this PhD I used data from the 225 practices in England that consented to data linkage.

Data quality and implications of QOF on heart rate

CPRD has its own data quality control and includes only patients whose data is of "acceptable research quality". The GP contract in 2004, introduced the Quality and Outcomes Framework which stipulates specific information which must be recorded and levels of preventive treatment to be attained.[195] This subsequently brought a rise in heart rate value recordings, since CALIBER data show an increase of heart rate measurements that reaches 44% (28% of CALIBER measurements were recorded any time before 2004 whereas 72% after that date).
The criteria that CPRD uses for inclusion of practices are listed in **Table 3.2**. A data quality audit of the patients' records is also being used. A proportion of 80% of the practices in the CALIBER dataset achieved up-to-standard status by 1st January 2000, with the remaining achieving it in subsequent years. Financial incentives were provided to general practitioners to improve data completeness and quality.

Read codes (NHS Read Clinical Terms Version 3)

"Read codes" is a hierarchical standard clinical terminology system used by General practitioners in the UK to encode data on symptoms, signs, diagnoses, treatments, referrals, laboratory test with or without results, hospital admissions, procedures, administrative information and health behaviours. (31) GPs use 7-character Read codes and is named after Dr James Read who designed it in 1980s for use in his own clinical practice (33). CPRD created the "medcodes" system as a more convenient method in addition to save space. The CPRD Read dictionary contains the medcode to Read mapping, and only includes the subset of Read codes actually used in CPRD. The groupings of diagnoses are approximately similar to ICD-10, but the hierarchy within chapters is less strict, so it is necessary to search by term text as well as by code to ensure that all relevant codes are included in a codelist. With over 100,000 codes in the Read classification, compared to approximately 20,000 in ICD-10, there are the potential for multiple codes for individual diseases and endpoints.

In 1990, the NHS made Read the default scheme for the NHS and general practice, while in 1994 formally replaced the so far used OXMIS medical codes. The Systematized Nomenclature of Medicine - Clinical Terms (SNOMED-CT), an international hierarchical coding system for use with electronic health records is the natural successor to Read codes and has been developed with the knowledge gained through this terminology.[196] It is applicable to all healthcare professions in all health care settings and meets the requirements of both primary and secondary care in the UK in contrast to Read codes that cannot be extended to support all healthcare needs.[196] In primary care, where uptake of structured electronic records is already advanced, much of the benefit of using SNOMED CT within the patient record will be seen through improved sharing of information across care settings, the ability to receive electronic

data such as discharge summaries in a coded format, and the ability to aggregate data across care settings to support for example quality outcomes analysis.[196]

Table 3.2 Data quality standards used by CPRD[193, 197]

Patient-level quality standards: Acceptable research quality (ARQ)	**Practice-level quality standards: Up to standard (UTS)**
An empty or invalid 1st registration date	Monthly prescription rate comparable to other practices
Absence of a record for a year of birth	Percentage of prescriptions with a medical indication
A first registration date prior to birth year	Death rates comparable to other practices
A transferred out reason with no transferred out date	Cause of death recorded
A transferred out date with no transferred out reason	Outcome of pregnancy recorded
A transferred out date prior to their first registration date	Referral rate comparable to other practices
A transferred out date prior to their current registration date	Percentage of referrals with recorded clinical speciality
A current registration date prior to their first registration date	
A current registration date prior to their birth year	
A gender other than Female/Male/Indeterminate	
An age > 115 at end of follow up	
Recorded health care episodes in years prior to birth year	
Registration status of temporary patients	

CPRD provides data in several files consisting of unsorted records, which are described in **Table A3.3** (Appendix 3).The clinical file for instance has 356,446,923 records, 751,165 for heart rate and at least one record for each consultation by every patient registered with GPs in CPRD over the time frame of the dataset. The records of interest in HES and ONS have to be selected from each relevant file and after being combined with other appropriate records if necessary, to provide comprehensible information about individual patients, unlike MINAP data that are provided in specified variables. In CALIBER, data sources are easily identifiable and distinguished since each entry specifies the dataset used in creating each variable.

3.2.2. HES records

Hospital Episodes Statistics (HES) consists of data on admissions since the financial year 1989/90 and provide no information on heart rate measurements or other anthropometric, numerical measurements. These data are recorded by non-clinical trained coders based on the discharge summary weeks after discharge.[198] The hospital admission data includes private patients treated on NHS premises, NHS patients treated by independent providers on behalf of the NHS and non-England patients, as well as NHS patients treated in NHS premises.[193] HES data available in the linked CALIBER dataset covers the period from 1st April 1997 to 31st October 2009. In any given year the completeness of HES in recording admissions to NHS hospitals is very high. Admissions to or procedures done privately by independent providers are not included in HES and therefore not included in my PhD. HES discharge data has nearly complete coverage of admissions and procedures performed in NHS hospitals, though unmeasured private admissions and procedures may be as high as 10% of the overall number for some procedures, particularly in London.

ICD-10 (International classification of disease, 10th Edition, World Health Organisation) and OPCS4.6 (Office for Population Censuses and Surveys codes)

ICD-10 is used in the UK and many other countries to record morbidity and causes of death. In CALIBER, HES and ONS data are coded using ICD-10. ICD-10 has fewer terms than Read, and some specific conditions (e.g. ST elevation myocardial infarction) do not have an individual code. The record for each episode includes up to 20 diagnoses, coded using the International Classification of Disease, Version 10 (ICD-10),[199] and up to 24 procedures, coded using the Office of Population Censuses and Surveys (OPCS) Version 4 codes.[200]Unlike Read, there are associated documents detailing when certain codes may be used, and which combinations of codes can be used to record conditions affecting more than one body system. For example, if an ICD-10 code states '... not otherwise specified', there is an associated list of conditions that have to be excluded (or coded more specifically) for this term to be valid. In Read there are no such guidelines for GPs, so terms should be taken on face value. **OPCS** is used by UK hospitals to encode procedures.

3.2.3. MINAP records

MINAP is the national registry of patients recording continuous data from every hospital that manages acute coronary syndrome (ACS) patients and includes only acute admission health records. Information on the timing of symptom onset and admission, clinical features and investigations (including ECG results and biomarkers of myocardial necrosis), past medical history, hospital treatment and discharge diagnoses collected prospectively at participating hospitals, and submitted to the Central Cardiac Audit Database (CCAD). The data is recorded usually by an audit nurse, days or weeks after admission, by abstracting data from hospital

records.[198] These records are regularly linked by CCAD to mortality data from the Office of National Statistics and made available in anonymised form to researchers as well as fed back to individual hospitals for quality purposes. MINAP was started in 2000, with a limited number of hospitals submitting data. The Registry achieved near national coverage in 2009 with 242 hospitals in 2009, 100% of NHS hospitals in England and Wales.[193]

Resolution of MINAP phenotypes

Clinical phenotypes recordings derived my MINAP records are not offered by any other national source, and has shown that the reduced rates of heart attack in the early part of this century have been largely confined to ST-segment elevation acute myocardial infarction (STEMI) while rates of non-ST-segment elevation acute myocardial infarction (NSTEMI) have remained static.[193] For this PhD, the distinction between the different types of MI was not feasible during analyses, due to limited subjects in each individual phenotype and STEMI and non-STEMI codes have been merged together. However, this detailed epidemiology is less easily available for other manifestations of CVD, such as abdominal aortic aneurysm and ischaemic stroke, because disease-specific registries have either not been developed or have only recently started recording data. This represents an important gap in our knowledge, and it is not clear whether the risk factors and changing epidemiology for CHD can be generalised to other manifestations of CVD.[193]

3.2.4. ONS records

Data on mortality originate from ONS records. Any death occurring within England and Wales must be registered with the registrar of births and deaths, generally within 5 days of the death. The mortality data for England and Wales is highly complete. Doctor (general practitioner or hospital) completes death certificate with cause of death and ICD codes are added by trained non-clinical coders.[198]UK mortality data do not, however, include people either normally or formerly resident in the UK who die abroad. Evidence applicable to the UK suggests that the coding on death certificates for IHD is likely to be accurate, although possibly up to 10% of cases may be missed. The primary, underlying and up to 14 secondary causes of death are recorded using ICD-10.

Besides mortality data, ONS also provided information on the index of multiple deprivation, a deprivation index at the small area level. It is a measure of geographical access used as a surrogate for socio-economic status.

The CALIBER variables and coding algorithms were developed through a process of multiple clinical speciality review across two institutions (University College London and the London School of Hygiene and Tropical Medicine). Professor Harry Hemingway (HH) – Cardiovascular Epidemiology, Professor Liam Smeeth (LS) – General Practice, Professor Adam Timmis (AT) – Clinical Cardiology, Dr Anoop Shah (AS) – Clinical Pharmacology, Dr Kate Walters (KW) –

General Practice, Dr David Osborne (DO) – Psychiatry, all provided clinical expertise in the development of the CALIBER code lists. Spiros Denaxas (SD) provided technical advice and wrote the programs to extract the relevant records. Emily Herrett (EH) and Julie George (JG) wrote the STATA do-files for selecting the Read code lists, further do-files of the mental health portion of the CALIBER manual were developed by Ruzan Udumyan (RU).

3.3. From raw data to research-ready data

The manner and reason for the generation, capture, and recording of EHR data vary substantially between healthcare settings. Additionally, different medical classification systems are used in different data sources and consequently clinical information may be recorded in multiple sources but at different levels of clinical detail. Integrating data from these different sources is therefore complex, but doing so is advantageous for research, and consequently for clinical, purposes.

3.3.1. Converting raw data to research-ready data: curated common data model

The key stages in creating research-ready data are:

1) Development of code lists used to define the exposure of interest, risk factors and endpoints and select relevant data from each data file. in the case of clinical diagnoses, this includes both the identification of diagnosis codes and of other pieces of information that can help to support a given diagnosis.
2) Definition of such variables, i.e. how the records extracted from data files will be used to specify the value of research variables
3) Development of Algorithms for dealing with duplication and contradiction in the variables created

In order to select the relevant records from the study population's data, a code list for each variable is needed. At its simplest, a small number of ICD codes are required to select either mortality or hospital diagnosis data; much more extensive lists are required to select records from CPRD. Exchange and discussion about code lists is an important aspect of making EHR research transparent and reproducible.

To generate each code list, initial search terms were agreed by at least two clinicians, and the relevant code dictionary searched for matching codes. For ICD-10 codes, OPCS-4 codes and entity codes (used by CPRD to specify the content of subsequent fields in the additional and test files (**Table 3.2**), the search was done by hand by researchers at Farr with reference to any published studies found. For Read codes, STATA do-files were used to search the electronic code dictionary provided by CPRD. Additional codes were identified by hand-searching the NHS Read code browser, asking for suggestions from colleagues who had

produced lists for other studies or, in some cases, identifying code lists in published studies or government reports. A preliminary sifting of the identified codes for relevance was completed, and then two clinicians rated the resulting lists for relevance and assigned response categories. Any disagreements were resolved in face-to-face meetings.

All variable definitions and coding lists used are available through the CALIBER web portal. In creating the variable and coding algorithms, an inclusive approach was adopted, but identified codes which the researchers thought were less definitive for the assignment of response categories. Principles on the ways in which codes would be assigned to the different response categories were agreed, to ensure consistency and increase transparency about coding decisions. Within CPRD, clinical signs or test results can be recorded either as a Read code (e.g. “O/E blood pressure raised”) or as additional data linked to specific entity codes. The variable definitions were agreed by both clinical and non-clinical researchers.

The complexities of EHR data mean that a structured method for combining diverse data sources and creating EHR “phenotypes” is needed, but no internationally recognised framework currently exists. An EHR phenotyping algorithm translates these clinical requirements into queries that leverage multiple linked EHR sources, identify relevant patients and extract disease onset, severity and sub-phenotype information. Defining phenotyping algorithms for a study (disease end-points, disease start-points, exclusions, covariates and risk factors) consists of identifying relevant codes for diagnosis (e.g. diagnosis of cancer) or risk factors (e.g. recording of smoking status) and defining how they should be combined. However these definitions, on which research findings are based, are poorly described in published literature with the exception of cases where the curation of phenotyping algorithms occurs upstream by the data provider (e.g. eMERGE Network).

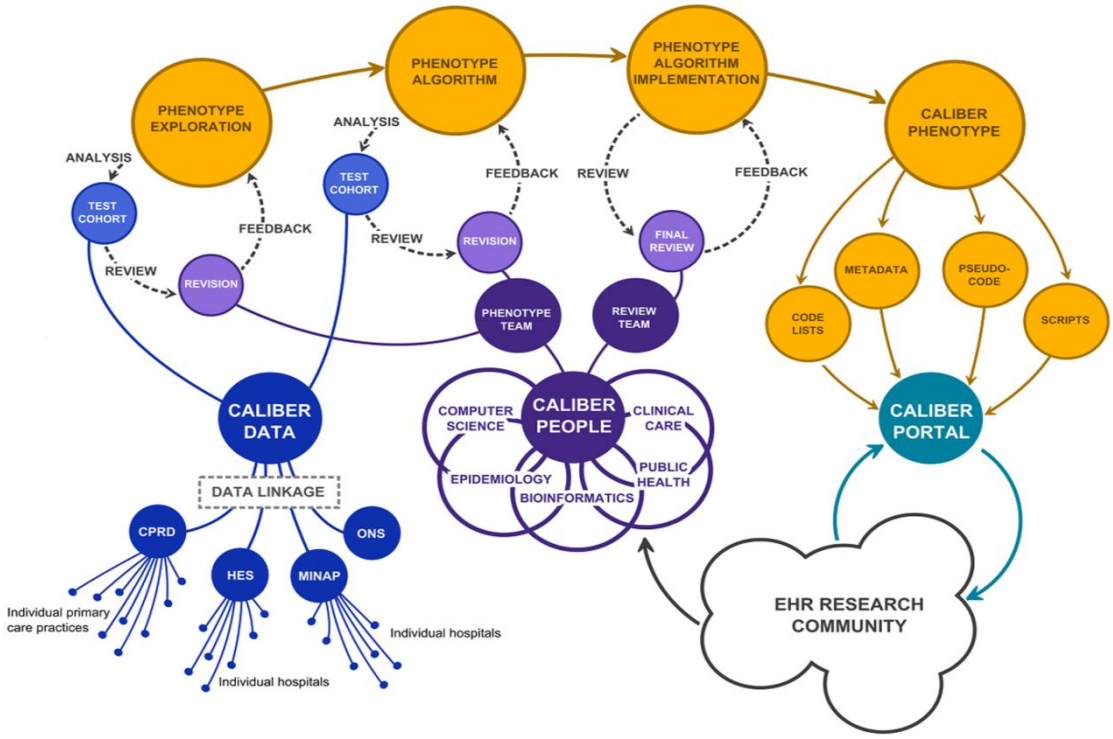
Bioinformaticians and other relevant experts including clinicians and epidemiologists based at Farr, created and evaluated a framework (**Figure 3.2)** for transforming raw EHR data into-research ready phenotypes in a collaborative and transparent manner by involving domain experts across disciplines (epidemiology, computer science, public health, health informatics) and using a centralized repository for their distribution and curation. Below are illustrated the steps involved in creating a phenotype using the example of myocardial infarction for which data is derived by primary (CPRD) and secondary care (HES and MINAP):

The framework consists of multiple iterative steps from initial phenotype definition with domain experts to algorithm implementation, validation and distribution to the scientific community.

A large volume of clinical information in primary care is not coded within the EHR but stored as freetext, isolating it from researchers. It is often in uncoded freetext that the apparently ‘trivial’ presenting symptoms, signs and test results of life-threatening disease are recorded before a

coded diagnosis is arrived at. This uncoded freetext is therefore a potentially rich source of diagnostic information, and there is considerable interest in methods of accessing it for research purposes. Farr has developed algorithms to extract useful information from freetext fields of EHRs, as a step towards identifying early symptoms of CVD before a formal diagnosis is made. The linked CPRD record in CALIBER includes coded information but also freetext fields containing information recorded by general practitioners or derived from hospital letters.

Figure 3.2 Development of a phenotype algorithm using the Clinical research using LInked Bespoke studies and Electronic health Records (CALIBER) programme (Source Morley, K et al.)[201]



3.3.2. Population definition

Before I describe the main exposure of this PhD which is resting heart rate, I will explain the rationale behind the selection of participants included in each cohort of the individual studies of this PhD. CPRD was the only constituent dataset used to define the inclusion criteria for the cohorts populations, assembled from the total number of patients registered with CPRD practices.

The populations included in the individual studies were restricted to patients who met the CPRD's relevant quality standards of eligibility as described in the previous sub-section. I afterwards imposed a period of one year of up-to-standard GP attendance prior to study entry to improve the quality of baseline data and allow for sufficient medical history to be captured. All cohorts finally structured and implemented by the data manager (Dr S. Denaxas) further

consisted of patients aged 30 and above, were of acceptable research quality, gender recorded as either male or female, registered with the GP practice on or after 1st January 2000, their current registration period contained at least one year of up-to-standard (UTS) observation time before each study entry and finally, had at least one heart rate measurement recorded.

For each of the individual studies in this PhD, a further criterion was applied depending on the research question. In the first cohort, the purpose was to investigate the onset of different specific CVDs in relation to subjects' resting heart rate, hence I excluded any patient with a prior symptomatic atherosclerotic disease (i.e. a record of coronary disease, ischaemic cerebrovascular disease, peripheral arterial disease or unspecified atherosclerotic disease) or a ventricular arrhythmia event, cardiac arrest or heart failure in any of the constituent data sources of CALIBER. Patients that their endpoint record after study entry indicated a historical event were also excluded.

The date of entry in the study (i.e. the date the follow-up started) for all the cohorts of this study, was set as the date the patients had their first heart rate measurement after the application of the aforementioned criteria. Hence, the date of entry coincides with the baseline heart rate measurement.

3.4. Heart rate: From codes to research ready data

This section presents the heart rate marker in CALIBER, from the identification of heart rate sources and relevant codes and raw data retrieval, to final research-ready data exploration in the different cohorts.

3.4.1. Heart rate coding

A large piece of work on heart rate coding was already done previously by researchers at Farr (JG, AS, EH, KM). After the initial retrieving, identification and coding of heart rate that was performed prior to the commencement of the PhD, I was responsible to explore the variable and its clinical relevance, process it and incorporate it in the necessary research context, analyse its associations with adverse cardiovascular events and develop and disseminate the results.

To identify all possible data elements related to heart rate the aforementioned researchers, agreed on a set of search terms with two clinicians, and the relevant code dictionary searched for matching codes. For Read codes, STATA do-files were used to search the electronic code dictionary provided by CPRD. For entity codes that are used by CPRD to specify the content of subsequent fields in the additional and test CPRD data files (**Table A3.3**) the search was done by hand by the same researchers with reference to any published studies found. Only one entity

code for heart rate was identified (Entity 131). Following the process described above, the Read codes used to define heart rate variable are listed in **Table 3.4** below. It is noteworthy that codes characterizing heart rate as tachycardic or bradycardic have been incorporated in the variable structure and kept during the variable's process. However, a very low number of measurements has been recorded as bradycardia or tachycardia. In the main cohort, N=4,808 patients had at least one bradycardia recording and N=2,000 of tachycardia. Since the percentage of bradycardia and tachycardia recordings was too low (less than 2%) compared to the pulse rate code (98.3%) I incorporated them in the main heart rate variable. These codes identified below were used alone or in concert to define heart rate variable and retrieve the relevant population with at least one record of these codes.

Table 3.4. Heart rate and its Read terms in CPRD (top percentages)

Medcode	Read code	Read term	n	Percent
Healthy population (IP cohort)				
6154	242..00	O/E - pulse rate	408,629	98.3
22442	2431	O/E - pulse rhythm regular	2258	0.54
23018	2424	O/E - pulse rate normal	2186	0.52
7128	2426.11	O/E - tachycardia	835	0.20
1352	2422.11	O/E - bradycardia	721	0.17
26716	2426	O/E - pulse rate tachycardia	252	0.06
17413	243..00	O/E - pulse rhythm	130	0.03
13608	2422	O/E - pulse rate - bradycardia	90	0.02
26670	2432	O/E - pulse irregularly irreg.	86	0.02
47594	242Z.00	O/E - pulse rate NOS	31	0.01
26715	2423	O/E - pulse borderline slow	28	0.01
26713	2425	O/E - pulse borderline fast	25	0.01
CAD population				
6154	242..00	O/E - pulse rate	25977	95.05
23018	2424	O/E - pulse rate normal	1143	4.18
7128	2426.11	O/E - tachycardia	67	0.24
17413	243..00	O/E - pulse rhythm	37	0.13
22442	2431	O/E - pulse rhythm regular	24	0.08
26716	2426	O/E - pulse rate tachycardia	15	0.05
1352	2422.11	O/E - bradycardia	10	0.03
47594	242Z.00	O/E - pulse rate NOS	3	0.01
13608	2422	O/E - pulse rate - bradycardia	2	0.01

3.4.2. Heart rate characteristics

Mean heart rate in CALIBER populations vs consented cohorts-Representativeness of CALIBER

Mean heart rate in the CALIBER healthy cohort was found to be 76.5bpm (±14.3). There is insufficient literature evidence regarding the overall population mean heart rate of other epidemiological studies. In a study conducted in Japan by Fujiura et al. the mean heart rate was found to be 68.1 (±11.5) bpm. However, the small sample size restricts comparability with CALIBER that its sample size is over 233,900 patients (**Table 3.5**). Additionally, no report of

beta-blockers intake in this Japan population was found in the text. In CALIBER population, 34.4% of people had a recording of at least one beta-blocker intake during the year before the heart rate measurement. Given the values of mean heart rate in each study of the **Table 3.5** below and **Figure A3.3** in the Appendix between the two sexes, CALIBER marker's values are presented to be higher than the rest of the healthy population studies. Significant differences between CALIBER heart rate mean values and Shaper et al.[148] and Mensink et al. studies were found. Shaper et al. population was confined to men with a limited sample size, while the data was collected the year 1969, hence, secular trends (an increase to heart rate) could be responsible for the difference between that population and CALIBER's mean heart rate. Additionally, they found that men under hypertensive treatment (no specification of the type of treatment) had a 4bpm lower heart rate than those without (66.7bpm vs 70.5bpm) that could have affected the overall men mean heart rate. Mensink et al. that provided no information on the baseline beta-blocker (or other hypertension treatment medication) intake, showed a mean heart rate in men of 70bpm in men and 73.3bpm in women compared to CALIBER that showed 74.6bpm and 77.9bpm in men and women respectively (**Table 3.5**). Only the study of Tverdal et al.[152] with data collected in 1985 but with a high sample size showed a similar mean heart rate in women (77.1bpm) vs 77.9 in CALIBER women.

Heart rate in people with coronary artery disease in CALIBER was approximately 4.3bpm lower and its median 4bpm lower (72bpm) than the healthy cohort. Aboyans et al.[162] observed an overall mean heart rate of 65.8bpm. Its small sample size however might play a role on the difference of CALIBER. Further Aboyans et al. study had increased levels of beta-blockers intake (60.1%) and a 85.4% revascularization rate that could affect the overall mean HR values. Finally, Lonn et al.[145] had again lower mean values. The only exception was the study of Kolloch et al.[166] that showed a mean total heart rate of 75.7bpm, 3.5bpm higher of that of CALIBER (**Table 3.5**).

This difference between mean heart rate values in CALIBER and other epidemiological studies with CALIBER values being consistently larger, might be due to other confounders, such as acute effects, e.g. acute stress episodes. Other acute events that might have interfered could be a fever or pyretial symptoms, however data could not be retrieved due to time restrictions.

In both cohorts the degree of skewness was similar between the two genders. Additionally, in both cohorts the kurtosis was closer to 3 (kurtosis=4.6 for both genders in healthy population, 6.8 in men and 5.3 in women in the CAD population). In **Figure A3.4** I present the distribution, location and variability features of heart rate in the healthy CALIBER and CAD cohorts.

3.4.2.1. Mean heart rate in men and women

Women had consistently a mean heart rate approximately 3.3bpm higher than men (77.9 ±14.1 vs 74.6 ±14.5 respectively) and a median of 4bpm in CALIBER healthy population. Compared

to available literature, this difference in means was the same compared to that of Mensink et al. that the heart rate mean for men was 70bpm and women 73.3bpm (difference 3.3bpm), and Palatini et al. study in which men had a heart rate of 73.1bpm and women 76.3bpm (**Figure A3.3**). These similar findings confirm the representativeness of CALIBER heart rate recordings in a greater context of healthy populations and validate our assumption of the resting state of patients while these measurements were recorded.

In CALIBER CAD population the difference between sexes reached the 4bpm (74.4 bpm vs 70.5 bpm respectively) and a median difference of 2bpm. Women had 4bpm higher heart rate (74.4 vs 70.5), with an overall mean of 72.2bpm. Separate heart rate values for men and women are not reported in the literature, probably due to the small sample sizes that do not allow for individual estimations.

Table 3.5. Mean heart rate in CALIBER populations vs consented cohorts

	Study	Year of study	N of participants	Age (±SD)	Resting heart rate (±SD)		
					Men	Women	Total cohort
Healthy cohorts	**CALIBER**	2015	233,970	47.5 (±15.7)	74.6 (±14.5)	77.9 (±14.1)	76.5 (±14.3)
	Shaper et al.	1969	7,735	40-59 (N/A)	70.7 (±12.8)	-	-
	Mensink et. al.	1982	4,756	40-80 (N/A)	70 (±11.6)	73.3 (±10.6)	-
	Palatini et. al.	1999	1,938	72.7 in men & 73.3 in women	73.1 (±13.6)	76.3 (±10.9)	-
	Fujiura et. al.	1977	573	50.5 (±6.8)	-	-	68.1 (±11.5)
	Tverdal et. al.	1985	379,843	40-45 (N/A)	72.6	77.1	-
CAD cohorts							
	CALIBER	2015	51,703	72.3 (±11.4)	70.5 (±14.4)	74.3 (±14.3)	72.2 (±14.5)
	Aboyans et. al.	1998-2002	1,022	66.9 (±9.2)	-	-	65.8 (±13.5)
	Kolloch et. al.	1998	22,192	65.9	75.2 (±9.7)	76.2 (±9.4)	75.7 (±9.6)
	Lonn et. al.	-	31,531	66.5	-	-	68.1 (±12.2)

Note: N/A, Mean not available in the text

3.4.2.2. Atrial fibrillation and sinus rhythm

The normal regular rhythm of the heart is set by the natural pacemaker of the heart called the sinoatrial (sinus) node. It is located in the wall of the right atrium and it is the place where normal cardiac impulses start and are transmitted to the atria and down to the ventricles and this type of rhythm is called sinus rhythm. Although normally sinus node sends out regular electrical impulses, sometimes these impulses are fired off from different places in the atria in a disorganised way and this is called atrial fibrillation rhythm. To explore normal heart rate effects, it is vital to distinguish between those two types of pulses and make sure that the patients in the cohorts have been recorded with the sinus type of rhythm. However, the type of heart rate is not easily identifiable and there is a possibility that could be entangled in a complex link with atrial fibrillation (AF) rhythm. To investigate whether or not it is possible that AF rhythm often represents the normal sinus heart rate rhythm in my data, I checked whether AF events diagnoses frequently coincide with the day of heart rate measurement in total AF events on the same day or within a month from a heart rate recording, AF events exclusively recorded in primary care and secondary care. The results are presented in **Table 3.6** below.

Table 3.6. Atrial fibrillation events by heart rate level

AF events	Heart rate categories				
Healthy cohort (excluding baseline symptomatic CVDs)	<60	60-69	70-79	80-89	>90bpm
AF total events ǂ	13 (0.07%)	28 (0.05%)	57 (0.08%)	74 (0.13%)	178 (0.49%)
AF total events*	126 (0.69%)	277 (0.53%)	345 (0.49%)	418 (0.74%)	612 (1.70%)
AF in Primary careǂ	10 (0.05%)	26 (0.05%)	40 (0.06%)	63 (0.11%)	177 (0.49%)
AF in Primary care*	74 (0.45%)	150 (0,74%)	185 (0,89%)	150 (0,73%)	133 (0,68%)
AF in secondary careǂ	3 (0.03%)	2 (0.01%)	17 (0.00)	11 (0.01%)	1 (0.09%)
AF in secondary care*	52 (0.28%)	127 (0.24%)	160 (0.23%)	268 (0.48%)	479 (1.33%)

ǂ AF event experienced on the same day as heart rate measurement

*AF event experienced within a month before or after the heart rate measurement

The above data show a very low incidence of AF events on the day or within a narrow window of one month from a heart rate measurement, in both healthy and CAD populations. Therefore,

there is a strong basis to assume that the heart rate nature under investigation of this PhD is majorly represented by sinus rhythm.

3.4.2.3. Digit preference

A common phenomenon observed in clinical practice recording is the terminal digit preference phenomenon. Measurement of continuous variables is often in practice transformed into discrete data, "rounding off to the next multiple of five or 10. [122] Keary et al reported that doctors have a 12-fold bias in favour of the terminal digit zero when measuring blood pressure.[22] Terminal digit preference can lead to overestimation or underestimation of actual blood pressure and can distort the distribution of observations. This error can potentially reduce the power of statistical tests - the chance that the study will find a significant association if one is truly present. Therefore, accuracy is important. A recent study done in Quebec[202] showed that although recommendations have been available for years, a persistent lack of technical and practical knowledge in digit preference of blood pressure measurements, is still present. Exclusively blood pressure studies have addressed and treated this problem, since in contrast to heart rate, is more "objectively" measurable when relies on manual measurement, which is a common practice in primary care. The increasing use of digital sphygmomanometers in many practices will eventually decrease the errors due to terminal digit preference as well as mercury and aneroid device errors, therefore decreasing the sources of variability and increasing the quality of BP measurement.[203]
Available literature on heart rate has so far failed to explore the digit preference phenomenon. As part of my PhD I assessed evidence for this potential systematic bias by examining the distribution of recorded heart rate values. Some evidence of digit preference in heart rate measurements of CALIBER, which not necessarily end in odd numbers was identified. In the CALIBER healthy cohort we observe a higher frequency of recording in values ending in odd numbers and multiples of 10 (**Figure 3.5(a&b)** and **Table A3.7 (Appendix 3).**

One of the challenges of EHR is the absence of evidence related to the way of specific recordings such as heart rate measurements. There are several ways of measuring heart rate, e.g. palpation at the wrist, auscultation of the heart or electrocardiogram (ECG) and more objective such as sphygmomanometer. Since I am not able to define the way of heart rate measurement, hence the accuracy of these recordings, I will use as a proxy of accuracy the proportion of heart rate measurements that were taken on the same day as blood pressure measurements, given that the latter were recorded using an automated device. This implies that heart rate measurements might have been taken using the same device, hence the recordings are more accurate. Of the total number of patients, 82.6% of people with a heart rate record had a blood pressure measurement on the same day in the healthy cohort and 100% in the CAD cohort, suggesting a large proportion of heart rate measurements were obtained using an automated blood pressure device. In healthy CALIBER, 76.8% (n=179,588)

of heart rate measurements end in odd numbers, while 25.2% (n=59,665) end in multiples of ten. After restricting to those that had a blood pressure measurement on the same day, 74.91% (n=121,691) end in odd numbers and 23.8% (n=38,785) end in multiples of ten. Restricting to those with the baseline heart rate measurement not taken on the same day as the blood pressure, the difference was not significant as 76.8% (n=178,260) end in odd numbers and 25.5% (n=59,239) end in zero (**Table A3.8**). In the CAD CALIBER cohort, returned higher percentage of measurements ending in even numbers (81.7%) and a 28.8% ending in multiples of zero. The restriction to those with blood pressure measurements on the same day as heart rate gave similar results, with 78.1% of measurements end in odd numbers and 25.5% in zeros. Restriction to those without heart rate and blood pressure measurements on the same day showed a percentage of 81.7% ending in odd numbers and 28.7% end in multiples of ten (**Table A3.8)**.

Identifying heart rate recordings taken on the same day as blood pressure that would imply measurement of heart rate using an accurate clinical device and not taken on the same day, showed little evidence of a difference in heart rate values ending in even numbers or zeros. This could be interpreted either as: i) Heart rate measured on the same day as blood pressure is not indicative as to what and if a device was used, ii) Possible methods of heart rate measurements were palpation at the wrist or auscultation of the heart by clinicians or nursing staff, hence questionable accuracy of measurements (although reading errors have clinical relevancy when heart rate is near the high risk thresholds (>90bpm), iii) These observed values are the true heart rate values in the general population.

Figure 3.5 (a)) Histogram of heart rate in CALIBER healthy cohort

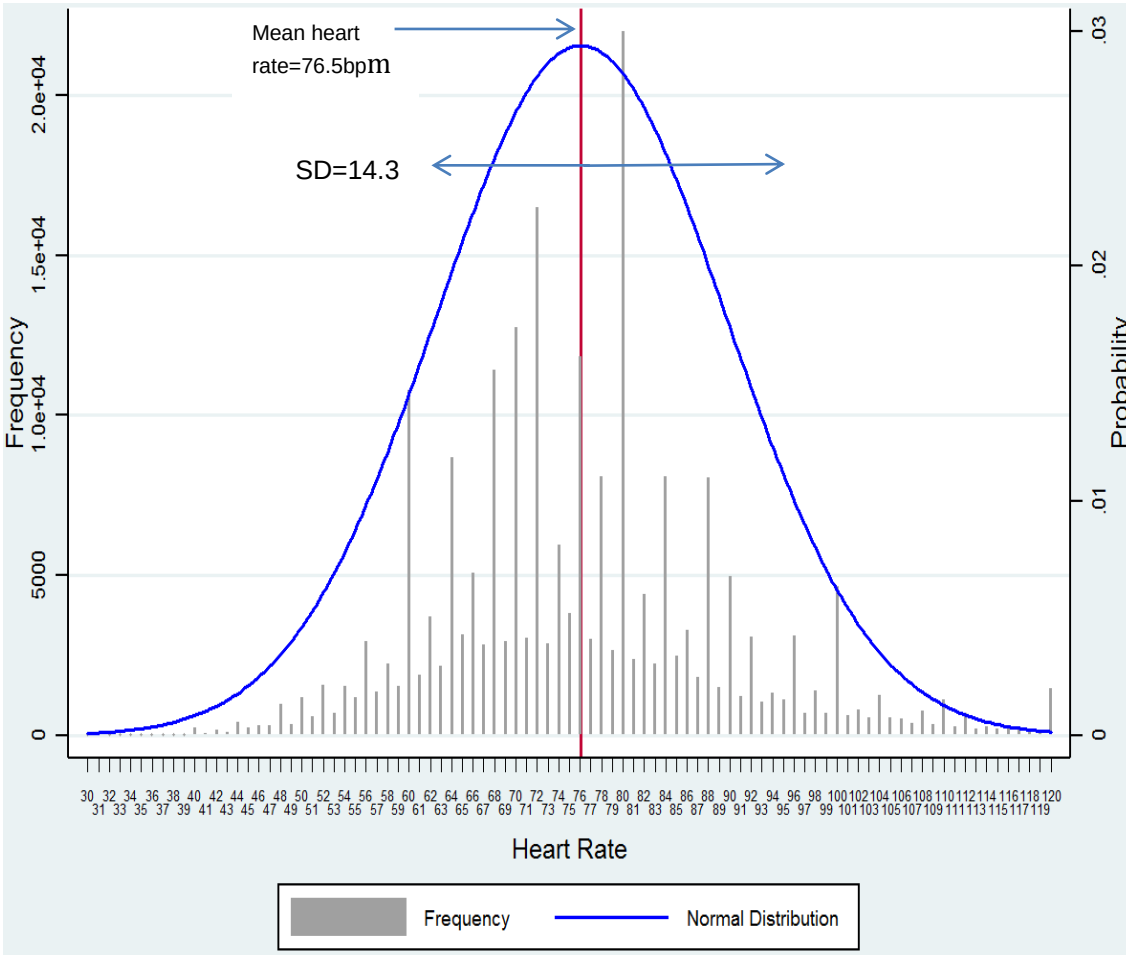
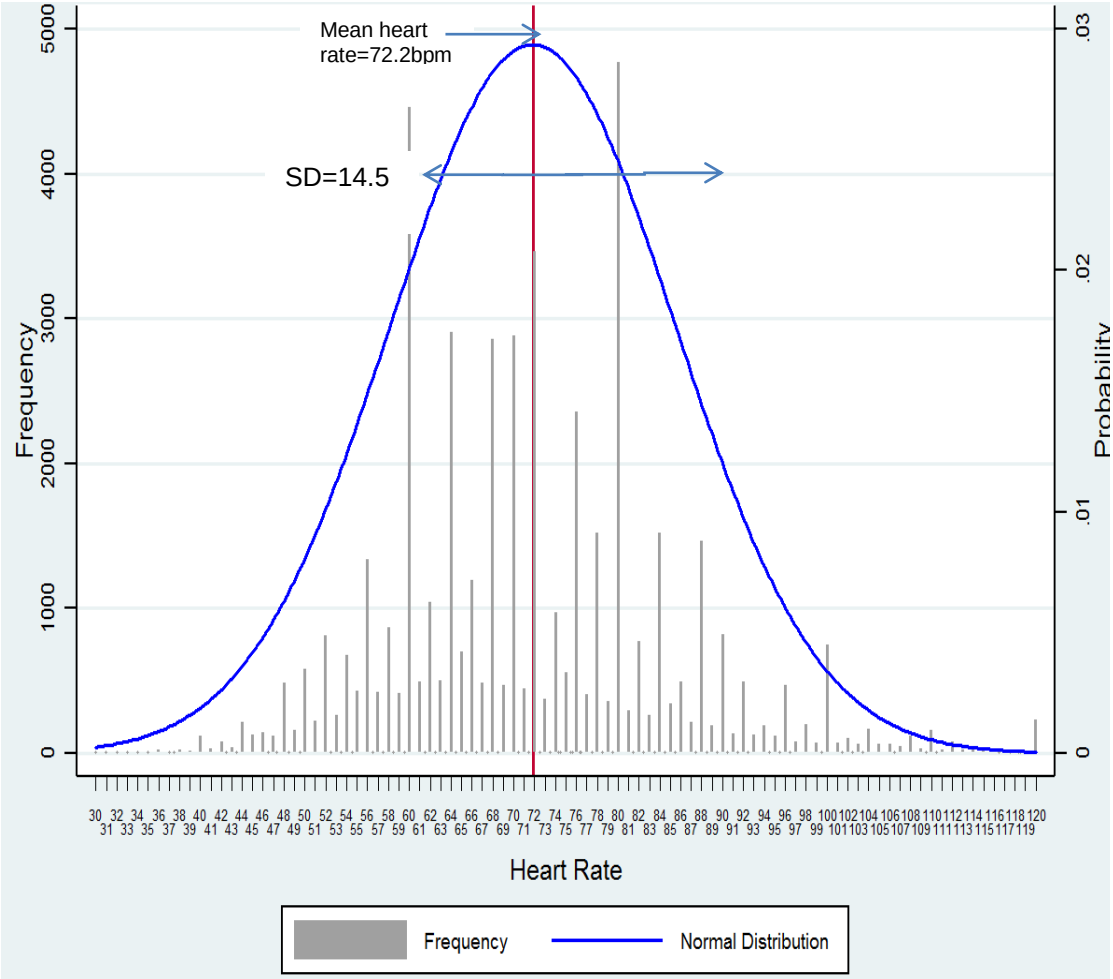


Figure 3.5 (b) Histogram of heart rate in CALIBER CAD cohort



3.4.2.4. Repeated heart rate measurements

Over a mean time of 3.67 years, 41.8% of the population with heart rate measurements had a single heart rate measurement, 19.9% had 2 measurements, 24.4% had 3 to 5 and the rest 13.9% had >5 heart rate measurements (**Figure 3.6**). To assess the amount of patients that had a change in their heart rate it is useful to set heart rate ranges across which any change in the rhythm could be identifiable.

To that effect I will use heart rate ranges with clinical relevance that will be also used in the following chapters as the main heart rate levels included in my analyses. These ranges are defined as: <60bpm, 60-69bpm, 70-79bpm, 80-89bpm, >90bpm. Of 445,510 heart rate measurements in total (including repeated measurements), 14.9% remained in the same heart rate level in the subsequent measurement. When heart rate of patients showed an increase or decrease in a subsequent GP visit, it would not often observed more than one level up or down with levels (**Figure 3.7**). In my PhD, I used the baseline heart rate measurement which was

closer to, and right after the date of entry after applying the general eligibility criteria described in section 3.4.

Figure 3.6. Frequency of heart rate measurements in CALIBER

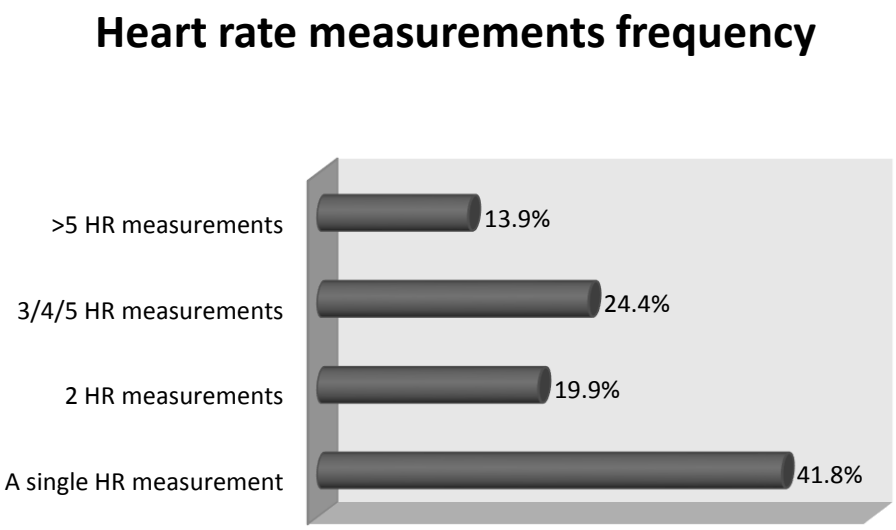
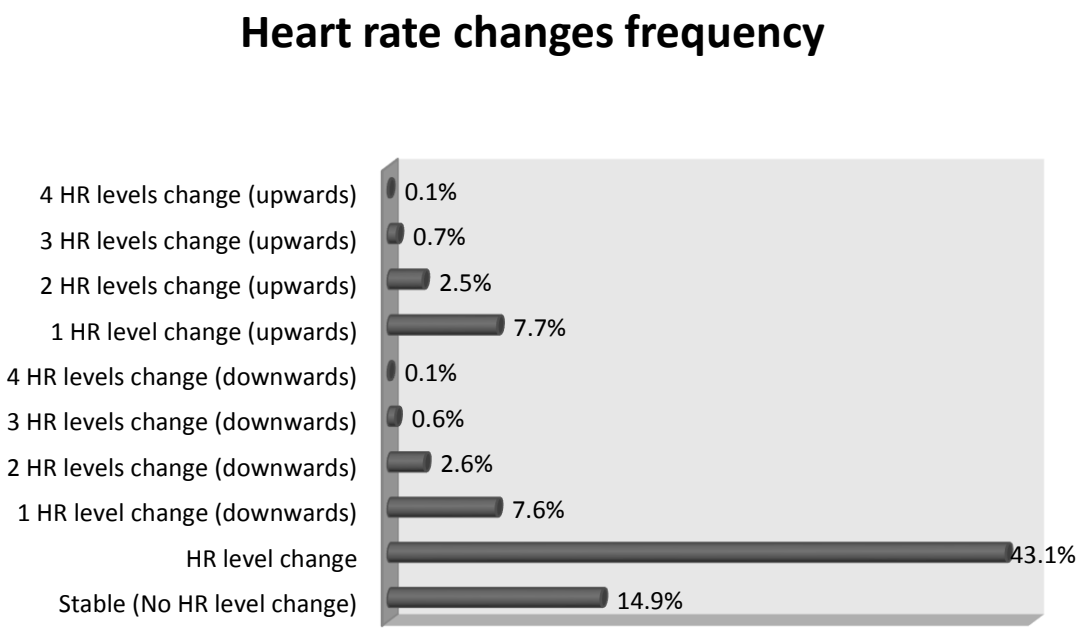


Figure 3.7.Frequency of heart rate changes across GP visitations



3.4.2.5. Subjects without heart rate measurements

As I will describe in 3.8.2.1 section, one of the concerns with EHR data is the extent of information which is unrecorded for patients and particularly when information on the main exposure (i.e. heart rate) is missing. Below in T**able 3.9** I have compared in greater detail the baseline characteristics of patients with heart rate recordings and without a recording.

It is apparent from the table above that patients with a heart rate measurement included in the analysis were 14 years older, more likely to be women and to suffer from diabetes compared to patients without heart rate measurements. People with heart rate measurements are also more often hypertensive with more frequent systolic blood pressure recordings and higher intake of bet and calcium channel blockers. These findings are potentially due to the fact that older people visit GPs more often, have additional medical reasons which affect the cardiac regulatory system or due to the family history, a more thorough clinical examination is required (**Table 3.9** above). There is clearly a difference between these two types of patients that could potentially lead to important clinical and methodological implications, such as overestimation of heart rate effect and reduced generalizability and representativeness of findings. Due to the nature of the fraction of population that attended GP practices for various health reasons (either they are hypertensive, or diabetic) that had consequently heart rate recordings in primary care, the distribution of people's characteristics is not equal between the two cohorts (with and without heart rate recordings). As a consequence, we have to be very careful during the interpretation and dissemination part of this PhD results.

3.5. Additional risk factors and cardiovascular diseases

3.5.1. Risk factors

In order to explore associations of heart rate with CVDs, further confounders that might affect these associations should be examined. I used additional risk factors to control for in my statistical models and these risk factors (or co-variates) are presented below. Sex, age and index of multiple deprivation variables were taken as static values from the CPRD patient file. All the rests have commonly multiple records per patient. For these records I used the one recorded on the date closest to the patient's study entry up to a year prior to date of entry. CALIBER research platform contains the algorithms for research-ready data which incorporate data definitions, including meta-data, and the code lists required to produce research-ready datasets. This information can be accessed electronically via the CALIBER web data portal at https://www.caliberresearch.org/portal. Below, the sources of the most common risk factors implemented in this PhD analyses are briefly presented.

Table 3.9 Baseline characteristics of people with and without heart rate recoded

	Heart Rate non recorded			Heart rate recorded (all			
	N	Mean (% proportion	sd	N	Mean (% proportion	sd	N% recorde
Demographic factors							
Age at entry	1,701,96	46.2	14.	233,97	58.3	16.	100
Female	675,025	(44.8)		110,43	(56.2)		100
White ethnicity	534,500	(70.3)		98,764	(73.2)		52.5
IMD score (5th quintile-most	293,615	(19.6)		44,933	(22.9)		99.5
Clinical factors							
Systolic blood pressure,	581,414	129.9	18.	125,24	139.8	20.	63.7
Diastolic blood pressure,	581,414	78.7	10.	125,24	81.6	11.	63.7
High density lipoproteins,	72,060	1.40	0.4	46,186	1.43	0	6.94
Low density lipoproteins,	59,436	3.30	1.0	37,460	3.18	1.0	5.69
Total cholesterol (mmol/L)	112,033	5.45	1.1	59,095	5.33	1.1	10.0
Triglycerides (mmol/L)	80,875	1.69	1.3	45,949	1.64	1.1	7.45
Creatinine µmol/L	145,268	85.4	23.	79,752	88.0	27.	13.2
Haemoglobin (g/dL)	150,980	13.9	1.5	67,849	13.7	1.5	12.8
Lymphocytes (10^9 / L)	120,836	2.13	1.2	60,506	2.10	1.2	10.6
Neutrophils (10^9 / L)	120,413	4.07	1.8	60,618	4.25	1.8	10.6
Diabetes II	18,717	1.24		10,338	5.26		
Behavioural/Environmenta							
Smoking							85.5
Non-smokers	758,298	(60.0)		116,72	(60.8)		
Ex-smoker	173,235	(13.7)		30,262	(15.7)		
Current smoker	332,070	(26.2)		44,836	(23.3)		
BMI (kg / m^2)	432,269	26.3	5.1	68,548	28.2	6.1	29.4
Family history of CHD	51,548	(3.42)		3,744	(1.91)		100
Medication							
Beta blockers	62,098	(4.12)		28,245	(14.3)		
Calcium channel blockers	35,404	(2.35)		23,456	(11.9)		
Statins	26,904	(1.79)		22,385	(11.4)		
Aspirin	24,031	(1.60)		16,916	(8.61)		
Diltiazem	1,990	(0.13)		1,384	(0.70)		
Verapamil	1,638	(0.11)		742	(0.38)		
Hypertensives	58,434	(3.88)		22,871	(11.6)		
Other cardiac and rhythm							
Atrial fibrillation	3,116	(0.18)		4,785	(2.05)		
Valve disease	16,819	(0.97)		7,452	(3.19)		

Gender

Gender was recorded in the patient file in CPRD. Patients with indeterminate gender were excluded from the study. Gender was used in my analyses as a covariate in the standard Cox models or as a binary classification for exploration of absolute differences in hazards during subgroup analyses.

Smoking

Smoking status was routinely recorded by GPs in their daily practice, practices nurse, healthcare assistants or administrative staff either in the context of new patient questionnaires or individual consultations. This data is provided by CPRD, using Read codes. In the present thesis, smoking status was classified as ex-smoker, current smoker or non-smoker. Where a patient's last smoking status prior to study entry was non-smoker, their status was changed to ex-smoker if there was any previous record of being a smoker at any point in the patient's history.

Blood pressure

The blood pressure measurements used in this study were recorded as part of routine care in general practice. The measurements were made by a wide variety of staff, including GPs and practice nurses, using different machines under a variety of conditions, ranging from GP consultations for potentially unrelated illnesses to new patient checks to hypertension clinics. The data was provided by CPRD. No information on the circumstances under which the measurements were taken was available for this study. Systolic blood pressure (SBP) at baseline was defined as the mean SBP over the two years prior to study entry. Diastolic blood pressure (DBP) at baseline was similarly defined.

Age

Age at study entry was derived from the year of birth recorded in CPRD, assuming a date of birth of 1st January of that year. The actual date of birth is not available in pseudo-anonymised data to protect patient identities.

Social deprivation

The index of multiple deprivation (IMD), was used to measure social deprivation. For analytic purposes of this PhD, IMD was divided into quintiles with the lowest quintile indicating the greatest deprivation.

Lipids

Total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides in mmol/L were recorded in the CPRD test file. Records with unit in mmol/L or those with none were extracted, but there were significant differences in the

distribution of those with units recorded and those with none, so only those with mmol/L specified were used.

Use of statins

Use of statins was derived from a minimum of a single prescription of a statin recorded in CPRD during one year before study entry.

Body mass index

Patients' body mass index (BMI) in kg/m2 recorded in the CPRD additional file was used for this variable.

Diabetes mellitus

Patients with diabetes mellitus were identified by any record in CPRD prior to study entry of:

- A diagnosis of Type I, Type II or not further specified;
- A monitoring or treatment which specifically identified diabetes;
- Complications of diabetes; or
- One or more prescriptions for insulin or oral anti-diabetic medication.

This approach to defining diabetes did not take into account any measurements of blood glucose (although these are available in limited patients in CPRD) and may have under-estimated diabetes. Although the date of onset of diabetes is generally difficult to determine, the approach to analysis used in this thesis did not treat diabetes as a time-varying co-variate, so the timing of onset of diabetes did not pose a problem for these particular set of analyses.

Use of anti-hypertension medication

Use of anti-hypertensive medication was derived from at least two successive prescriptions for commonly used agents [beta-blockers, angiotensin-converting-enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), thiazides] as well as other less common preparations.

3.5.2. Cardiovascular diseases

Sources and description of the cardiovascular diseases used by this PhD to investigate whether specific vascular, cerebral or peripheral phenotypes are affected by resting heart rate are presented below. An overview of codes used to define these endpoints along with their information sources are showed in **Table A3.10** in Appendix.

Stable angina (SA)

- Sources: CPRD, HES and MINAP

Patients with stable angina were identified by a record of:

- A diagnosis of stable angina or angina pectoris not further specified (ICD-10 I20, excluding I20.0);
- A coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI) not within 30 days of an admission for myocardial infarction or unstable angina;
- Two or more subsequent prescriptions for nitrates or other specific anti-anginal medication; or
- An abnormal result following an exercise ECG, stress echocardiogram, radioisotope scan, or an invasive, computed tomography (CT), magnetic resonance imaging (MRI) or unspecified angiogram.

Acute myocardial infarction (AMI)

➢ Sources: Acute myocardial presentations are derived from three data sources; CPRD, HES & MINAP.

Acute myocardial infarction includes three subtypes; ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (nSTEMI) and myocardial infarction not otherwise specified (MI NOS). Patients with STEMI were identified by a combination of ST-elevation on ECG, raised troponins and clinical findings indicative of MI in MINAP data, as defined by the internationally agreed definition of STEMI.[204] A record of diagnosis of STEMI in CPRD was also included, on the basis that this would reflect information from a discharge letter from an acute admission.[193] Similarly, patients with nSTEMI were identified by no ST-elevation on ECG, raised troponins and clinical findings indicative of MI in MINAP data and diagnosis code alone from CPRD.[193] All other records which did not specify type of myocardial infarction (MI), including AMI codes from HES (ICD-10 I21, I22, & I23), were included in MI not otherwise specified (NOS). Patients with unheralded fatal MI were included in the unheralded coronary death category. Due to sample size restrictions, in the present PhD individual studies (chapters 4, 5, 6) STEMI, nSTEMI and MI NOS endpoints were merged into a single cardiovascular event, MI.

Unstable angina (UA)

➢ Sources: CPRD, HES and MINAP

Patients with unstable angina were identified in MINAP by clinical findings of acute coronary syndrome but no raised ST elevation on ECG and no raised troponin levels.[193]UA was further identified by diagnosis of unstable angina (ICD10 I20.0) or acute ischaemic heart disease (I24, I 24.0, I24.8 & I24.9) in HES or unstable/worsening angina or acute coronary syndrome in CPRD.

Coronary heart disease not otherwise specified (CHD NOS)

- Sources: CPRD, HES

Patients with coronary heart disease not otherwise specified (CHD NOS) were those with a variety of non-specific diagnoses such as CHD NOS, chronic ischaemic heart disease and silent myocardial ischaemia (I25 excluding I25.2, old myocardial infarction) in either CPRD or HES.

Heart failure (HF)

- Sources: CPRD, MINAP, HES, ONS

Patients with heart failure were identified by a record of:

- A diagnosis of heart failure in HES (I50, I26.0, I11.0, I13.0 & I13.2) or CPRD; or
- A result of left ventricular hypertrophy on a resting ECG in CPRD; or
- An underlying cause of death (UCOD) of HF in mortality data as the first presentation of atherosclerotic disease after study entry.

Unheralded coronary death (UCD)

- Source: ONS

UCD was exclusively identified by mortality records of ONS. Patients with unheralded coronary death were identified by an UCOD from coronary heart disease (ICD-10 I20-I25) which was not preceded by any other atherosclerotic code.

Sudden cardiac death, ventricular arrhythmias, cardiac arrest (SCD, V/A, CA)

- Sources: CPRD, MINAP, HES, ONS

Patients with ventricular arrhythmias, cardiac arrest or sudden cardiac death were identified by:

- A diagnosis of ventricular tachycardia (I47.2) or fibrillation (I47.0); or
- Asystole, cardiac arrest (I46, I46.0 & I46.9), cardiac resuscitation, electro-mechanical dissociation; or
- Implanted cardiac defibrillation device; or
- A diagnosis of sudden cardiac death in HES or CPRD; or
- Mortality from cardiac arrest, sudden cardiac death or ventricular arrhythmia.

Ischaemic stroke

- Sources: CPRD, HES and ONS

Patients with stroke were identified by:

- A record of ischaemic stroke (I63); or

- A record of stroke not otherwise specified (I64, G46.3-G46.7); or
- Mortality from any of the above as the first presentation of CVD.

Patients with stroke not otherwise specified (NOS) were included since the large majority of such unspecified strokes are commonly ischaemic. Under ischaemic category however, fall also some patients with haemorrhagic stroke. Ischaemic stroke will be used as an independent endpoint in chapter 4 for the assessment of heart rate on 12 CVDS and as a part of a composite stroke endpoint in chapter 5 where I will explore heart rate relationships and prognosis of CVDs in patients with CAD.

Subarachnoid haemorrhage

- Sources: CPRD, HES and ONS

Subarachnoid haemorrhage events were identified as:

- Subarachnoid haemorrhage from carotid siphon and bifurcation (G601.00)
- Subarachnoid haemorrhage from middle cerebral artery (G602.00)
- Subarachnoid haemorrhage from intracranial artery, unspecified (G60X.00)
- A record of subarachnoid haemorrhage (I60)
- Mortality from any of the above as the first presentation of CVD.

Similarly as ischaemic stroke, subarachnoid haemorrhage will be used as an independent endpoint in chapter 4, whereas as a part of a composite stroke endpoint in chapter 5.

Intracerebral haemorrhage

- Sources: CPRD, HES and ONS

Intracerebral haemorrhage events were identified as:

- A record of subarachnoid haemorrhage (I61)
- Mortality from any of the above as the first presentation of CVD or
- A record of haemorrhage not otherwise specified (I64, G46.3-G46.7)

Intracerebral haemorrhage, similarly to ischaemic stroke and subarachnoid haemorrhage, will be used as an individual endpoint in chapter 4 and as a part of the composite stroke endpoint in chapter 5.

Transient ischaemic attack (TIA)

- Sources: CPRD, HES and ONS

TIA events were identified as:

- A record of transient ischaemic attack (G458)

- Mortality from any of the above as the first presentation of CVD

Abdominal aortic aneurysm event (AAA)

➢ Sources: CPRD, HES and ONS

Patients with AAA were identified by:

- A diagnosis of AAA (I71), other than thoracic AAA ; or
- An abnormal results on abdominal ultrasound or CT indicating AAA; or
- A procedure for AAA; or
- Mortality from AAA as the first presentation of CVD.

Peripheral arterial disease (PAD)

➢ Sources: CPRD, HES, MINAP and ONS

Patients with PAD were identified by:

- A diagnosis of PAD (I73, I73.1, I73.8, I73.9) including peripheral complications of diabetes, peripheral ischaemia, peripheral vascular disease, gangrene and intermittent claudication; or
- An abnormal results on abdominal ultrasound or CT indicating PAD; or
- A procedure for PAD; or
- Mortality from PAD as the first presentation of CVD.

3.6. CALIBER strengths and weaknesses

The most important CALIBER strengths and limitations are:

Strengths

- Large sample size, hence great resolution in exposures
- Clinical phenotypes resolution
- Data readily updateable- Absence of any manual effort of investigators spanning from recruitment process to data recording
- Efficiency- Recruitment, baseline and follow up phenotypic assessment zero cost to research funder
- Flexible opportunities to define disease follow-up (start point and endpoints), based on availability in the clinical record of 'Phenome wide' information
- Flexibility in cohorts definition
- Flexibility in inclusion criteria of individual cohorts-diverse population that allows for investigation of various research questions applicable to different populations

Weaknesses:

- Missing information at a practice, patient and data level
- Linkage process difficulties
- Difficult to handle and curate, demand high degree of expertise-large datasets to handle.

3.6.1. CALIBER strengths

The CALIBER platform is a part of a greater vision to provide evidence across different stages of translation, related to cardiovascular research using linked electronic health records. Its strengths are stemming from a combination of primary and secondary care and disease registry data that cover the whole spectrum of clinical phenotyping in a large UK population. For research purposes of the present PhD, linked electronic health records offered a vast resource of diverse clinical data that allowed the exploration of research questions regarding heart rate and its impact on CVDs to be performed with accuracy, high resolution and completeness.

Large sample sizes-High statistical power

By consenting 225 GP practices with the subsequent linkage of additional sources not only at the follow-up phase but also at the baseline level (which is defined by the requirements of each individual study), that yielded >3 billion records of raw data, >700 clinical terms and 10^6 cohort sample sizes and makes it one of the biggest clinical information sources of real world data worldwide. Higher sample is also translated into sufficient power and accuracy to explore differential effects across different subgroups, for instance gender or age, etc. that without it epidemiological studies have failed to produce clinically important findings such as differential effects of heart rate on CVD phenotypes[172] or null effects in women e.g. on heart failure by Nanchen et al.[159] In clinical research this is of crucial importance since personalised care promotes the delivery of a more effective and sustainable health care.

Resolution of clinical phenotypes

This substantial body of research data further allows for an in depth exploration of a massive pool of diverse risk factors and clinical phenotypes, and also a high degree of resolution which covers the detection of an array of specific, severe and non-severe, fatal and non-fatal diseases. The majority of investigator led (bespoke) studies treat cardiovascular diseases as pooled, unified phenomena implying a common root, while this aggregation of endpoints renders findings unclear and potentially inaccurate. A typical example of this is the heart rate and CVD existing literature that addresses the hazard of increased resting heart rate on coronary artery disease and cardiovascular or non-cardiovascular mortality which commonly treats these endpoints in a composite form. In that way, constituent phenotypes or disorders of the heart conduction system and muscle such as atrial fibrillation and heart failure have not

been properly explored. CALIBER enables the disaggregation of complex phenotypes into distinct cardiovascular endpoints of coronary, cerebral, abdominal and vascular beds. Besides outcomes' accuracy, flexibility in exposure investigation is also provided with large numbers of risk factors measured and recorded in primary care.

Data readily updateable

All information of clinical research interest such as clinical variables, lab test values, treatments, procedures and medication records are available for studying and readily updatable. It is an automated recording process not only for data gathering at a baseline level, but also allows a "low effort" follow-up monitoring for events recording.

Efficiency

Furthermore, one of the significant advantages of this linkage lies on the practical aspect of data gathering and information collection. Unlike clinical cohorts or surveys, the recruitment process of patients is eliminated, since after GP practices opt in, automatically all patients' data that attended these practices between 2001-2010 becomes available for research purposes in our dataset. Hence, there is no research cost of data collection to the research funders. Since the whole stage of participants' recruitment and data collection as I described in chapter 7 was both tedious and time consuming especially with the manual component incorporated in the process, the value of the electronic patients' collection process in CALIBER proved extremely valuable.

Temporal resolution and follow-up time flexibility

Additionally, long follow-up times highly contribute towards accuracy achievement, since the time windows to observe cardiovascular events which might not be chronic but more acute, are sufficient for safe inferences. Flexibility in observational start point and endpoint timelines is one of the many benefits of EHR that enables investigators to adapt the time frames and follow-up to their personal research preferences. Furthermore, the platform that mainly aims at CVD investigation provides additional information for further pathophysiological disorders and diagnoses such as cancer, musculoskeletal and genetic disorders, etc. An additional benefit is temporal resolution which allows disentangling the sequential issue of events. CPRD data capture amongst others mild non-fatal manifestations of diseases that are not recorded at secondary health care level. Consequently, first events of diseases in CALIBER are easier to distinguish whether or not they were initial manifestations (e.g. unheralded coronary death) or were preceded by any symptoms or events.

Inclusion criteria flexibility

The flexible inclusion criteria of CALIBER (all patients regardless age, gender, etc.) without any clinical or health status restriction allows for various research questions' investigations that the results can be applicable and representative of different populations. It offers the possibility of

bespoke research that it is not restricted to specific risk factors collected exclusively for research purposes, or narrow diagnosed outcomes. To that effect, chapter 4 which is focus on the impact of resting heart rate on CVDs in a healthy population, differs in the cohort design from chapter 5 that investigates heart rate and CVD prognosis in people with CAD, hence the inclusion criteria fundamentally differs, while the underlying sources of data remain the same.

Population based design-Generalisability

That particular characteristic of CALIBER, the non-selective nature of the population included in the dataset, hence the inclusion of healthy population or population with diverse health background, enhances the applicability and generalizability of the findings outside this study or even outside UK population and strengthens its external validity. This platform provides a knowledge pool that can be used to investigate gaps identified in clinical research, flexible enough to investigate questions from different clinical backgrounds. In the individual studies of this PhD that examine associations of heart rate with CVDs, I was able to define with flexibility the baseline populations without applying specific clinical criteria, unlike published epidemiological studies that a restricted by rigid patients' characteristics or procedures (e.g. in prognosis research, inclusion exclusively of patients that belong to specific registries and have undergone cardiovascular procedures such as cardioversion, etc.).

3.6.2. CALIBER weaknesses

3.6.2.1. Reasons for missing clinical information

One of the main challenges of EHR and subsequently CALIBER, is the large numbers of missing information stemming from various sources and spanning general practices, patients numbers, missing measurement values, or not collected clinical information unavailable in general practice. The variability in completeness of data across practices, patients and across clinical measurements requires careful consideration. An illustration of this hierarchy is showed in **Figure 3.8** below.

3.6.2.1.1. Missing practices

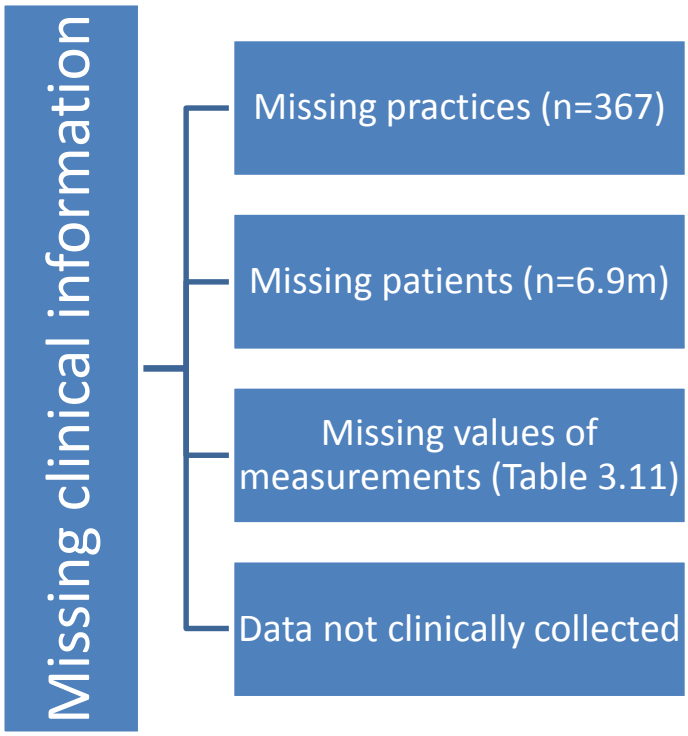
Of the total 592 practices in the CPRD in November 2010, 465 are based in England, and 244 practices participated in the linkage (52% of English practices, 41% of all CPRD practices).[194] Roughly 45% of 592 CPRD practices in the UK consented to linkage of their registered patients, hence CALIBER uses data from only 225 practices in England. For these participating practices, all patients registered at the practice were included. Nowadays, CPRD database has reached the 674 practices in the UK with a coverage of 11.3 million patients.[205]

3.6.2.1.2. Missing patients

Apart from information missing due to limited number of GP practices participating in CPRD and hence lower number of GP practices consented to CALIBER participation, there is

information missing due to patients' failure to register with GPs. Of the 6,623,382 CPRD patients with follow-up post 2000, 3,892,042 (58.8%) were eligible for linkage (of those, 3,854,106 (99.0%) had a valid NHS number as indicated by the trusted third party).[194] At the mid-year date of 2 July 2013, the dataset held information on 11.3 million patients who were deemed acceptable for research based on data quality checks. The population of active patients (alive and currently registered) on 2 July 2013 was 4.4 million, representing 6.9% of the total UK population (based on the UK 2013 mid-year population of 64.1 million). The remaining 6.9 million records represent inactive patients who have died or are no longer registered with a participating practice.[205]

Figure 3.8 Missing clinical information sources



This problem is further enhanced by the fact that even if patients are registered with the GP practices, they fail to attend, which leads to important information missingness. CPRD patients are broadly representative of the UK population in terms of age and sex. Patients are also comparable to the UK census in terms of ethnicity[206] and comparable to the Health Survey for England for body mass index distribution in most patient subgroups.[207] However, the CPRD may not be representative of all practices in the UK based on geography and size, which is something that one has to take into careful consideration when draw inferences on generalizability regarding particularly socio-economic research.[205, 208] However, given the nature of my PhD aims related to heart rate, the possibility of systematic bias stemming from missing patients is rather relatively limited.

3.6.2.1.3. Missing values of variables

Missing values in EHR are very common and their extent varies across different variables mainly due to different frequencies of recordings. Not all information is captured during GP visits and even if it is reported by patients, it is unknown what percentage of that information was used and what was discarded during the information recording process, or if this information was prompted by the GP. Moreover, possibly biomarkers and other factors were requested and collected by GPs only when considered needed. As a result, a potential pattern behind specific variables' recording might be hidden (i.e. missing non randomly values). In this case, significant systematic biases (e.g. reporting bias) might interfere with the data and conceal true associations with risk factors, whereas overestimate others non-significant. Various statistical techniques have been implemented for the treatment of that phenomenon, however one must be very careful not to miss any potential biases systematic or sampling that might interfere with the results. An example of missing values in my CALIBER cohort is shown in **Table 3.11**. It is a common practice for researchers to address missing data by including in the analysis only complete cases, i.e. those individuals who have no missing data in any of the variables required for that analysis. However, results of such analyses can still be biased.[209] Furthermore, the cumulative effect of missing data in several variables often leads to exclusion of a substantial proportion of the original sample, which in turn causes a substantial loss of precision and power.[209]

The risk of bias due to missing data depends on the reasons why data are missing. Reasons for missing data are commonly classified as: missing completely at random (MCAR), missing at random (MAR), and missing not at random (MNAR), where missing values are systematically different from the observed values and the reason for missingness is directly related to the factor being observed.[210] When it is plausible that data are missing at random, but not completely at random, analyses based on complete cases may be biased. Such biases can be overcome using methods such as multiple imputation that allow individuals with incomplete data to be included in analyses. Unfortunately, it is not possible to distinguish between missing at random and missing not at random using observed data. For example, it could be more possible for women in reproductive age to attend GP practices potentially due to disorders of menstrual cycle and hence have their heart rates measured more often than men. In the present PhD I used multiple imputation techniques to overcome the missing values phenomenon. However, it is possible to identify how many people did not have a heart rate recording, but it is not equally easy to capture people that while suffer from thyroid disease have actually a record of thyroid disease. In this missingness category, I will also include another challenge related to recording, as the absence of a Read code for disease must be interpreted as an absence of the disease itself, or when GPs record information as free text, valuable information is ultimately missing despite being recorded.

3.6.2.1.4. Not clinically collected data

Another aspect of data missingness lies on the lack of codes that would allow clinicians to capture phenotypic details although it is observable. Specific forms of research questions that need qualitative parameters to get explored, such as quality of life scales to assess psychological or behavioural functioning, or specific symptomatic descriptions (such as degree of pain severity) are unable to be addressed, since this kind of data is scarce in CALIBER dataset and if there is any, it is difficult to handle during the curation process. Another drawback present at data recording is the absence of information related to the techniques, devices or methods used to measure biomarkers and other clinical parameters. (e.g. whether or not a blood pressure device or palpation was used to measure heart rate).

3.6.2.2. Lack of genetic information

The growth of EHRs has been recognized as a viable and efficient model for genetic research. The absence of genetic information in CALIBER limits at the moment its research power and demands alternative sources of genetic information. By overcoming that obstacle, CALIBER will have the ability to respond with accuracy and credibility to any research question that emerges from contemporary clinical science with extension to causal mechanisms. Genome wide association studies have highly contributed towards giving insight into complex relationships between biomarkers and adverse cardiovascular events such as the work of Den Hoed et al. [140] which identified important information on heart rate and CAD outcomes by overcoming the reverse causality issues inserted by pure observational studies. Now that linked electronic health records are on the rise, further work on heart rate loci and specific cardiovascular phenotypes using EHR is feasible and crucial. As a matter of fact, the eMERGE-PGx project aims at the initiation of a multi-site test of the concept that sequence information can be coupled to electronic health records (EHRs) for use in healthcare. For sequencing data, the workgroup uses the PGRN-Seq platform, developed by the Pharmacogenomics Research Network (PGRN). The long-term goal of the eMERGE-PGx project is to begin to develop strategies for the optimal implementation of genetic sequence data into the clinical environment, something that will shed further light into important clinical questions.[211] Moreover, the Genomics England 100,000 Genomes Project, an ambitious discovery project involving the sequencing of 100,000 genomes and linkage of genomic information to EHR data, makes this a priority area. The Research Program for Genes Environment and Health in Kaiser,[212] and the “precision” medicine initiatives[213] all place a major emphasis on specific disease types and follow-up through health records.

Table 3.11 Percentages of recordings in baseline cohort characteristics

	N	N% recorded
Demographic factors		
Age at entry	233,970	100
Female	110,436	100
White ethnicity	98,764	52.5
IMD score (5th quintile-most deprived)	44,933	99.5
Clinical factors		
Heart rate (bpm)	233,970	
Systolic blood pressure, (mmHg)	125,241	63.7
Diastolic blood pressure, (mmHg)	125,241	63.7
High density lipoproteins, (mmol/L)	46,186	6.94
Low density lipoproteins, (mmol/L)	37,460	5.69
Total cholesterol (mmol/L)	59,095	10.0
Triglycerides (mmol/L)	45,949	7.45
Creatinine µmol/L	79,752	13.2
Haemoglobin (g/dL)	67,849	12.8
Lymphocytes (10^9 / L)	60,506	10.6
Neutrophils (10^9 / L)	60,618	10.6
Diabetes II	10,338	*
Behavioural/Environmental factors		
Smoking		85.5
Non-smokers	116,726	
Ex-smoker	30,262	
Current smoker	44,836	
BMI (kg / m^2)	68,548	29.4
Family history of CHD	3,744	100
Medication		
Beta blockers	28,245	*
Calcium channel blockers	23,456	*
Statins	22,385	*
Aspirin	16,916	*
Diltiazem	1,384	*
Verapamil	742	*
Hypertensives	22,871	*
Other cardiac and rhythm conditions		
Atrial fibrillation	4,785	*
Valve disease	7,452	*

*Diagnosis or medication

3.6.2.3. Linkage issues

The linkage of different data sources, which is the cornerstone of the CALIBER platform along with the post-collection data curation and its transformation into research ready data results to big challenges that one comes across when dealing with linked records. Starting from the latter, the obstacle that prevails in the use of linked electronic health records is the form of data itself as recorded by the different sources and particularly as recorded in primary care. Linkage process is prone to several inconsistencies that are observed across the different datasets. Some examples of these inconsistencies are the differences in values of measurements or even types of diseases between datasets, the differences in the dates of recording for risk factors, or events. Information linked to the wrong patients has also been observed, as well as discrepancies in the way information is recorded which stems from the diverse data sources is also a quite common phenomenon, e.g. levels and categories of variables that overlap. However the latter is easily treatable after appropriate decisions are made by researchers depending on the study aim, while data derived exclusively by primary care is not affected by inconsistencies. Hence, a thorough exploration of the data and careful cleaning combined with necessary clinical decisions is vital to overcome discrepancies across different data sources.

3.6.2.4. Too large datasets-Occasional lack of accuracy

Finally, I would like to highlight that at the last stage of data handling, cohort data cleaning in such large datasets plays an important part of the process to ensure data quality. In this Big Data paradigm it is easy to overlook that concept given that it is expected that when dealing with vast volumes of data and that can come from a multitude of sources, “messiness” is to be expected. As Mayer-Schönberger & Cukier [214] note, “What we lose in accuracy at the micro level we gain in insight at the macro level.” This common conception can often be misleading. Data quality and its provenance do matter and the question is important in establishing generalizability of the Big Data findings.

3.7. Conclusions

In this chapter I presented and described the CALIBER platform, its data sources, processes from raw to research ready data, as well as HER weaknesses and strengths. I finally presented the characteristics of heart rate marker collected by GP practices in both healthy and CAD populations investigated in the present PhD. Electronic health record (EHR) have the potential to transform the health care system from a mostly paper-based industry to one that utilizes clinical and other pieces of information to assist providers in delivering higher quality of care to their patients. CALIBER dataset, a platform that connects four sources of electronic health data spanning primary care records from General Practitioner practices and secondary and mortality

data and these data were used to address and explore the three main research questions posed by this PhD. The manner and reason for the generation, capture, and recording of EHR data vary substantially between these healthcare settings. Additionally, different medical classification systems are often used for different data sources and consequently clinical information may be recorded in multiple sources but at different levels of clinical detail. "Read codes" clinical terminology system used by General practitioners in UK to encode combined with ICD-10 codes to record morbidity and causes of death provided the raw platform that after necessary process produces research ready data. The key stages in this process are: i) Development of code lists used to define the exposures, risk factors and endpoints, ii)Definition of such variables and iii)Algorithms for dealing with duplication and contradiction in the variables. In CALIBER, heart rate was somewhat higher than values recorded in literature with no significant deviations. Among the important strengths of CALIBER are large sample sizes, Clinical phenotypes resolution, efficiency, flexible time-scales, flexible cohort definitions, whereas among its weaknesses belong missing information at practice, patient and data level and linkage process difficulties.

4. Specificity of associations of heart rate in the normal range with the incidence of a wide range of cardiovascular diseases in 233,970 women and men: a linked electronic health records CALIBER study[1]

The aim of this chapter is to identify potential correlations of heart rate with initial presentations of 12 specific cardiovascular diseases. Intrinsically, the term "initial presentation" refers to the first manifestation of these diseases (first symptomatic presentation), hence the analysis will exclusively include population free of any cardiovascular disease, or prior manifestation or history.

4.1. Introduction

Resting heart rate is a readily accessible biomarker that is routinely measured by clinicians and increasingly, with wearable sensors,[215] by patients themselves. In healthy population cohorts, resting heart rate is associated with mortality from coronary heart disease (CHD)[216] and all-causes[9, 151, 152, 157, 216] but there are no established thresholds for public health education or clinical practice defining a "normal" HR at which risk of cardiovascular events is at its lowest. About a third of the adult population has a resting heart rate of 70-79 beats per minute, yet only a few, small, studies have evaluated the risk of cardiovascular events at this level.

Furthermore, little is known about the specificity of the associations between resting HR and the incidence of different CVDs. To date studies have examined either mortality only, or at most 2 incident non-fatal diseases, including myocardial infarction, stroke and heart failure. Some studies reporting sudden cardiac death, coronary mortality or aggregated cardiovascular disease (CVD) have suggested that an effect is present for SCD but not for MI as we presented in chapter 2 (**Table 2.2**). There have been no studies that have disaggregated CVD and examined associations of heart rate with the incidence of a wide range of cardiac, cerebrovascular or peripheral vascular diseases. It is well known that women have higher resting heart rates than men,[152, 156] but there is a lack of sufficiently large studies powered to reliably detect gender differences. Existing studies report either that women have no associations of heart rate with CVD [153, 159] or that associations are weaker compared with men.[21, 85, 154]

The objectives therefore of our research were i) to determine the extent to which heart rate, adjusted for conventional risk factors, is associated with the incidence of 12 different cardiac,

[1] The present piece of work was submitted and orally presented at the ESRC Multi-disciplinary Health & Biomarkers Conference, ISER, University of Essex, 2015

coronary, cerebrovascular and peripheral vascular diseases, ii) to determine the extent to which women and men show similar associations and iii) to determine the shape of any associations, in particular whether there is evidence of a threshold and whether risk extends into “normal ranges”. We used large scale, population based linked primary-secondary care electronic health records in the CALIBER (ClinicAL disease research using LInked Bespoke studies and Electronic health Records) resource,[217] We have previously demonstrated that the validity of these data for a wide range of cardiovascular risk factors (age, and sex,[129] systolic and diastolic blood pressure,[218] type II diabetes[187] and smoking[189]) and have discovered novel, associations across a wide range of CVDs.[129, 218]

4.2. Methods

4.2.1. Data resource

The Cardiovascular disease research using Linked Bespoke studies and Electronic Records (CALIBER) e-health database was the data resource for this study. CALIBER links patient records from four different data sources: Clinical Practice Research Database (CPRD)[192] MINAP (Myocardial Ischaemia National Audit Project registry)[219] Hospital Episodes Statistics (HES)[220], the Office for National Statistics (ONS).[221] CPRD data were used to obtain heart rate measurements, demographic variables and other risk factors. Primary care practices and the subset of linked practices used in the present study analysis are representative of the UK primary care setting[194] and have been validated for epidemiological research.[222] A detailed description of CALIBER has been presented elsewhere.[198]

4.2.2. Study population

An open cohort of 2,23 million people was drawn from registrants between January 1997 and March 2010 with 225 primary care practices who consented to data linkage. People included in the final study cohort were 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 during the study period. Follow-up started from the date of their first heart rate measurements after applying the above eligibility criteria. Participants were censored on the dates of leaving the practice, or last submission of data, or death, or endpoint occurrence. The study flow diagram is shown in **Figure 4.1**.

4.2.3. Heart rate

Heart rate was prospectively collected by general practice staff 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 a large proportion of heart rate

measurements were obtained using an automated blood pressure device. However, distributions of heart rate measurements showed some evidence of digit preference suggesting also more subjective measurement techniques (e.g. palpation at the wrist) (**Figure A3.7 (a)**).

4.2.4. Cardiovascular risk factors

Information on risk factors was obtained from CPRD, as recorded during consultations in primary care. The most recent measurement (or prescription) recorded in CPRD up to one year before or on the date of study entry (index date, coinciding with first heart rate measurement) was used to define baseline covariates. Socioeconomic status was derived from ONS using the Index of Multiple Deprivation (IMD) 2007.[223] It was divided into five categories (quintiles), the 1st quintile corresponding to the least deprived and the 5th quintile to the most deprived groups. The most recent smoking record before the index date was used to classify participants as never, ex or current smokers. Phenotyping algorithms combining Read, ICD-10, drug and procedure codes to define risk factors and endpoints are available at http://www.caliberresearch.org/portal/.

4.2.5. Endpoints

The onset of CVD with specific initial presentations was defined as the recording of a specific diagnosis on first recorded date that would prevent for evolvement of a disease and its conversion into another CVD phenotype. To disable misclassification of phenotypes, the data used from both HES and the Myocardial Ischaemia National Audit Project (MINAP) are based on discharge rather than admission diagnosis. Additionally, the time elapsed between the first recorded diagnosis and the subsequent one for a sample of patients from CALIBER; was investigated and found that the mean number of days between different types of events was over 60 days for all presentations, suggesting that using the first recorded diagnosis is a robust approach to studying onset of CVD.[224] Where more than one diagnosis was recorded on one day, the most specific and serious presentation was used. Endpoints are allocated a priority order so if a more severe or advanced form of the disease occurs on the same day as a milder form the more severe form is counted. This hierarchy is presented in **Table A4.1** in Appendix 4.

All four constituent data sources (CPRD, MINAP, HES, ONS) were used to define the cardiovascular phenotypes used in this study. Both historical and incident codes were used to exclude patients from the cohort, but only incident codes were used to identify initial presentation of CVD. Both fatal and non-fatal presentations are included, with the exception of stable angina, which does not include fatal presentations, and unheralded coronary death which does not include non-fatal presentations.

The primary endpoints were the initial presentation of non-fatal or fatal CVDs across the four data sources. The CVD outcomes analysed entailed stable angina (SA), acute coronary diseases (unstable angina (UA), myocardial infarction (MI)); heart failure (HF), unheralded coronary death; a composite of cardiac arrest, ventricular fibrillation and sudden cardiac death (SCD); abdominal aortic aneurysm (AAA); peripheral arterial disease PAD and cerebrovascular diseases including transient ischaemic attack (TIA), ischaemic stroke, subarachnoid haemorrhage (SAH) and intracerebral haemorrhage. Additional composite endpoints analysed were Coronary artery disease events (CAD), total CVD events and mortality outcomes (i.e. 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). All ICD-10 and Read codes used to define each cardiovascular endpoint and data sources were presented in chapter 3 (**Table A3.9).**

4.2.6. Statistical analysis

For analytic purposes, heart rate was divided into levels (<60, 60-69, 70-79, 80-89, >90) (<60bpm reference level) and outliers (<30 and >150bpm) were removed. 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) (**Figure A4.2**). We also used heart rate as a continuous variable per 10 bpm increase. Differences in risk factors by level of heart rate were tested using the F statistic from analysis of variance or its non-parametric version (Kruskal Wallis test) and the chi-square statistic, as appropriate. The association between heart rate and each disease was assessed using Cox proportional hazard models with time since study entry as the timescale, adjusting for baseline age and 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, HDL, LDL, type 2 diabetes and BMI) and stratified by primary care practice. For covariate adjustments the missing at random covariate values were imputed using multiple chained equations.[225] To assess the shape of association between heart rate and the different CVD endpoints we used restricted cubic splines with 4 knots and the reference value of 70bpm (**Figure 4.10**).[226]

In sensitivity analyses, we excluded i) cardiovascular events that occurred within the first year of follow-up to account for potential reverse causality effect, ii) events that were diagnosed in primary care to validate the diagnostic accuracy of cardiovascular events and then iii) all patients that reported beta-blockers or blood pressure medication intake (**Figures A4.3-A4.6)**. Additionally, we restricted the analysis to those that had their heart rate and blood measurement recorded on the same date (consequently probably measured by the same device). To further explore associations of severe stable angina events with increased heart rate we restricted the analysis to patients who underwent a Coronary Artery Bypass Graft (CABG) before after a

stable angina event. Statistical analyses were performed using Stata statistical software (StataSe v13 and R version 3.0.3).

4.3. Results

4.3.1. Baseline characteristics

We included 233,970 patients (58% women) with heart rate measurements available at baseline (mean (SD) HR in men 74.6bpm,(±14.5) and in women 77.9bpm (±14.0)) who experienced 28,381 events during 641,843.5 person-years of follow-up (mean follow-up per patient 3.26 years). Cohort characteristics by heart rate are shown in **Table 4.1**. Higher heart rates were associated with female sex, social deprivation, current smoking and type 2 diabetes and lower use of beta-blockers.

Table 4.1. Baseline characteristics of patients by heart rate level

	<60 bpm (N=18,278)		60-69bpm (N=52,630)		70-79 bpm (N=70,549)		80-89bpm (N= 56,235)		90-150bpm (N=36,098)		N total (%)
	Mean (%)	SD	Mean (%)	SD	Mean (%)	SD	Mean (%)	SD	Mean (%)	SD	N total (%)
Demographic factors											
Age at entry (years)	59.7	15.5	58.2	16.1	58.0	16.4	58.9	16.9	57.2	16.3	233,970 (100%)
Women	41.3		50.9		57.2		60.9		61.0		135,599 (57.9%)
White Ethnicity	75.5		73.6		73.7		73.5		73.7		126,650 (54.2%)
Deprivation (most deprived quintile)	18.7		20.9		22.0		24.4		26.6		52,541 (22.5%)
Clinical biomarkers and risk factors											
Heart rate (continuous) (bpm)	53.4	4.81	64.5	3.07	73.8	2.83	83.0	3.10	101.1	11.3	233,970
Systolic blood pressure, (mmHg)	143.1	21.3	139.5	20.2	138.6	19.5	139.4	19.8	141.4	20.8	225,766
Diastolic blood pressure, (mmHg)	80.8	11.4	80.9	10.8	81.1	10.7	81.8	10.8	83.5	11.6	225,766
High density lipoproteins, (mmol/L)	1.41	0.39 .39	1.43	0 .4	1.44	0.4	1.43	0.4	1.44	0.4	71,902
Low density lipoproteins, (mmol/L)	3.20	0.99	3.20	0.99	3.21	1.0	3.17	1.0	3.12	1.0	37,460
Total cholesterol (mmol/L)	5.30	1.10	5.31	1.1	5.35	1.2	5.34	1.1	5.34	1.3	63,412
Triglycerides (mmol/L)	1.55	0.92	1.56	0.9	1.62	1.1	1.69	1.2	1.76	1.3	45,949
Creatinine (µmol/L)	93.1	25.4	89.3	25.9	87.5	26.2	86.8	29.4	86.5	30.5	79,752
BMI (kg/m^2)	27.9	5.3	27.8	5.6	28.2	5.7	28.5	6.1	28.5	6.4	68,548
Smoking											
Non-smokers	63.5		61.6		60.2		57.8		55.1		107,346 (45.9%)

Ex-smoker	17.8	16.0	15.2	15.0	14.1	53,872 (23.0%)
Current smoker	16.8	20.1	22.3	24.2	28.0	68,630 (29.3%)
Diabetes type II	4.83	4.48	4.77	5.74	6.77	23,006 (9.84%)
Medication						
Beta-blockers	39.7	21.1	11.1	8.71	8.07	80,525 (34.4%)
Calcium channel blockers	15.3	11.8	10.8	11.3	13.5	67,533 (28.8%)
BP medication	48.5	39.1	38.7	39.0	41.7	131,937 (56.4%)
Statins	14.1	11.6	10.8	10.7	11.8	45,280 (19.3%)
Aspirin	11.38	8.78	7.90	8.47	8.66	45,560 (19.5%)

Note: Blood pressure (BP) medication includes diuretics, b-blockers, calcium channel blockers and ACE inhibitors intake; N total % latest recording within a year before baseline (HR measurement)

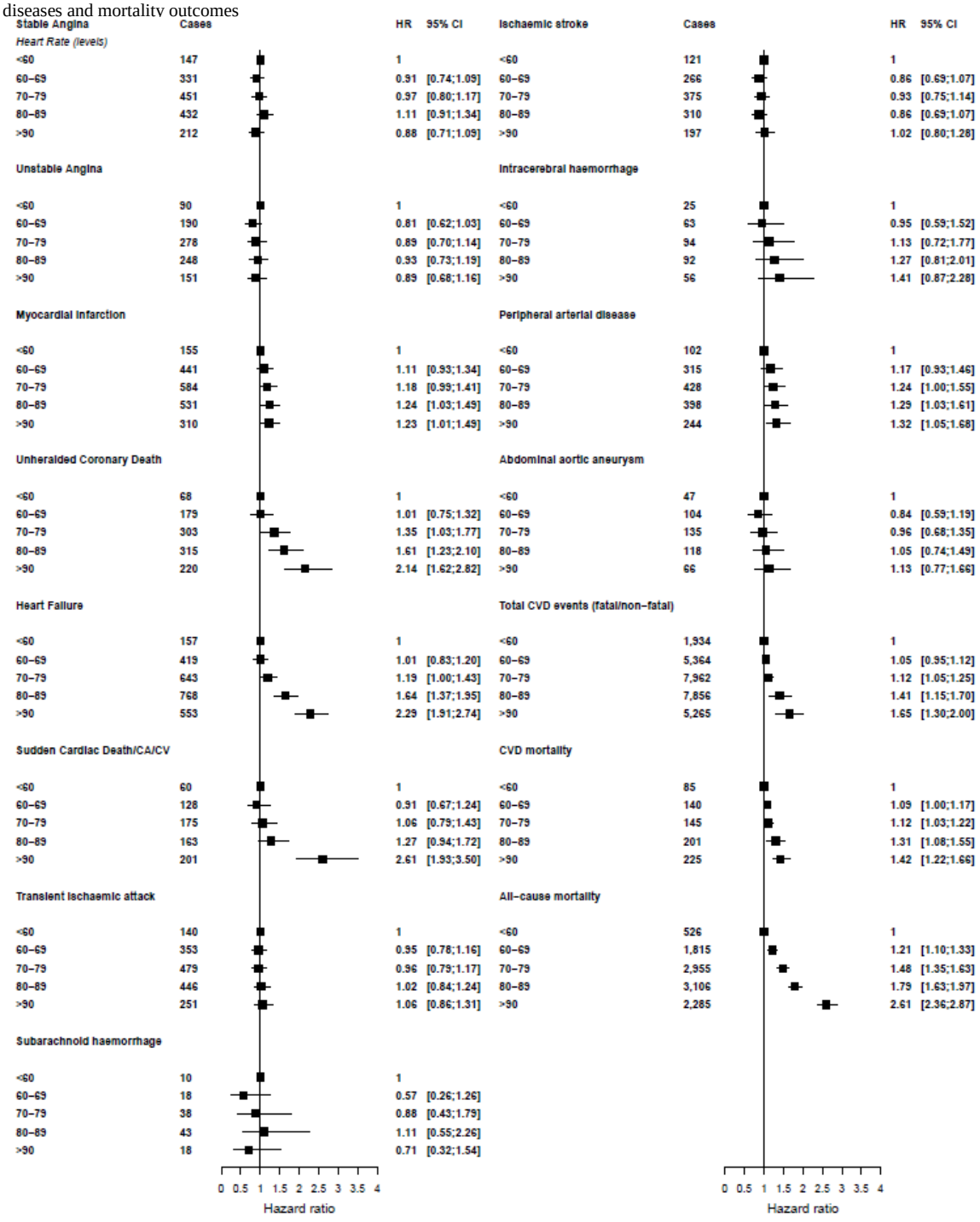
4.3.2. Specificity of associations across different incident CVDs

The age and sex adjusted Cox analysis (**Fig A4.8-Appendix 4**) showed significantly increased hazard of unheralded coronary death, heart failure, sudden cardiac death, myocardial infarction and peripheral arterial disease in >90bpm values compared with <60bpm.

However, in the fully adjusted model, heart rate was specifically, strongly associated with the incidence of three cardiac diseases: heart failure, sudden cardiac death and unheralded coronary death, The fully adjusted hazard ratios comparing a heart rate of >90bpm vs <60bpm were for unheralded coronary death (UCD) (HR=1.93, 95%CI 1.46-2.55), sudden cardiac death (SCD) (HR=2.41, 95% CI 1.79-3.24) and heart failure (HF) (HR=1.92, (95%CI 1.60-2.29) (**Figure 4.9, Table 4.2**). Heart rate was not in adjusted analyses associated with the incidence of coronary diseases (stable angina, unstable angina, myocardial infarction), cerebrovascular diseases (transient ischaemic attack, subarachnoid haemorrhage, ischaemic stroke, intracerebral haemorrhage), peripheral arterial disease or abdominal aortic aneurysm. For lower heart rate values 70-79bpm compared to <60bpm an increased risk of UCD (HR= 1.35, 95% CI 1.03-1.77) and all-cause mortality (1.48, 95% CI 1.35-1.63) was found, while for 80-89bpm heart rate, an increased risk for HF was also observed (HR=1.64, 95% CI 1.37-1.95). The composite total CVD events endpoint, showed an increase in risk of 1.40 and 1.65 times in 80-89bpm and >90bpm respectively.

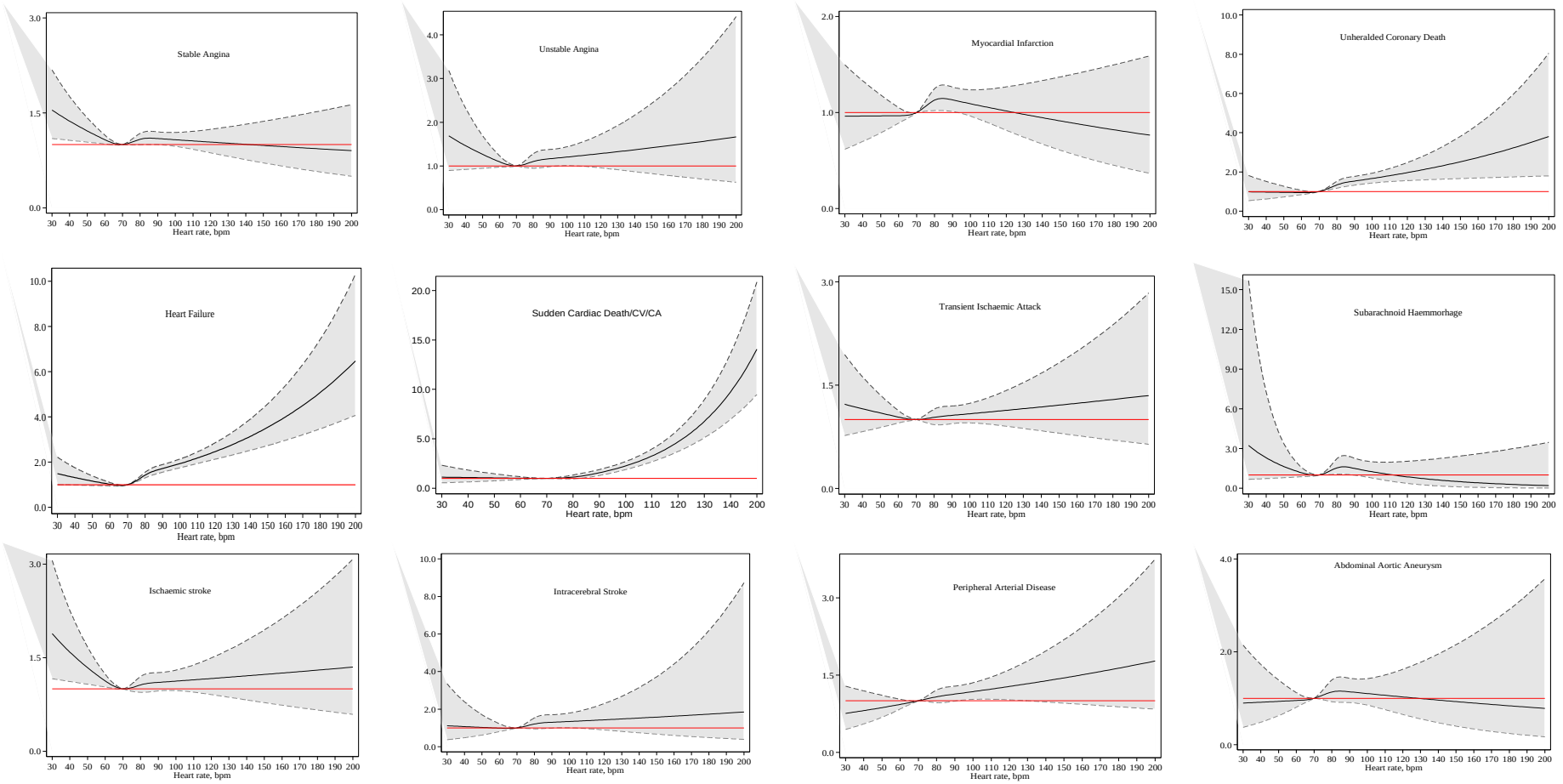
The shapes of the associations showed no strong evidence of a threshold with the hazard of unheralded coronary death, heart failure and cardiovascular mortality increasing progressively with heart rates that would usually be regarded as normal (**Figure 4.10**).

Figure 4.9. Multivariable adjusted hazard ratios for the association between heart rate and the initial presentation of 12 cardiovascular diseases and mortality outcomes



Note: CI, confidence interval; HR, hazard ratios adjusted for age, sex, social deprivation, smoking, systolic blood pressure, BP medication, total cholesterol, HDL, LDL, diabetes II and BMI; CA, Cardiac Arrest; CV, Cardioversion

Figure 4.10. Restricted cubic splines of heart rate and 12 cardiovascular diseases



.Note: Adjustments include age, quadratic age, and stratification by sex and primary care practice

Table 4.2. Adjusted hazard ratio of heart rate with 12 CVDs

Outcomes	N of events	<60bpm	60-69bpm	70-79bpm	80-89bpm	>90bpm	P-value HR#per
CARDIAC			HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Stable Angina							
Men	823	1.00(ref)	1.12	1.28[0.99-1.66]	1.48 [1.14-1.93]	1.17 [0.87-1.58]	0.067
Women	750	1.00(ref)	0.65 [0.48-0.87]	0.65[0.49-0.86]	0.73 [0.56-0.97]	0.60 [0.44-0.81]	
Unstable Angina							
Men	429	1.00(ref)	0.69 [0.49-0.98]	0.96[0.69-1.33]	0.89[0.63-1.26]	1.09 [0.76-1.57]	0.210
Women	528	1.00(ref)	0.93 [0.64-1.36]	0.85[0.59-1.23]	0.97[0.67-1.40]	0.76[0.51-1.14]	
Myocardial infarction							
Men	1,113	1.00(ref)	1.16[0.92-1.46]	1.20[0.96-1.51]	1.29[1.02-1.63]	1.39 [1.08-1.79]	0.047
Women	908	1.00(ref)	1.01[0.74-1.37]	1.07[0.79-1.44]	1.10[0.82-1.49]	1.01 [0.74-1.39]	
Unheralded coronary death							
Men	530	1.00(ref)	1.05	1.65[1.13-2.41]	2.14[1.46-3.13]	3.06[2.07-4.52]	0.000
Women	555	1.00(ref)	0.86[0.58-1.29]	0.97[0.66-1.41]	1.08[0.74-1.58]	1.32[0.89-1.96]	
Heart Failure							
Men	1,038	1.00(ref)	1.18[0.89-1.56]	1.65[1.26-2.16]	2.11[1.61-2.76]	3.26[2.48-4.30]	0.005
Women	1,502	1.00(ref)	0.81[0.63-1.04]	0.85[0.67-1.07]	1.23[0.97-1.55]	1.62[1.28-2.06]	
Sudden cardiac death/							
Men	442	1.00(ref)	0.93[0.64-1.33]	1.05[0.73-1.50]	1.25[0.87-1.80]	2.69[1.89-3.83]	0.683
Women	285	1.00(ref)	0.87[0.47-1.58]	1.07[0.61-1.88]	1.28[0.73-2.25]	2.52[1.45-4.40]	
Coronary heart disease (NOS)							
Men	1,038	1.00(ref)	0.78[0.63-0.97]	0.92[0.75-1.13]	0.84[0.68-1.05]	0.94[0.74-1.20]	0.226
Women	883	1.00(ref)	0.93[0.70-1.24]	0.96[0.73-1.26]	0.81[0.62-1.08]	0.76[0.57-1.03]	
CEREBRAL							
Transient Ischaemic Attack							0.325
Men	659		0.890.67-1.17]	0.85	1.17	1.03	

Women	1,010	1.00(ref)	0.97[0.73-1.29]	1.01[0.77-1.33]	0.92[0.70-1.22]	1.04[0.78-1.40]	
Subarachnoid Haemorrhage							
Men	30	1.00(ref)	0.55[0.14-2.11]	1.03[0.31-3.43]	1.14[0.33-3.97]	0.68[0.14-3.19]	0.964
Women	97	1.00(ref)	0.60[0.22-1.59]	0.86[0.35-2.12]	1.13[0.47-2.75]	0.71[0.27-1.88]	
Intracerebral Haemorrhage							
Men	136	1.00(ref)	0.91[0.48-1.75]	0.95[0.50-1.80]	1.26[0.66-2.42]	1.78[0.91-3.48]	0.422
Women	194	1.00(ref)	0.95[0.48-1.90]	1.19[0.62-2.29]	1.29[0.67-2.48]	1.17[0.58-2.36]	
Ischaemic Stroke							
Men	489	1.00(ref)	0.79[0.57-1.09]	1.05[0.77-1.42]	1.02[0.74 -1.41]	0.92[0.64-1.34]	0.851
Women	780	1.00(ref)	0.92[0.68-1.24]	0.85[0.63-1.14]	0.77[0.57-1.04]	1.04[0.76-1.42]	
PERIPHERAL							
Peripheral Arterial Disease							
Men	685	1.00(ref)	1.50[1.09-2.06]	1.45[1.06-1.99]	1.76[1.28-2.42]	1.45[1.03-2.06]	0.182
Women	802	1.00(ref)	0.86[0.62-1.19]	0.99[0.73-1.35]	0.92[0.67-1.26]	1.09[0.79-1.50]	
Abdominal Aortic Aneurysm							
Men	320	1.00(ref)	0.86[0.57-1.29	0.98[0.66-1.47]	1.22[0.81-1.83]	1.12[0.70-1.78]	0.938
Women	150	1.00(ref)	0.68[0.33-1.40]	0.82[0.42-1.62]	0.71[0.35-1.42]	1.01[0.48-2.09]	
COMPOSITES							
Total CVD events							
Men	12,439	1.00(ref)	1.23[1.16-1.30]	1.21[1.14-1.28]	1.52[1.44-1.61]	1.79[1.70-1.89]	0.055
Women	15,942	1.00(ref)	1.10[1.04-1.16]	1.03[0.97-1.09]	1.25[1.18-1.31]	1.45[1.38-1.53]	
CVD mortality							
Men	1,613	1.00(ref)	1.11[0.96-1.30]	1.25[1.05-1.48]	1.58[1.36-1.84]	1.77[1.52-2.06]	0.059
Women	2,369	1.00(ref)	1.12[0.98-1.28]	0.89[0.76-1.03]	1.16[1.02-1.32]	1.23[1.07-1.40]	
All-cause mortality							
Men	3,968	1.00(ref)	1.17[1.02-1.34]	1.55[1.36-1.77]	1.99[1.74-2.28]	2.90[2.52-3.33]	0.000
Women	7,023	1.00(ref)	0.86[0.58-1.29]	0.97[0.66-1.41]	1.08[0.74-1.58]	1.32[0.89-1.96]	

4.3.3. Effects of gender and age

Interactions with sex were found to be significant for heart failure, unheralded coronary death, myocardial infarction and composite mortality outcomes. There was a profound risk at average heart rate values in men. Specifically, the increased hazard of unheralded coronary death with a heart rate >70bpm was particularly marked in men but in women was eliminated. The increased hazard of heart failure was also greater in men and evident at heart rates >70bpm compared with women in whom the hazard was confined to heart rates >90bpm (**Table 4.2, Fig A4.11, A4.12**). An increased risk of all-cause mortality was found in men starting from lower heart rate values (>70bpm) but no risk at all was present in women at any level, while cardiovascular mortality was strongly associated with heart rate >70bpm in men, whereas in women was barely evident. Stable angina risk was slightly high increased in men for heart rate values 80-89bpm, whereas a protective effect was observed in women with HR 60-69bpm, 70-79bpm and >90bpm heart rate levels. We observed no other gender differences in the associations between heart rate and hazard of CVDs. In the age group analysis the increased hazard of the majority of outcomes (unheralded coronary death, heart failure, sudden cardiac death and cerebrovascular outcomes) for >90bpm compared with <60bpm appeared less pronounced in people aged >80 compared with younger age groups while the increased hazard of heart failure and UCD was more prominent in people aged <60 (**Figure A.4.13**).

4.4. Discussion

4.4.1. Main findings

This is the first study to demonstrate the specificity of the heart rate associations across a wide range of pathologically diverse incident cardiovascular diseases. In by far the largest healthy population cohort of women and men of representative age (>30 years of age) we show that heart rate is strongly specifically associated with cardiac diseases (unheralded coronary death, sudden cardiac death, heart failure) but not associated with coronary, peripheral diseases or stroke. We found strong associations at heart rate levels that would be commonly considered “normal” with no strong evidence of a threshold. We found that men had stronger associations with diseases than women and at lower heart rate levels. Resting heart rate of 70-79bpm, seen in 29.1% of men, should not be considered normal, whereas for women risk was largely confined to >90bpm rates.

4.4.2. Associations of HR with myocardial and arrhythmic disorders

The specificity of associations of heart rate with specific CVDs contrasts with findings for BP which showed linear associations of systolic and diastolic blood pressure with each of the same 12 CVD presentations.[188] The graded association between resting heart rate and incident heart

failure, with hazard doubling for rates >90bpm compared with rates <60bpm, is consistent with previous reports.[159, 227] Certainly, in established heart failure, rate reduction with beta-blockers and with ivabradine, improves prognosis regardless of gender.[228, 229] Nevertheless, contemporary guidelines continue to classify heart rate as a minor risk factor for heart failure, making no recommendations for rate-lowering preventive treatment in the absence of randomised trials to support such a strategy.[230] Associations between heart rate with unheralded coronary death, that is a fatal myocardial infarction event unheralded by prior symptomatic disease and have not been previously explored, were also found for lower than conventionally considered heart rate of 70-79bpm and above.

The association we found between heart rate and sudden cardiac death is also consistent with previous reports but unlike heart failure there appeared to be a steeper risk increase, hazard ratios increasing when heart rate exceeded 90bpm.[21, 85, 147, 148, 231] Only one previous large study of 379,843 people aged 40-45 years included an adjusted gender analysis but its finding of no association between heart rate and sudden cardiac death in either men or women may be explained by the age-range of the study participants.[152] Associations of heart rate with sudden cardiac death 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.[232] Further evidence of a mechanistic link of heart rate with cardiomyopathy and sudden death comes from genome-wide association studies that have identified single nucleotide polymorphisms influencing heart rate regulation in genes also involved in the pathophysiology of dilated cardiomyopathy, congestive heart failure and sudden cardiac death.[233]

4.4.3. Why do men and women differ?

In the present study, we found an increased hazard of heart failure that was greater in men and evident at heart rates >70bpm compared with women in whom the hazard was confined to heart rates >90bpm. Epidemiological studies on resting heart rate and heart failure have shown weaker associations in women and in other smaller studies it was confined to men perhaps reflecting under-powering rather than a true gender difference.[227] Unlike heart failure risk that showed a progressive increase starting at lower rates in men, sudden cardiac death appeared with a steeper risk that was increasing when heart rate exceeded 90bpm in both men and women.[21, 85, 147, 148, 231] Average heart rate of 70-79bpm, showed strong associations with unheralded coronary death but only men, whereas for women the risk was not present. Finally, associations with stable angina showed a protective effect in 60-69bpm, 70-79bpm and >90bpm in women, whereas in men associations were of the opposite direction. Although women have a higher resting heart rate than men, the weaker association of heart rate with outcome in women might arise from a greater variability of heart rate within female individuals. However, a trial of Palatini et al.[234] showed that the reproducibility of measured heart rate either at the clinic or by using ambulatory device was similar in the two genders. The higher heart rate

and volume contraction in female populations could also be the result of a higher sympathetic outflow.[235] Alternatively, oestrogens, like digitalis, may exert a direct positive inotropic effect, thereby increasing cardiac output[236] and in healthy young women, oral contraceptives increase cardiac output, produce little change in arterial pressure, and decrease total peripheral resistance.[237]

4.4.4. Lack of associations between HR and CAD, PAD, stroke or AAA

An important finding in the present study was that heart rate associations were specific to diseases of heart muscle and were not detected for atherosclerotic disorders. Small associations of heart rate with acute myocardial infarction and peripheral arterial disease were found, in sex and age adjusted >90bpm versus <60bpm comparisons that were eliminated in the fully adjusted model. Associations with stable angina were weak and a further sensitivity analyses restricted to more severe cases of angina and to those without beta-blockers intake recorded, did not alter the results. A non-specific effect of increased heart rate on mortality outcomes was also observed. Moreover, there was no association of heart rate with the other manifestations of coronary or cerebrovascular disease or with abdominal aortic aneurysm. 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 endothelial dysfunction and accelerated atherosclerosis.[238] Adjustment for conventional atherogenic risk factors had little effect on our risk estimates. Observational studies in general populations showed a lack of association of HR with fatal MI, however the sample was restricted to male subjects[147], while findings 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 myocardial infarction in patients with stable coronary artery disease.[239] Mendelian randomization studies show that the genetic loci that are associated with HR are not with CAD or MI,[240] suggesting that these diseases and heart rate are not causally associated.

4.4.5. Clinical and research implications

Heart rate is one of the most ubiquitous clinical measurements and is increasingly recorded by healthy people monitoring personal fitness with mobile devices and phone applications.[241, 242] Our findings can be used to help establish normal values for men and women. Approximately 74% of women and 63% of men have heart rates >70bpm and are at risk of cardiac events, with a risk for HF, UCD, CVD mortality and all-cause death more pronounced in men. In other words, average heart rate values particularly in men, cannot be considered normal any more and further attention should be given to those males with heart rates lower than those so far considered as “normal” rhythm values. Trials are required of heart rate lowering in high risk

groups, e.g. in patients with resting tachycardia (≥90bpm) present in 17% of women and 13% in men. Remarkably there are no guidelines to inform clinical decision-making regarding behavioural, pharmacological, etc. for these patients. Heart rate may contribute to the identification of patients at high risk of severe outcomes such as sudden cardiac and unheralded coronary death. Finally, our findings require re-evaluation of the contribution that heart rate makes to risk prediction, taking account of specific outcomes of interest 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.[243]

4.4.6. 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 Electronic Health Records and therefore has intrinsic clinical relevance. We have recently demonstrated the validity of using electronic health record cohorts in high resolution cardiovascular epidemiology by replicating and extending associations from smaller studies for BP, type 2 diabetes, sex and smoking.[186-189] Robustness of results for this paper, was assessed by excluding endpoints exclusively recorded in primary care (**Figure A4.4**).

Limitations include the digit preference in the heart rate measurements that were not taken under standard conditions (**Figure 3.5(a)** in chapter 3.). Although associations between heart rate and CVDs are not influenced by variation of resting values over time or by the measurement method used[152] we can assume that more accurate measurements would likely show stronger associations. Additionally, we were unable to adjust for physical activity which was recorded in only 50,069 patients. However, this is unlikely to have affected our findings based on previous studies where adjustment for exercise had little effect on heart rate associations with CVD.[148, 153, 154] Moreover, the possibility that heart rate might be acting as a surrogate for physical fitness in these associations is not supported by recent physiological data.[158] The potential for imbalance between baseline beta-blocker prescription rates to distort our findings was excluded in a sensitivity analysis (**Figure A4.5**). Finally, patients with a resting heart rate recorded within CALIBER were an average of 14 years older than those without a heart rate record. These findings are potentially due to the fact that older people visit GPs more often, have additional medical reasons which affect the cardiac regulatory system and a more thorough clinical examination is required. However, mean heart rate values in men and women (74bpm in men and 77bpm in women) were fairly similar to subjects of observational studies of similar characteristics.

4.5. Conclusions

Resting heart rate shows specific associations with myocardial and arrhythmic disorders, but not with coronary disease, stroke or PAD. Average resting heart rate of >70bpm in the general population increases the hazards of specific cardiovascular diseases and mortality particularly in men and should not be considered as normal. No substantial effect on the hazard of vascular events in the coronary, cerebrovascular and peripheral arterial beds was found. Disaggregation of CVD into its constituent phenotypes can help our understanding of disease mechanisms with implications for clinical practice and the design and interpretation of clinical trials.

5. Heart rate and the risk of a wide range of cardiovascular events in 51,703 people with stable coronary artery disease (sCAD): a CALIBER study[2]

This chapter will attempt to estimate the prognostic ability of heart rate on people with established stable coronary artery disease using data from the general primary and secondary care in UK and will allow for more precise investigations with higher resolution not only among different CVDs but also between the two genders

5.1. Introduction

The relationship between resting heart rate (RHR) and cardiovascular diseases (CVDs) and total and cardiovascular mortality, has been investigated in patients with stable coronary artery disease (CAD)[169] and in the general population (IP HR paper). However, associations between heart rate and specific cardiac phenotypes and rhythm disorders are unclear. Recent clinical trials on heart rate lowering medications direct their focus on composite endpoints consisting of combinations of non-fatal myocardial infarction with CVD outcomes and subsequently fail to establish any associations between those and RHR while the invest large amounts of sources.[128]

Contemporary data regarding the association between higher heart rate and CVD events of CAD patients is derived from clinical trials or angiographic registries that is collected solely for research purposes and is majorly focused on high risk patients[125] or people admitted to hospital for acute coronary syndromes[168, 244], referred for specific cardiovascular procedures or hospitalized and not to the general population.[125, 169] However, the selective nature of the populations studied might compromise the external validity of the findings. Composite cardiovascular endpoints do not allow for investigations of associations with specific types of cardiovascular events that can provide insights into the pathophysiological mechanisms of disease progression in a stable CAD population. These mechanisms can be further explored through the assessment of resting heart rate associations with rhythm disorders such as atrial fibrillation in populations with stable coronary artery disease that so far remain under-examined. Available observational studies that assessed specific endpoints present old findings, hence the update of evidence is crucial. Additionally, gender differences in heart rate effects on cardiovascular events have not been sufficiently examined as the majority of findings particularly derived by clinical trials include male participants.[163, 168] A summary of the available studies was presented in chapter 2 (**Table 2.4)**.

[2] The present piece of work was submitted and presented orally at the Farr Institute Conference, St Andrews, Scotland, 2015

Using linked electronic health records we will investigate the prognosis of CAD in relation to heart rat[3]e levels that are relevant in clinical practice. We have previously demonstrated the validity of these data by developing prognostic models that incorporate clinical measures recommended in guidelines and target patients with SCAD.[245] The associations and shape of the relationships with a large range of recurrent cardiovascular diseases previously unexplored will be studied in a large population of patients with stable CAD, and evidence for gender interactions will be assessed. Specifically our objectives entail: i) The identification across a large range of CVDs of those important for the design of clinical trials on heart rate lowering medication, ii) examine potential differences in CVDs prognosis between men and women with sCAD.

5.2. Methods

5.2.1. Data resource

The Cardiovascular disease research using Linked Bespoke studies and Electronic Records (CALIBER) e-health database was analysed. CALIBER links patient records from four different data sources: the Clinical Practice Research Datalink (CPRD)[192], the Myocardial Ischaemia National Audit Project registry (MINAP)[219], Hospital Episodes Statistics (HES)[220], and the Office for National Statistics (ONS)[221]. The primary care practices and the subset of 225 linked practices consenting to data linkage are representative of UK primary care settings[194] and have been validated for epidemiological research.[222] Primary care data were used to obtain heart rate measurements, demographic variables and other risk factors.

5.2.2. Study population

An open cohort of 2,23 million people covering approximately 5% of the UK population was drawn from patients registered between January 1997 and March 2010. People eligible for study inclusion were aged ≥30 years at study entry ('index date'), had ≥1 year registration prior to the index date and being diagnosed with stable coronary artery disease, that is at least 1 year prior to index date a diagnosis of one of the following CVDs: stable/unstable angina, myocardial infarction (at least 6 months after a MI or UA event to be stable) and finally at least one recorded heart rate measurement after the index date. CVD events that ensured eligibility should have been experienced any time prior to the index date or in case of its absence, any time after that date. In case of existence of an event prior to and after the eligibility index date, the date used for analysis was the former one. Participants were censored on the earliest of the following dates: leaving the practice, last collection date of the practice, death, or endpoint occurrence. The study flow diagram is shown in **Figure A5.1** (Appendix 5).

5.2.3. Heart rate

Heart rate was prospectively collected by general practice staff and values ranged from 20-240 bpm. The method of measurement is not recorded in the database but it is likely to have been obtained through palpation at the wrist, auscultation of the heart and readings from an automated blood pressure device or electrocardiogram (ECG). Because 100% of people with a heart rate record at baseline had a blood pressure measurement the same day. However, digital preference was identified in heart rate distributions as we observed in chapter 3 (**Figure 3.5(b) and Table A3.7**) and consequently I cannot infer with certainty that heart rate was recorded using the same device as in blood pressure measurements.

5.2.4. Cardiovascular risk factors

Information on risk factors was obtained from CPRD, as recorded during consultations in primary care. The most recent measurement (or prescription) recorded in CPRD up to one year before or on the date of study entry (first heart rate measurement after the index date) was used to define baseline covariates. Socioeconomic status was derived from ONS using the Index of Multiple Deprivation (IMD) 2007.[223] It was divided into five categories (quintiles), the 1st quintile corresponding to the least deprived and the 5th quintile to the most deprived groups. The most recent smoking record before the index date was used to classify participants as never, ex or current smokers. Phenotyping algorithms combining Read, ICD-10, drug and procedure codes to define risk factors are available at **http://www.caliberresearch.org/portal/.**

5.2.5. Endpoints

The primary endpoints were the first presentation of a new non-fatal or fatal CVDs after the date of entry across the four data sources: acute coronary diseases (myocardial infarction (MI)); heart failure); a composite of cardiac arrest, ventricular fibrillation and sudden cardiac death (CA-SCD); a composite of cerebrovascular diseases including ischaemic stroke, subarachnoid, and intracerebral haemorrhage and unknown stroke type; and peripheral arterial disease. Additionally, two mortality outcomes were assessed, CVD and all-cause mortality, and atrial fibrillation. 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 (CPRD) and bespoke variables in MINAP).

5.2.6. Statistical analysis

In primary analyse heart rate was grouped into clinically relevant categories (<60 bpm, 60-70 bpm, 70-80, 80-90, >90bpm) and the lowest level (considered as sinus bradycardia in adults

[246]) was used as the reference category. In secondary analyses heart rate was analysed as a 10 bpm increase continuous variable. Analyses were also conducted separately for patients with different types of pre-existing CHD (i.e. stable angina, unstable angina and myocardial infarction). And evidence for interaction by age, sex and hypertensive status (sbp/dbp>140/90) was assessed. The association between heart rate and each endpoint was assessed using Cox proportional hazard models with time since study entry as the timescale and stratified by primary care practice.. Covariates were added in the models in two steps for estimated adjustment: 1) Sex and age adjusted; 2) additionally by established cardiovascular risk factors (index of multiple deprivation, systolic blood pressure, smoking status, body mass index (BMI), diabetes type II, high density lipoprotein cholesterol and total serum cholesterol).

For covariate adjustments the missing at random covariate values were imputed using multiple chained equations[225] with a similar process as described in chapter 4. To assess the shape of associations between heart rate and CVD endpoints I used restricted cubic splines with 4 knots.[226] Several sensitivity analyses were performed. First, repeating the analyses after excluding CVD events occurring during the first year after the heart rate measurement (**Figure A5.7**). Second, performing analyses restricted to patients without baseline prescription of beta-blockers, blood pressure lowering medication or warfarin/digoxin medication (**Figures A5.8, A5.9, A5.10**). Third, conducting separate analyses for patients who had pre-existing CHD prior or after their index date (**Figures A5.11, A5.12**) and normotensive/hypertensive people (**Figures A5.13, A5.14**). Finally, after excluding patients with history of heart failure and after ignoring CVD events recorded in primary care data (**Figures A5.15, A5.16**). Statistical analyses were performed using Stata statistical software (StataSE 13) and R (v3.0.3).

5.3. Results

5.3.1. Baseline characteristics

I included 51,703 patients (44.1% women) who experienced 9,043 cardiovascular events during 132,359.7 person-years of follow-up (mean follow-up per patient 2.6 years). Patient characteristics by heart rate level are shown in **Table 5.1**. Compared with patients with heart rate <60 bpm, those with >90 bpm were more commonly females, socioeconomically deprived, current smokers, hypertensive and diabetic. Proportions of beta-blocker, aspirin and statin users decreased with higher heart rate levels, while the proportions of warfarin, digoxin and verapamil increased with higher heart rate levels. Baseline prevalence of pre-existing heart failure, stroke and atrial fibrillation also increased with higher heart rate levels. People with history of unstable angina were more likely women, of white ethnicity, have hypertension and diabetes and receive anti-arrhythmic and blood pressure lowering medication, compared to people with pre-existing stable angina or myocardial infarction (**Table A5.2**-Appendix 5).

Table 5.1. Baseline characteristics of people with stable coronary artery disease by heart rate level

	L1 (<60 bpm)		L2 (60-69 bpm)		L3 (70-79 bpm)		L4 (80-89 bpm)		L5 (>90 bpm)		Total (%)
	Mean (%)	SD	Mean (%)	SD	Mean (%)	SD	Mean (%)	SD	Mean (%)	SD	N Total (%)
Demographic factors											
Age (years)	71.7	10.3	71.5	11.1	72.6	11.6	73.1	11.7	72.2	11.9	51,703 (100%)
Female	31.5		39.4		46.9		52.0		53.1		22,809 (44.1%)
White Ethnicity	79.8		79.7		80.2		80.6		80.4		37,980 (80.1%)
Socioeconomic	16.5		18.2		20.3		22.3		24.4		10,300
Clinical biomarkers and											
Heart rate (continuous)	52.7	4.97	63.7	3.11	73.5	2.85	82.7	3.08	101.1	12.6	51,703
Systolic blood pressure,	139.0	20.3	137.3	19.5	138.2	19.8	138.8	19.8	138.8	21.1	44,297
Diastolic blood pressure,	75.4	10.9	76.1	10.5	77.0	10.5	77.8	10.6	78.9	11.7	44,297
High density lipoprotein	81.3	36.9	82.8	38.5	86.3	40.4	89.0	42.6	91.6	43.1	26,461
Low density lipoprotein	2.39	0.83	2.46	0.88	2.53	0.93	2.56	0.96	2.60	1.02	21,381
Total cholesterol	42.8	9.89	44.0	10.5	45.3	11.0	46.0	11.2	46.5	11.6	35,078
Triglycerides (mmol/L)	1.52	0.84	1.57	1.02	1.60	1.04	1.62	1.00	1.67	1.40	26,382
Creatinine (µmol/L)	103.3	34.0	102.1	40.8	102.9	108.4	102.0	41.5	101.9	43.5	37,083
BMI (kg/m^2)	27.9	4.77	28.1	5.20	28.1	5.47	28.4	5.95	28.5	6.30	23,928
Smoking											
Non-smokers	37.9		39.3		41.1		42.1		38.4		19,713 (95.2%)
Ex-smoker	51.6		47.7		44.6		42.5		43.3		22,670 (95.2%)
Current smoker	9.7		11.8		12.7		13.5		16.4		6,177 (95.2%)
Type 2 Diabetes	10.0		10.9		11.9		12.5		14.8		51,703 (100%)
Current alcohol drinker	60.6		57.9		54.7		54.1		51.9		9,367 (18%)
Hypertension diagnosis	5.68		5.07		6.35		6.97		9.47		2,791 (6.3%)
Medication											
Beta-blockers	79.7		63.1		43.1		31.8		28.2		26,212 (50.7%)

Antianginal medication*	69.1	65.5	64.6	64.9	66.5	34,040 (65.8%)
Blood pressure lowering	79.8	76.1	73.9	72.3	74.2	38,871 (75.2%)
Warfarin	6.56	7.52	8.47	9.65	11.47	4,365 (8.44 %)
Digoxin	2.91	3.65	5.23	6.48	8.66	2,594 (5.02 %)
Verapamil	0.66	1.39	1.74	2.24	3.04	884 (1.71%)
Diltiazem	10.4	10.7	12.1	13.0	11.8	6,007 (11.6%)
Aspirin	76.6	71.3	65.9	62.1	58.7	34,975 (67.6%)
Statins	75.9	68.6	60.2	54.0	52.9	32,611 (63.1%)
CVD comorbidities &						
Heart failure	12.2	12.7	15.2	17.4	20.6	7,769 (15.0%)
Stable angina	47.8	50.1	53.6	56.5	58.0	44,370 (37.7%)
Myocardial infarction	25.2	24.2	22.5	21.1	20.3	5,597 (16.5 %)
Stroke	4.61	5.32	6.15	6.67	6.80	3,023 (5.85%)
Peripheral arterial	0.75	0.90	1.24	1.50	1.78	607 (1.17%)
Atrial fibrillation	14.1	14.7	17.0	19.2	23.9	8,820 (17.1%)

Note: Blood pressure (BP) medication consists of BNF codes that refer to diuretics, b-blockers, calcium channel blockers and ACE inhibitors intake.

For categorical variables the means represent % proportions. *Antianginal medication consists of: Ca channel blockers, nitrates, vasodilators and other angina medication

5.3.2. Heart rate and CVDs prognosis

In multivariable models, the hazard of heart failure, atrial fibrillation, CVD and total mortality increased with increasing levels of heart rate. These associations were present regardless of the type of pre-existing coronary event (**Table A5.3-Appendix 5**). Hazards of sudden cardiac death and stroke were also higher in patient with >=90 vs. <60 bpm (HR=2.23, 95%CI 1.41-3.51 and HR=1.30, 95%CI 1.10-1.55) (**Figure 5.2, Table 5.4**) although the risk of stroke was found attenuated compared to the analysis adjusted just for sex and age (**Figure A5.3-Appendix 5**). However, no evidence of association with stroke was found for people with pre-existing MI or UA (**Table A5.3-Appendix 5**). The heart rate level was not associated with subsequent occurrence of myocardial infarction or peripheral arterial disease.

5.3.3. Interactions with age and gender

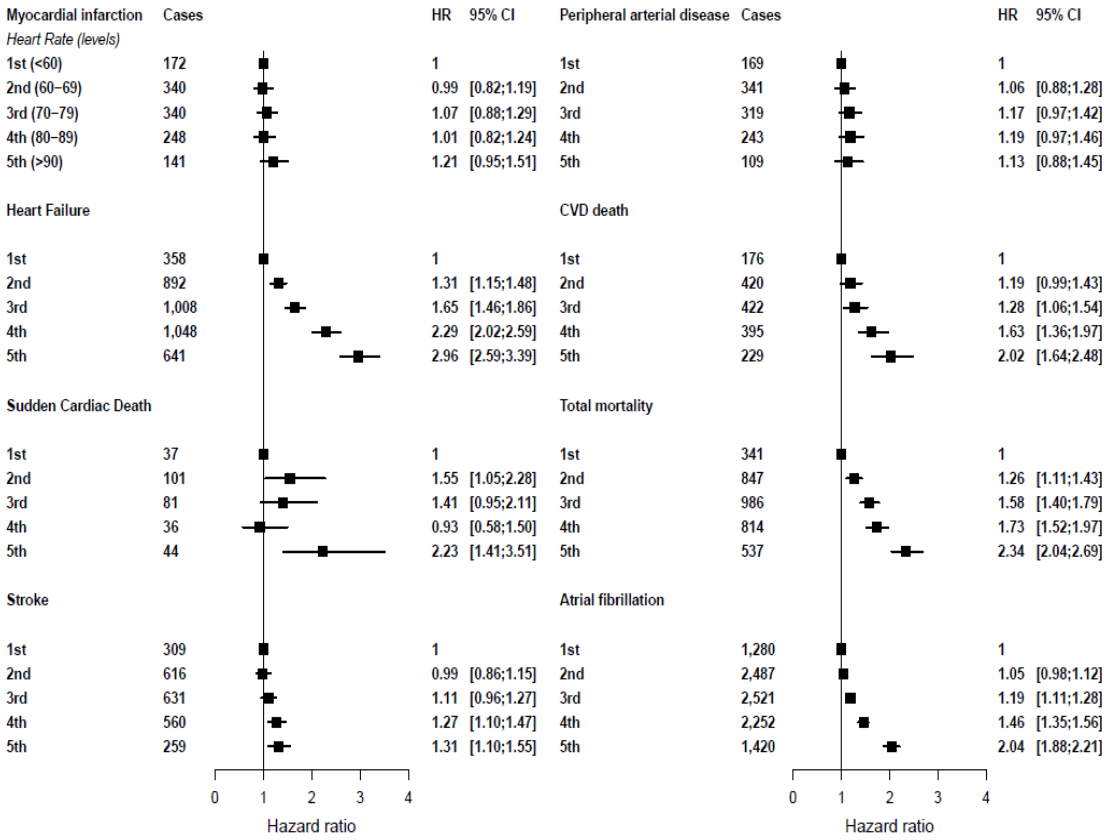
Overall, interactions with sex were found to be significant for PAD, AF and cardiovascular death (**Table 5.5**). Separate analysis for men and women are presented in **Figures A5.4 and A5.5**). For every 10bpm heart rate increase, the risk for mortality (CVD and all-cause) was attenuated in people >80 years of age. Mild but consistent decrease of HF and AF was also found >80 age, with the risk for heart failure getting lower for ages >60 years (**Figure A5.6-Appendix 5**).

Table 5.4. Multivariable adjusted hazard ratios for the association between heart rate levels and the subsequent fatal and non-fatal events among people with stable coronary artery disease

	N of events	Level1 (<60 bpm) (N= 12,147)	Level2 (60-69 bpm) (N= 10,199)	Level 3 (70-79 bpm) (N= 9,188)	Level 4 (80-89 bpm) (N= 10,501)	Level 5 (>90 bpm) (N= 9,668)	Heat rate/sex Interactions	Per 10 bpm
Cardiac outcomes			HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	p-value	HR (95% CI)
Myocardial infarction	1,041	REF	0.99(0.82-1.19)	1.07(0.88-1.29)	1.01 (0.82-1.24)	1.20(0.95-1.51)	0.71	1.02 (0.98-1.07)
Atrial fibrillation	9,960	REF	1.05(0.98-1.12)	1.19(1.11-1.28)	1.46(1.35-1.56)	2.04(1.88-2.21)	0.01	1.15 (1.13-1.16)
Heart Failure	3,465	REF	1.30(1.15-1.48)	1.65(1.46-1.86)	2.29(2.02-2.59)	2.69(2.59-3.39)	0.17	1.21 (1.19-1.23)
CA-SCD	237	REF	1.55(1.05-2.28)	1.41(0.95-2.11)	0.93(0.58-1.50)	2.23(1.41-3.51)	0.95	1.07 (0.99-1.16)
Peripheral arterial disease	1,181	REF	1.06(0.88-1.28)	1.17(0.97-1.42)	1.19(0.97-1.46)	1.13(0.88-1.45)	0.03	1.03 (0.99-1.07)
All cause stroke	1,746	REF	0.99(0.86-1.15)	1.10(0.96-1.27)	1.27(1.10-1.47)	1.30(1.10-1.55)	0.26	1.06 (1.03-1.10)
CVD death	1,477	REF	1.19(0.99-1.43)	1.28(1.06-1.54)	1.63(1.36-1.97)	2.02(1.64-2.48)	0.05	1.14 (1.10-1.17)
Total mortality	3,098	REF	1.26(1.11-1.43)	1.58(1.40-1.79)	1.73(1.52-1.97)	2.34(2.04-2.69)	0.00	1.15 (1.13-1.18)

Note: CVD, cardiovascular; SCD-CA, Sudden cardiac death-Cardiac arrest; CI, confidence interval; HR, hazard ratios from Cox proportional hazard model stratified by general practice and adjusted for sex, age, index of multiple deprivation, smoking, systolic blood pressure, type 2 diabetes, total cholesterol, HDL cholesterol and body mass index

Figure 5.2. Multivariable adjusted hazard ratios for the association between heart rate (top vs bottom level) and the subsequent fatal and non-fatal events among people with stable coronary artery disease



Note: CI, confidence interval; HR, hazard ratios from Cox proportional hazard model stratified by general practice and adjusted for sex, age, index of multiple deprivation, smoking, systolic blood pressure, diabetes type II, total cholesterol, HDL cholesterol and body mass index

Table 5.5. Adjusted hazard ratios for the association between heart rate levels and the subsequent fatal and non-fatal events in men and women with stable coronary artery disease

	N of events	Level1 (<60 bpm)	Level2 (60-69 bpm)	Level 3 (70-79 bpm)	Level 4 (80-89 bpm)	Level 5 (>90 bpm)	Heat rate/sex Interactions
Cardiac outcomes			HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	p-value
Myocardial Infarction							
Men	720	1	0.95 (0.75-1.19)	1.02 (0.80-1.28)	0.99 (0.76-1.28)	1.22 (0.90-1.64)	0.71
Women	521		1.08 (0.77-1.53)	1.14 (0.81-1.59)	1.03 (0.73-1.46)	1.23 (0.83-1.81)	
Atrial Fibrillation							
Men	5,396	1	1.06 (0.97-1.16)	1.25 (1.15-1.37)	1.65 (1.50-1.81)	2.18 (1.96-2.43)	0.01
Women	4,564		1.01 (0.90-1.13)	1.09 (0.97-1.22)	1.25 (1.11-1.40)	1.84 (1.62-2.08)	
Heart Failure							
Men	2,178	1	1.28 (1.10-1.49)	1.60 (1.37-1.87)	2.41 (2.07-2.82)	2.94 (2.47-3.49)	0.17
Women	1,769		1.30 (1.05-1.62)	1.70 (1.38-2.10)	2.13 (1.72-2.64)	2.96 (2.37-3.70)	
CA-SCD							
Men	235	1	1.71 (1.11-2.63)	1.49 (0.95-2.35)	1.09 (0.64-1.86)	2.38 (1.41-4.01)	0.95
Women	64		0.94 (0.37-2.38)	1.08 (0.44-2.65)	0.52 (0.17-1.56)	1.84 (0.70-4.83)	
Peripheral Arterial Disease							
Men	739	1	0.95 (0.75-1.19)	1.21 (0.96-1.52)	1.20 (0.93-1.54)	1.31 (0.96-1.77)	0.03

Women	442		1.34 (0.93-1.91)	1.14 (0.79-1.64)	1.20 (0.83-1.74)	0.99 (0.64-1.55)	
All-cause stroke							
Men	1,108	1	0.98 (0.82-1.19)	1.15 (0.95-1.39)	1.31 (1.06-1.61)	1.09 (0.83-1.42)	0.26
Women	1,267		1.05 (0.84-1.31)	1.10 (0.88-1.37)	1.31 (1.05-1.64)	1.47 (1.15-1.88)	
CVD death							
Men	912	1	1.23 (0.98-1.54)	1.35 (1.07-1.70)	1.72 (1.35-2.20)	2.23 (1.70-2.93)	0.05
Women	730		1.08 (0.79-1.48)	1.21 (0.89-1.65)	1.49 (1.09-2.03)	1.78 (1.27-2.50)	
Total mortality							
Men	1,840	1	1.26 (1.08-1.49)	1.63 (1.38-1.91)	1.87 (1.58-2.22)	2.65 (2.21-3.19)	0.00
Women	1,685		1.23 (1.00-1.52)	1.50 (1.22-1.84)	1.56 (1.27-1.93)	2.03 (1.63-2.54)	

5.4. Discussion

5.4.1. Main findings

In this prospective study, we report an association between elevated heart rate and the risk of cardiovascular endpoints and morbidity in patients with stable coronary artery disease. Our study confirms previous reports that elevated heart rate is a predictor of mortality and heart failure in CAD patients.[125, 166, 169] However, our results also extend these observations to cerebrovascular and atrial fibrillation events. In line with recent trials findings we found no association between increased heart rate with subsequent coronary events, i.e. myocardial infarction.

5.4.2. Choice of primary outcomes in trials

We dissected the primary endpoint used in a number of trials that commonly incorporates a mortality (cardiovascular or non) combined with ischaemic events mainly represented by myocardial infarction into separate specific cardiac outcomes and we further explored a number of other cardiac phenotypes including atrial fibrillation. We observed a strong association of increased HR with CVD mortality but not with MI, which puts trials' findings in a clinical context and largely explains their findings.

Specifically, a recent large clinical trial, SIGNIFY by Fox et.al. of 19,102 patients with CAD and no clinical heart failure on ivabradine, failed to show a significant difference between the ivabradine group and the placebo group in the incidence of the primary end point (a composite of death from cardiovascular causes or nonfatal MI) nor did they show significant differences in the incidences of death from cardiovascular causes and nonfatal myocardial infarction separately. In beta-blocker trials such TIBET (Total Ischaemic Burden European Trial),[247] atenolol resulted to no reduction in the primary endpoint (a composite of cardiac mortality, MI, UA, CABG) compared with placebo and just a greater HR reduction. In the Angina and Silent Ischaemia Study (ASIS), patients with RHR >80 bpm were twice as likely to develop ischemia as those with rates <60 bpm.[102] Furthermore, the INternational VErapamil-SR/trandolapril Study (INVEST)[166] of hypertensive patients with stable CHD, showed a modest linear association with risk of death, MI, or stroke from 55 to 100 bpm, which did not retain significance in the multivariate analysis. Further evidence found by observational studies such as the TNT study (CAD-patients),[248] the study of Bemelmans et al, [144]the 3C study (elderly subjects from the population)[249] also supported the absence of significant relation between RHR and risk for MI. Genome Wide Association Studies (GWAS) support these findings as they failed to identify associations of heart rate loci with coronary artery disease (CAD) or MI.[240] The lack of

association between heart rate and coronary artery disease found in the above studies, contrasts with results from previous post hoc analyses of 5,438 CAD patients with reduced LVEF of the BEAUTIfUL trial, in which ivabradine was reported to be associated with a 24% reduction in the primary endpoint and a 42% reduction in hospitalization for MI in patients with limiting angina.[125]

5.4.3. Further cardiovascular outcomes

Associations between resting heart rate values (without the mediation of heart rate medication in analyses) and other specific cardiovascular endpoints outside the coronary disease spectrum, are not clear. In the present study we found a strong and consistent increase in hazard in L5 compared with L1 for heart failure, sudden cardiac death, AF and CVD mortality independent of blood pressure, beta-blockers and arrhythmia medication (**Fig A5.8-10**) or past heart failure events **(Fig A5.15)** and a mild association with stroke events, while we failed to show any associations with coronary heart disease manifestations.

In our study, associations of heart rate with heart failure, CVD and total mortality, AF and stroke was strong not only in the general CAD population but also in a subset of patients after the exclusion of those with heart failure diagnosed at baseline (**Figure A5.15**). In patients with heart failure, the reduction in heart rate with ivabradine has been shown to improve clinical outcomes, beyond the improvements observed with beta-blockers.[229] The benefit observed with lowering the heart rate in patients with heart failure but not in those with stable coronary artery disease may reflect the fact that an elevated heart rate is due to different pathophysiological mechanisms in these two conditions[90] such as neurohormonal activation in patients with heart failure and further ventricular remodelling.

A significantly increased risk of AF was also found for heart rate values >70bpm above which the hazard increased progressively. Sympathetic activation and progressive disruption of autonomic balance may also be important in the pathogenesis of atrial fibrillation after CABG.[250] White and his colleagues found a significant increase in the incidence of AF in patients in whom administration of b-adrenoceptor antagonists was ceased when compared with those whose drug treatment was continued after surgery.[251] Tachycardia can shorten the atrial effective refractory period and make the atrium more susceptible to atrial fibrillation,[252] however the majority of studies available have been conducted on animal models. Further evidence of a mechanistic link of heart rate with atrial fibrillation comes from genome-wide association studies that have identified heart rate increasing alleles of five loci that are associated with both increased and decreased risk of atrial fibrillation.[240]

Whether the effects of an increased RHR on CVDs are a reflection of the harmful effects of an increased sympathetic tone or of an increase in heart rate itself is unclear. However, in our

exploratory analyses we adjusted for some determinants of sympathetic activity (BMI, type 2 diabetes mellitus) and another measure of present sympathetic tone (systolic blood pressure). Correction for these variables did not lead to substantial differences in the results, suggesting that is it not only sympathetic activity, but increased RHR itself that plays a role in the increased risk of mortality and heart failure.

5.4.4. Gender differences

Additionally, a gender-related difference in the association between heart rate and mortality has been found in some studies conducted either in subjects from general populations or in patients with MI.[253] In particular, in most studies high heart rate appeared to be a weak predictor of death from coronary artery disease in the female gender with the exception of CASS study by Diaz et al.[169], which indicated that tachycardia can be deleterious also in the female gender. In our study we found a slightly higher increase in risk of stroke in women in L5 (HR: 1.47, 95% CI: 1.15-1.88) compared to men (HR: 1.09, 95% CI: 0.83-1.42), while a higher risk for atrial fibrillation was found in men in L3, L4 and L5 compared to women that the risk was restricted to heart rate values >80bpm.

5.4.5. Shape of associations

Our study provides evidence for a steep increase in risk for heart failure and cardiovascular mortality above 70bpm, a threshold significantly lower than the majority of the available studies. Quite steep is also the increase to atrial fibrillation events above 70bpm, while the risk of sudden cardiac death shows an increase in higher heart rate values above 90bpm (**Figure A5.17**). Published studies have suggested a threshold effect of heart rate on mortality outcomes, above which the risk increases steeply. Data from the Coronary Artery Surgery Study (CASS) registry suggested an increased risk of all-cause mortality for a heart rate >77 beats/ min and of CV death at a HR>83 beats/min.[169] In contrast, other studies have supported a slightly lower threshold of >70 beats/min[15,18,19] while others have demonstrated an increased risk at relatively low HRs, suggesting a J-shaped, rather than a linear, relation.[18,20,21] In line with our findings, data from the BEAUTIFUL study, however, has suggested that the increase in death and heart failure outcomes rose continuously ≥70 bpm, whereas the relationship was less pronounced for MI and revascularization.[125]

5.4.6. Main implications of linked electronic health records

Heart rate is one of the most easily accessible biomarkers that recent studies have given impetus to its examination. Private companies and academic institutes have invested significant amount of financial, scientific and infrastructural sources to design and conduct clinical trials investigating the effect of heart rate lowering medication such as ivabradine or beta-blockers on specific coronary disease phenotypes such as MI that as showed by our study are not linked.

These quantitative (money) and qualitative (investigators' or patients' time) investments could have been avoided if the application of linked electronic health records had preceded the actual trial, while these sources could have been allocated towards investigation of heart rate links with other cardiac diseases such as people at early stages of heart failure and resting tachycardia. The design of such trials should take into account of the selective associations of heart rate with the non-vascular disease presentations identified in our study.

5.4.7. Strengths

The main strengths of this study lies in its large scale population based prospective design and our use of CALIBER's linked electronic health records to assemble a population based cohort of sufficient size, clinical resolution and follow-up to power the analysis of resting heart rate and its associations with different components that may influence the design and composition of primary endpoints in clinical trials.

5.4.8. Main limitations

Although associations between heart rate and CVDs are not influenced by variation of resting values over time or by the measurement method used[152] we can assume that more accurate measurements would likely show stronger associations with CVDs. Additionally, we were unable to adjust for physical activity which was recorded in only 10,137 patients. However, this is unlikely to have affected our findings based on previous studies where adjustment for exercise had little effect on heart rate associations with CVD.[169] The non-reporting of heart rate measurement techniques led to a digit preference (**Figure 3.5(b) and Table A3.7**). The potential for imbalance between baseline beta-blocker or blood pressure medication prescription rates to distort our findings was excluded in a sensitivity analysis (**Figures A5.8 & A5.9**).

5.5. Conclusions

Resting heart rate was strongly associated with outcomes not included so far in trials primary endpoints such as heart failure, and not associated with outcomes commonly used by trials as main endpoint or a part of composite primary endpoints such as myocardial infarction. Higher resting heart rates above 70bpm increase the hazard of heart failure events, stroke in women and atrial fibrillation, without substantially affecting the hazard of vascular events in the coronary arterial beds. Our findings show how disaggregation of CVD into specific phenotypes can help to disentangle the underlying disease mechanisms with implications for clinical practice and the design and interpretation of clinical trials.

6. Heart rate and the onset and prognosis of atrial fibrillation in 196,436 initially healthy men and women: a CALIBER study

The purpose of this chapter is dual. Initially, I will explore associations of resting heart rate with the incidence of atrial fibrillation in a healthy cohort using linked electronic health records. The nested cohort of patients with atrial fibrillation that I will identify will then be followed-up to estimate the risk of subsequent cardiovascular diseases. Further analysis by genders will shed light to the previously unexplored area of atrial fibrillation incidence differences between men and women.

6.1. Introduction

Resting heart rate is a powerful marker in a broad range of subjects in sinus rhythm (SR), with or without cardiovascular disease.[21,254] Various experimental and clinical observations suggest that sympathetic and vagal neural regulatory mechanisms play a critical role in altering cardiac electrical properties and in promoting the occurrence of arrhythmic events[255-257] and heart rate is an important marker of sympathetic tone. Genome-wide association studies (GWAS) have identified associations between genetic variants in the region of the gene HCN4, which codes for the main ion channel responsible for the If current, and both heart rate and atrial fibrillation (AF),[258, 259] while observational studies have shown that the pulmonary venous myocardium, which is an important source of AF initiation and maintenance,[260] demonstrates an If current which is affected by ivabradine (a pure heart rate lowering agent).[261]

Despite the evidence available from GWAS on the underlying genetic association between heart rate and atrial fibrillation, information from observational or experimental studies from a clinical and health care practice perspective of this association is limited. Specific links between resting heart rate and the incidence and prognosis of AF in healthy population without prior CVDs at baseline have not been addressed so far using large scale data. Epidemiological studies are few, old and have been extensively conducted in populations with specific comorbidities already at baseline, namely established cardiovascular diseases [171-175], or hypertensive populations.[173] Additionally, available studies have very low sample sizes and hence are of limited power to secure sufficient events number and follow-up to accommodate both an assessment of AF incidence and subsequent CVD events, while those exploring prognosis of CVD outcomes in AF populations are restricted to mortality outcomes.[178, 179] Additionally, no study so far has examined the impact of low heart rate on AF, since the reference levels commonly taken in available studies are pooled heart rate ranges of higher HR values (i.e. reference HR category: <100bpm[171] or 60-80bpm[175]). None examined sex differences in associations or described shapes of associations, potentially due to their limited sample sizes (**chapter 2- Tables2.6, 2.7**).

I will investigate the association of resting heart rate and incidence of atrial fibrillation and its links to subsequent cardiac, vascular and mortality events using real-world linked electronic health data. These data provides me the opportunity to i) explore the long-term course of patients initially free from prior atherosclerotic disease or arrhythmic disorder that experienced an atrial fibrillation event and ii) follow them up until the subsequent experience of a subsequent cardiovascular event while ensuring internal validity, as well as iii) to explore potential differences in risk between the two genders, in relation to their heart rate.

6.2. Methods

6.2.1. Data resource

The Cardiovascular disease research using Linked Bespoke studies and Electronic Records (CALIBER) e-health database was the data resource for this study. CALIBER links patient records from four different data sources: Clinical Practice Research Database (CPRD)[192]MINAP (Myocardial Ischaemia National Audit Project registry)[219] Hospital Episodes Statistics (HES)[220], the Office for National Statistics (ONS)[221] and the Office of the Population Censuses and Surveys Classification of Interventions and Procedures[262] (4th revision).
CPRD data were used to obtain heart rate measurements, demographic variables and other risk factors. The primary care practices and the subset of linked practices used in the present study analysis are representative of the UK primary care setting[194] and have been validated for epidemiological research.[222]

6.2.2. Study population

An open cohort of 2,23 million people covering approximately 5% of the UK population was drawn from registrants between January 1997 and March 2010 with 225 primary care practices who consented to data linkage. People included in the final healthy cohort were 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 during the study period. This population was initially followed-up to assess the risk of AF onset. At the second stage of the study, people that had at least one AF event and a heart rate measurement on the day of this event or up until a year after it, were further followed-up for subsequent CVD events (**Figure A6.1**). Participants were censored on the dates of leaving the practice, or last submission of data, or death, or endpoint occurrence. The study flow diagram is shown in **Figure A6.2**.

6.2.3. Heart rate

Heart rate was prospectively collected by general practice staff and ranged from 20-240 bpm. The method of measurement is not recorded in the database and recorded heart rate values

are likely to have been obtained through palpation at the wrist, auscultation of the heart and readings from an electrocardiogram (ECG) or automated blood pressure device. Since approximately 90% of the heart rate measurements were recorded on the same day as blood pressure, the most likely method of heart rate measurement is the latter.

6.2.4. Cardiovascular risk factors

Information on risk factors was obtained from CPRD, as recorded during consultations in primary care. The most recent measurement (or prescription) recorded in CPRD up to one year before or on the date of study entry (first heart rate measurement after the index date for the initially healthy population and the most recent heart rate measurement up to one year after a first AF event for people who consecutively experienced a AF event) was used to define baseline covariates for AF onset and prognosis respectively. Socioeconomic status was derived from ONS using the Index of Multiple Deprivation (IMD) 2007.[223] It was divided into five categories (quintiles), the 1st quintile corresponding to the least deprived and the 5th quintile to the most deprived groups. The most recent smoking record before the index date was used to classify participants as never, ex or current smokers.

6.2.5. Endpoints

The primary endpoint in the healthy population was the first presentation of atrial fibrillation after the baseline heart rate measurement date across the four data sources and its record was provided by primary and secondary care sources. The codes used to construct atrial fibrillation algorithm consist of i. a diagnosis of AF (first record of AF) without preference for primary versus secondary care and ii. inferred AF, in which no diagnosis code is present, but the patient record includes a warfarin prescription in the absence of prior deep vein thrombosis or pulmonary embolism, or a digoxin prescription in the absence of HF.[263] Details on the AF algorithm codes are presented in **Table A6.1**.

For the progression of AF events, the CVD outcomes analysed entailed acute coronary diseases (myocardial infarction (MI)); heart failure (HF)); a composite of cardiac arrest, ventricular fibrillation and sudden cardiac death (CA-SCD); a composite of cerebrovascular diseases including ischaemic stroke, subarachnoid haemorrhage (SAH), transient ischaemic attack (TIA) and intracerebral haemorrhage; and finally peripheral arterial disease (PAD). Additionally, two mortality outcomes were assessed (CVD 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 (CPRD) and bespoke variables in the ACS registry (MINAP). Codes used to define atrial fibrillation and each cardiovascular endpoint and data source are presented in **Tables A6.1, A3.10.**

6.2.6. Statistical analysis

In the final analysis heart rate was analysed in five categories (<60 bpm, 60-69 bpm, 70-79, 80-89, >90bpm) in order to be more clinically relevant taking as reference level the lower heart rate range of <60bpm for the AF incidence examination and the range of 70-79bpm at the stage of CVD prognosis. Differences in risk factors by level of heart rate were tested using the F statistic from analysis of variance or its non-parametric version (Kruskal Wallis test) and the chi-square statistic, as appropriate. The association between heart rate and each endpoint was assessed using Cox proportional hazard models to model cause-specific hazards, with time since study entry as the timescale. Separate analysis for AF incidence was performed using as reference level the lowest heart rate range of <60bpm for clinical relevance reasons and comparability with previous findings (**Figure A6.4**).

For covariate adjustments the missing at random covariate values were imputed using multiple chained equations[225]. To assess the shape of association between heart rate and atrial fibrillation incidence and prognosis, we used restricted cubic splines with 4 knots and the reference value of 70bpm[226] (**Figures A6.5, A6.6**). In sensitivity analyses, we repeated the analyses of atrial fibrillation incidence separately for those that had at least a CVD event before the atrial fibrillation event and those who did not to exclude the possibility of AF events that are post CVDs manifestations. Separate analysis was conducted restricted to those that had an AF event at least 6 months after an MI event and after exclusion of AF events up to a year after the heart rate measurement to account for reverse causality effects. Further analyses were performed restricted to those with beta-blockers and warfarin/digoxin prescriptions and those without thyroid disorder (**Figures A6.7(a-f**)). Statistical analyses were performed using Stata statistical software (StataSE 13) and R (v3.0.3).

6.3. Results

6.3.1. Baseline characteristics of initially healthy population and population with atrial fibrillation

We included 196,436 patients (56.2% women) with heart rate measurements available at baseline who experienced 6,983 atrial fibrillation events during 508,769.24 person-years of follow-up (median follow-up 2.59 years). Healthy cohort characteristics by heart rate level are shown in **Table 6.2**. Compared with a HR of <60 bpm, patients with >90 bpm were more commonly female, current smokers, diabetic, with higher diastolic blood pressure and greater proportions in the top deprivation quintile, while systolic blood pressure was particularly increased at <60bpm rates. Proportions on cardiovascular medications, particularly beta-blockers, were lower in the highest HR level compared with the lower or “normal” HR values of 70-79bpm. Few CVDs were experienced prior to the AF events with lower rates of stroke in >90bpm compared to <60bpm or 70-79bpm. In the second part of this study, baseline

characteristics of people that experienced an atrial fibrillation event showed similar traits only lower systolic blood pressure (**Table 6.3**).

Table 6.2. Baseline participant characteristics by heart rate (healthy population)

	<60 bpm (N=14,284)		60-69 bpm (N=43,326)		70-79 bpm (N=60,105)		80-89bpm (N=47,869)		>90 bpm (N=30,852)		N total (%)
	Mean (%)	SD	Mean (%)	SD	Mean (%)	SD	Mean (%)	SD	Mean (%)	SD	N total (%)
Demographic factors											
Age at entry (years)	59.7	15.5	58.2	16.1	58.0	16.4	58.9	16.9	57.2	16.3	196,436
Female	41.3		50.9		57.2		60.9		61.0		110,436
White Ethnicity	74.4		72.7		73.2		73.4		73.4		98,764
Deprivation (most deprived	18.7		20.9		22.0		24.4		26.6		44,933
Clinical biomarkers and											
Heart rate (bpm)	53.4	4.81	64.5	3.07	73.8	2.83	83.0	3.10	101.1	11.3	196,436
Systolic blood pressure,	143.1	21.3	139.5	20.2	138.6	19.5	139.4	19.8	141.4	20.8	125,241
Diastolic blood pressure,	80.8	11.4	80.9	10.8	81.1	10.7	81.8	10.8	83.5	11.6	125,241
High density lipoproteins,	1.41	0.39	1.43	0 .4	1.44	0.4	1.43	0.4	1.44	0.4	46,186
Low density lipoproteins,	3.20	0.99	3.20	0.99	3.21	1.0	3.17	1.0	3.12	1.0	37,460
Total cholesterol (mmol/L)	5.30	1.10	5.31	1.1	5.35	1.2	5.34	1.1	5.34	1.3	59,095
Triglycerides (mmol/L)	1.55	0.92	1.56	0.9	1.62	1.1	1.69	1.2	1.76	1.3	45,949
Creatinine (µmol/L)	93.1	25.4	89.3	25.9	87.5	26.2	86.8	29.4	86.5	30.5	79,752
BMI (kg/m^2)	27.9	5.3	27.8	5.6	28.2	5.7	28.5	6.1	28.5	6.4	68,548
Smoking											
Non-smokers	63.5		61.6		60.2		57.8		55.1		116,726
Ex-smoker	17.8		16.0		15.2		15.0		14.1		30,262
Current smoker	16.8		20.1		22.3		24.2		28.0		44,836
Diabetes type II	4.83		4.48		4.77		5.74		6.77		10,338
Medication											
Beta-blockers	39.7		21.1		11.1		8.71		8.07		28,245
BP medication	48.5		39.1		38.7		39.0		41.7		97,073
Calcium channel blockers	15.3		11.8		10.8		11.3		13.5		23,456
Statins	14.1		11.6		10.8		10.7		11.8		22,385
Aspirin	11.38		8.78		7.90		8.47		8.66		16,916
CVD events developed after											
Heart failure	3.5		5.44		5.55		7.04		5.7		402
Stable angina	7.94		8.23		6.83		6.92		5.07		485
Myocardial infarction	5.29		7.17		6.73		7.86		4.44		458
Stroke	8.87		7.70		8.06		6.34		4.44		488
Peripheral arterial disease	2.80		3.12		3.04		2.75		2.45		200
Note: Blood pressure (BP) medication: diuretics, b-blockers, calcium channel blockers, hypertension and heart failure											

Table 6.3. Characteristics of patients with new diagnosis of atrial fibrillation by heart rate level by heart rate level

	<60 bpm (N=401)	60-69 bpm (N=920)	70-79 bpm (N=1,075)	80-89 bpm (N=1,093)	>90 bpm (N=1,271)	N total (%)

	Mean (%)	SD	Mean (%)	SD	Mean (%)	SD	Mean (%)	SD	Mean (%)	SD	N total (%)
Demographic factors											
Age at entry (years)	74.3	10.7	75.4	11.6	76.2	11.2	77.2	11.3	75.1	11.6	4,760(100)
Female	41.4		49.4		54.6		58.2		57.2		2,573
White Ethnicity	74.0		77.1		77.9		77.3		73.9		3,630
Deprivation (most	16.9		18.5		20.2		22.6		23.8		1,007
Clinical biomarkers and											
Heart rate (bpm)	52.4	5.41	64.0	3.25	73.7	2.87	83.1	3.15	108.3	18.4	4,760
Systolic blood pressure,	145.2	22.6	142.4	20.1	141.0	19.4	142.0	20.5	141.0	21.2	3,988
Diastolic blood pressure,	78.1	11.5	78.8	11.6	78.8	11.2	79.7	11.7	80.7	12.3	3,988
High density lipoproteins,	1.38	0.39	1.50	0.41	1.43	0.43	1.54	0.47	1.47	0.43	1,615
Low density lipoproteins,	2.66	0.92	2.89	0.94	2.88	1.02	2.89	0	2.96	1.02	1,299
Total cholesterol	4.72	1.04	4.97	1.13	4.94	1.14	5.00	1.13	5.08	1.15	2,112
Triglycerides (mmol/L)	1.42	0.83	1.33	0	1.43	0	1.36	0.69	1.46	0.79	1,564
Creatinine (µmol/L)	103.6	36.4	96.7	28.3	97.6	42.5	100.5	62.3	97.9	44.5	3,119
BMI (kg/m^2)	27.9	6.16	27.8	5.92	27.5	5.62	27.5	6.62	28.3	7.14	1,952
Smoking											
Non-smokers	64.8		63.8		62.6		61.6		60.1		2,959
Ex-smoker	20.7		19.3		20.5		19.1		19.9		945 (19.8)
Current smoker	12.4		14.6		13.9		16.3		16.8		728 (15.2)
Diabetes type II	10.4		10.1		10.3		10.8		11.9		517 (10.8)
Current alcohol drinker	19.4		17.6		15.0		13.1		14.1		726 (15.2)
Hypertensives	14.7		14.1		11.7		12.2		14.2		630 (13.2)
Medication											
Beta-blockers	52.1		42.5		31.2		24.0		22.6		1,487
Nitrates	35.6		33.7		31.4		29.7		29.0		1,485
Ca-Channel blockers	28.6		27.1		27.7		26.5		26.5		1,291
BP medication	73.0		63.8		62.4		60.0		63.8		3,018
Warfarin	6.48		7.50		8.00		6.95		4.56		315 (6.62)
Digoxin	3.99		4.57		6.98		8.87		6.45		312 (6.55)
Aspirin	38.4		35.5		32.0		32.7		29.7		1,561
Statins	33.6		26.5		23.1		19.8		21.2		1,115

Note: Blood pressure (BP) medication: diuretics, b-blockers, calcium channel blockers, hypertension and heart failure medication and ACE inhibitors.

6.3.2. Heart rate and atrial fibrillation onset in initially healthy subjects

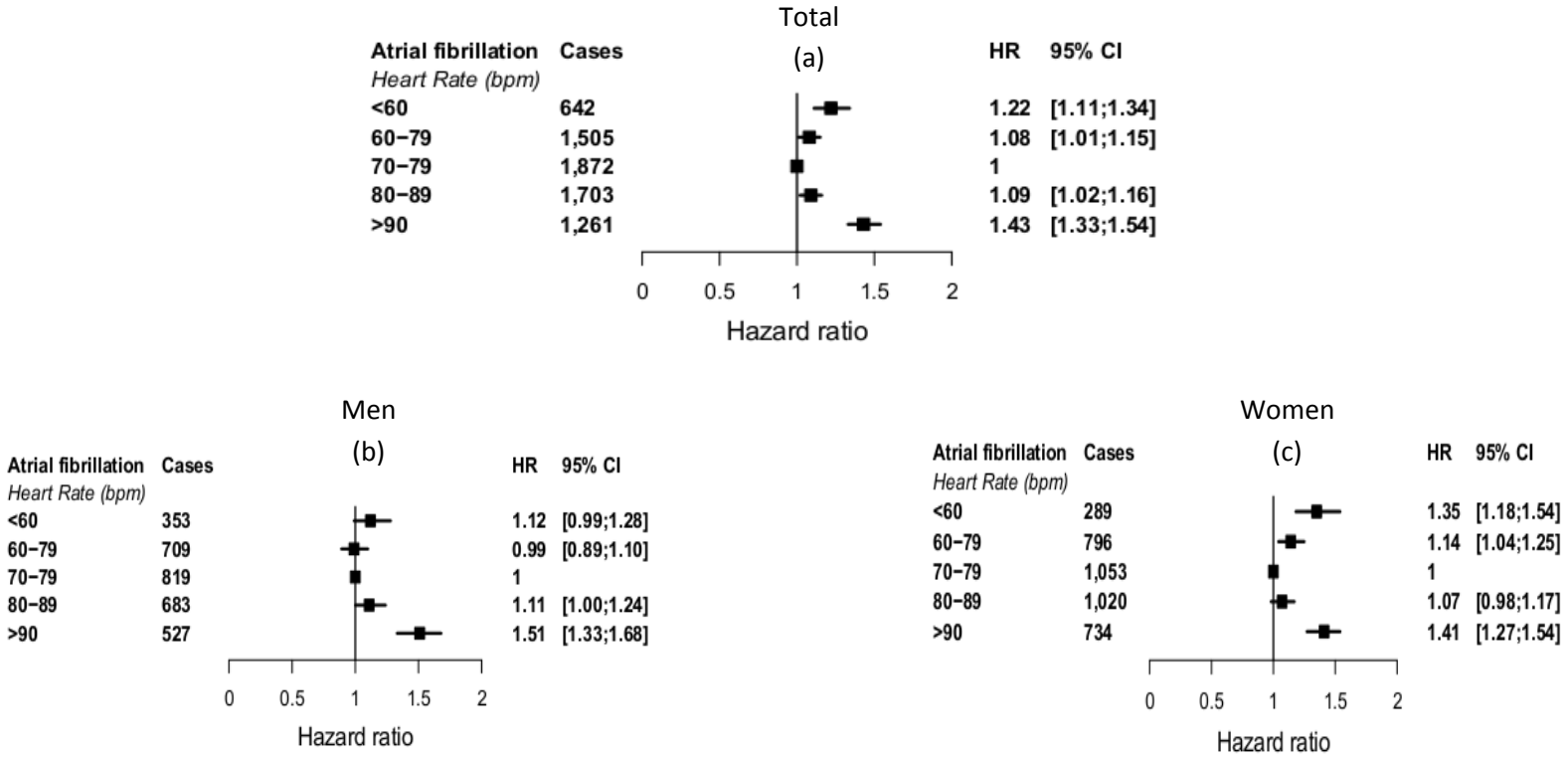
The age and sex adjusted Cox analysis (**Table 6.4**) showed significantly increased hazard of atrial fibrillation in both >90bpm (L5) (HR: 1.44, 95% CI: 1.34-1.55) and <60bpm (L1: HR=1.30, 95% CI: 1.19-1.43) compared with 70-79bpm (L3). In adjusted analysis for sex, age, smoking, systolic blood pressure, diabetes, cholesterol, hdl, bmi and imd (**Table 6.4**, **Figure 6.3**), these associations remained. After restricting to AF events not preceded by a CVD, the association between heart rate (L5 vs L3) and atrial fibrillation became stronger with a HR=1.53 (CI 95% 1.41-1.66). The association between L1 and L3 of heart rate event though attenuated was still significant with HR=1.18 (95% CI: 1.06-1.31).

Table 6.4. Multivariable analysis of heart rate (by heart rate level) with atrial fibrillation incidence (healthy population)

Atrial Fibrillation	N of events	Level1 (<60 bpm) (N=401)	Level2 (60-69 bpm) (N= 920)	Level 3 (70-79 bpm) (N= 1,075)	Level 4 (80-89 bpm) (N= 1,093)	Level 5 (>90 bpm) (N= 1,271)
Total persons			HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Adjusted for sex/age		1.30 (1.19-1.43)	1.10 (1.03-1.18)	REF	1.08 (1.01-1.16)	1.44 (1.34-1.55)
Multivariable adjusted model	6,983	1.22 (1.11-1.34)	1.08 (1.00-1.15)	REF	1.09 (1.02-1.16)	1.43 (1.33-1.54)
Men	3,091	1.12 (0.99-1.28)	0.99 (0.89-1.10)	REF	1.11 (1.00-1.24)	1.50 (1.33-1.68)
Women	3,892	1.35 (1.18-1.54)	1.14 (1.04-1.25)	REF	1.07 (0.98-1.17)	1.40 (1.27-1.54)
With preceded (first manifestation) CVDs	1,488	1.27 (1.05-1.54)	1.14 (0.98-1.32)	REF	0.96 (0.83-1.11)	1.11 (0.93-1.32)
Men	682	1.17 (0.88-1.54)	1.02 (0.82-1.28)	REF	0.96 (0.77-1.20)	1.05 (0.80-1.38)
Women	806	1.49 (1.12-1.98)	1.24 (1.01-1.53)	REF	0.95 (0.78-1.16)	1.20 (0.95-1.51)
Without preceded (first manifestation) CVDs	5,495	1.18 (1.06-1.31)	1.06 (0.98-1.15)	REF	1.12 (1.04-1.21)	1.53 (1.41-1.66)
Men	2,409	1.11 (0.95-1.29)	0.97 (0.86-1.09)	REF	1.15 (1.02-1.30)	1.65 (1.45-1.87)

Women	3,086	1.27 (1.08-1.48)	1.13 (1.01-1.25)	REF	1.10 (1.00-1.22)	1.45 (1.30-1.62)

Figure 6.3. Multivariably adjusted hazard ratios for the association between heart rate (70-79bpm vs >90bpm) and the risk of atrial fibrillation



Note: CI, confidence interval; HR, hazard ratios adjusted for age, sex, social deprivation, smoking, systolic blood pressure, BP medication, total cholesterol, HDL, LDL, diabetes II and BMI

6.3.3. The age and sex analysis

Subgroup gender analysis showed a strong association between heart rate >90bpm (vs 70-79bpm) and atrial fibrillation in both men (HR=1.50, 95% CI: 1.33-1.68) and women (HR=1.40, 95% CI: 1.27-1.54). The associations were particularly strong in cases that no CVD event preceded that of atrial fibrillation in men and women (HR=1.65, 95% CI: 1.45-1.87 and HR=1.45, 95% CI: 1.30-1.62, respectively) (**Table 6.4**). Risk of AF at lower heart rate range (<60 vs 70-79bpm) was found to be strong in women (HR=1.35, 95% CI: (1.18-1.54) but not significant in men (**Table 6.4, Figure 6.3**). Compared to men, heart rate range of 70-90bpm vs <60bpm (70-79bpm and 80-89bpm vs >90bpm) showed a protective effect for atrial fibrillation in women. Finally, atrial fibrillation risk was higher in people aged >80 that belonged to >90bpm heart rate range (HR=1.32, 95% CI: 1.10-1.59) (data not shown).

6.3.4. Heart rate and CVDs prognosis in patients with atrial fibrillation

In total, 2,474 of 4,760 patients with atrial fibrillation had a subsequent CVD event after a median time of 1.95 years. Strong associations were found between higher heart rate (70-79bpm, 80-89bpm, >90bpm) and the hazard of heart failure (70-79bpm HR=1.86, 95% CI: 1.29-1.68), (80-89bpm HR=2.00, 95% CI: 1.39-2.89), (>90bpm HR=1.89, 95% CI: 1.30-2.75) (**Table 6.5**). The risk increased above 70bpm and became stable but high above 85bpm. A positive but insignificant association was found between MI events and 60-69bpm, 70-79bpm and 80-89bpm heart rate levels but not >90bpm. Associations between heart rate and stable angina, sudden cardiac death, stroke or PAD were weak or imperceptible.

6.4. Discussion

6.4.1. Main findings on AF incidence

By linking electronic health records this is the first study to report associations of resting heart rate with onset of atrial fibrillation in a large healthy population cohort. We have shown that while increased heart rate is strongly associated with atrial fibrillation in men and women, lower HR ranges are linked with an increased AF risk which is confined to women (**Table 6.4, Figure 6.3, Figure A6.8**).

6.4.2. Findings on AF prognosis

People that at the first stage developed atrial fibrillation, subsequently showed a significant increase in heart failure and all-cause mortality risk (**Table 6.5**) when heart rate exceeded a threshold level of 70bpm that so far has been regarded as normal. A sensitivity analysis performed after exclusion of heart failure events experienced within 6 months after the baseline

heart rate measurement of the atrial fibrillation cohort yielded similar results, however insignificant due to the low number of events.

Table 6.5. Multivariable analysis of heart rate (by heart rate level) with prognosis of 10 CVDs in an atrial fibrillation population

	N of events	Level1 (<60 bpm) (N=401)	Level2 (60-69 bpm) (N= 920)	Level 3 (70-79 bpm) (N= 1,075)	Level 4 (80-89 bpm) (N= 1,093)	Level 5 (>90 bpm) (N= 1,271)
Cardiovascular endpoints in follow-up			HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Stable Angina	626	REF	1.06 (0.78-1.44)	0.98 (0.72-1.33)	1.05 (0.77-1.43)	0.83 (0.59-1.15)
Myocardial infarction	402	REF	1.27 (0.83-1.94)	1.32 (0.87-2.02)	1.35 (0.88-2.07)	1.00 (0.63-1.58)
Heart Failure	670	REF	1.46 (1.00-2.12)	1.86 (1.29-2.68)	2.00 (1.39-2.89)	1.89 (1.30-2.75)
SCD	65	REF	0.40 (0.15-1.05)	0.48 (0.20-1.17)	0.61 (0.24-1.54)	0.46 (0.17-1.24)
Stroke	528	REF	0.86 (0.59-1.23)	1.15 (0.82-1.63)	0.90 (0.62-1.30)	0.83 (0.57-1.23)
Peripheral Arterial Disease	183	REF	1.04 (0.57-1.88)	1.30 (0.74-2.30)	1.03 (0.56-1.89)	0.88 (0.47-1.67)
CVD mortality	380	REF	1.10 (0.72-1.70)	1.33 (0.87-2.02)	1.59 (1.04-2.43)	1.45 (0.94-2.23)
All-cause mortality	1,179	REF	1.19 (0.88-1.59)	1.32 (0.99-1.76)	1.60 (1.21-2.12)	1.60 (1.21-2.11)

6.4.3. Findings in the context of previous research

Associations of heart rate and AF incidence were found significant in only 2 previous studies that were both conducted more than 20 years ago, examined populations with established cardiovascular diseases,[171, 175] where one of them was solely focused on men[171] and neither examined low heart rates. Atrial fibrillation occurs in congestive heart failure and in myocardial infarction[264, 265] and has been related to the severity of infarction.[266, 267] We showed that atrial fibrillation occurs without these comorbidities and heart rate is -although not causally-, independently associated with it regardless other cardiovascular events. In a previous epidemiological study, 24% of heart failure hospitalizations occurred before or at diagnosis of atrial fibrillation and 17% after it. Atrial fibrillation is well known to cause or aggravate congestive heart failure, related to loss of systolic filling or rapid ventricular rate, but heart failure may also promote atrial fibrillation.[172] In our study, only 5.75% of people that developed atrial fibrillation had experienced heart failure and in a sensitivity analysis after excluding all CVD events, the risk of atrial fibrillation for people with heart rates >90bpm became higher (HR=1.53, 95% CI: 1.41-1.66). It has been also found that ischemic heart disease often precedes atrial fibrillation, and is an independent risk factor. This suggests that ischemic heart disease produces changes, particularly acutely, in the atria that predispose to the development of atrial fibrillation[268], and that atrial fibrillation infrequently precedes clinical ischemic heart disease.

A history of myocardial infarction or heart failure, high BMI and blood pressure have been shown to be strong predictors of atrial fibrillation.[172] However, after adjusting for these factors with the addition of blood pressure medication and lipids, heart rate remained an independent marker of AF incidence prediction. In the present study 6.55% of people that experienced AF had previously an MI event.

In follow-up, we showed that there is an association between heart rate and MI but for the 60-69bpm, 70-79bpm, 80-89bpm heart rate, however this risk was statistically insignificant. Strong associations were found between resting heart rate and subsequent heart failure events and total mortality. Only two recent studies examined the prognosis of AF patients but were limited to all-cause mortality outcomes.

6.4.4. Shape of associations

We also showed that atrial fibrillation risk has a U shape and increases steeply above 74bpm (**Figures A6.5**). This shape was particularly pronounced in women that their lower levels of heart rate showed a high increase of AF incidence. In follow-up of people that subsequently experienced an atrial fibrillation event we showed an increase in risk of heart failure above 70bpm (**Figure A6.6**), similar to the one we previously showed in people with CHD whereas in healthy population this risk is more obvious in heart rates above 75bpm.

6.4.5. Mechanistic considerations

Genome-wide associations studies (GWAS) showed that five of heart rate loci in human genome are associated with both increased and decreased risk of atrial fibrillation.[140] Three large studies in 2010 used a GWAS to analyze variability in PR interval. In one of these, Pfeufer et al [269] performed a meta-analysis of GWASs of PR interval that included 28,517 European subjects. They found 9 loci associated with PR interval (including SOX5), of which 5 were also associated with AF. Kolek et al[270] conducted a separate GWAS of PR interval in 2,334 subjects drawn from BioVU and replicated the finding that SCN10A variants are associated with variability in the PR interval.[271] The vast majority of subjects in these studies had no history of AF, the finding that genetic variants play a role in heart rate at rest and AV nodal conduction which might imply that they might also modify the response to rate control therapy in AF. For example, genetic variants in adrenergic receptor genes are associated with response to b blockers in patients with hypertension and heart failure[272] and also modify heart rate response to b blockade in healthy subjects.[273] In addition, more recent studies have suggested that there is no difference in outcomes between a strict and lenient target heart rate response during AF.[274] The common variant, rs6795970, in SCN10A has been also associated with PR interval duration in both healthy populations and those with atrial fibrillation. This variant may also be associated with heart rate response in atrial fibrillation, indicating its role in modulating atrioventricular conduction. [275] A meta-analysis in 2014 which identified an association between If current inhibition and AF supported by the associations recently found between genetic markers near HCN4, provide further evidence for the role of HCN4 and the If current in the pathophysiology of AF.[276]

6.4.6. Clinical and research implications

Although we cannot assume a causal link between heart rate and AF incidence and prognosis, identifying individuals at the highest risk for AF and then aggressively addressing a modifiable risk marker of developing AF such as heart rate in these individuals may be beneficial with respect to prevention of atrial fibrillation and subsequent heart failure, mortality and cost. Temporal trends suggest that by 2050, the ageing population could result in as many as 15.9 million cases of atrial fibrillation in the USA, with similar projected increases in prevalence for other developed countries,[277] while the lifetime risk of atrial fibrillation is about one in four individuals.[278]

Common CHD risk scores are not effective at predicting AF risk. CHD and AF share some common risk factors, such as hypertension, diabetes, and obesity, but heart rate has been shown to be a risk factor of development of AF only and not of CHD. This highlights the importance of a separate risk score to predict AF, and potentially, the need to develop different preventive interventions by incorporation of heart rate in such scores. Some AF risk prediction

models have been proposed which were based on single US-cohorts.[175] However, these models have not been validated thoroughly or included risk factors which are not routinely available in primary care such as heart rate (e.g. Framingham Heart Study).[174] Recently the CHARGE-HF consortium published a simple risk model derived from three US cohorts using variables readily available in a primary care setting (age, race, height, weight, blood pressure, smoking, antihypertensive medication, diabetes, myocardial infarction and heart failure) which showed good risk prediction. However this model was performed in elderly cohorts with the majority of people aged more than 65 years. We showed differences between genders with a focus in lower heart rates and hence potential differences in pathophysiologies of AF that should lead to a personalized clinical care.

In the light of these findings, targeting of drug interventions in routine clinical practice should be examined with caution. In a recent meta-analysis it was found that ivabradine has not been shown to limit the ventricular rate in patients in AF, and so authors concluded that those patients who develop AF are likely to have higher heart rates, thus negating any benefits of ivabradine as a rate-lowering therapy in treating either angina or heart failure.[276] Our findings that support that the increase of AF incidence is higher among men and women with higher baseline heart rate and in women with low heart rate, raise the possibility that the contribution of ivabradine in these patient groups could be possibly proved to be trivial if not adverse. In another clinical trial, it was provided solid preclinical evidence that ivabradine and ranolazine, alone or in combination, have roles in AF rate control.[279] A post hoc joint analysis of primary source data from 2 multicentre RCTs (AFFIRM and AF-CHF) showed that baseline heart rate of patients in sinus rhythm was independently associated with mortality in contrast with people's heart rate in atrial fibrillation rhythm which showed no evidence of an association.[280] In view of the lack of associations of heart rate in patients with atrial fibrillation rhythm as showed here and supported by previous literature findings, clinical practice professionals should be targeting medications for AF primary prevention with a personalized health care perspective and communicating of risk for individuals cautiously. Additionally, both short-term and long-term clinical trials in patients with AF will need to be conducted to determine appropriate doses and to measure changes in heart rate.[281]

6.4.7. Strengths and limitations

The main strength of this study lies in the size of the cohort of 196,436 men and women compared to the available studies with sizes in the low thousands. Our study further has large resolution and follow-up to power the analysis of resting heart rate and its association with atrial fibrillation incidence and the investigation of associations with subsequent CVD events in the sub-population of atrial fibrillation patients. The nature of the data recorded in clinical practice enhances the clinical relevance of our findings and their representativeness in the general population.

Limitations include the lack of accurate reporting regarding the device or technique used to record heart rate. However, it has been found that associations between heart rate and AF or CVDs are not influenced by variation of resting values over time or by the measurement method used.[152] The possibility of baseline beta-blocker intake different rates across heart rate levels distorting our findings was excluded in a sensitivity analysis (**Fig A6.7(d)**). Finally, LV dysfunction, early heart failure or even acute coronary events as a reason for higher heart rate over time may also impact directly on the risk of developing AF[282-284] via increases in left atrial pressure and stretch that can promote AF and act as a source of reverse causality bias.[285] This possibility was examined by excluding all CVD events prior to AF incidence and the AF events that were experienced within 6 months after an MI event, where in the first case associations were found to be stronger whereas the latter showed a slight attenuation but strong significance (**Fig A6.7(b),(f**)).

6.5. Conclusions

This is the first study to report associations of resting heart rate with onset of atrial fibrillation in a large healthy population cohort and follow-up the patients for subsequent cardiovascular diseases. We have shown that while heart rate is strongly associated with atrial fibrillation in men, its association in women is not established. Rates across heart rate levels show a constant increase of hazard of subsequent heart failure events compared to low heart rate values (<60bpm) in people with diagnosed atrial fibrillation. Further investigation of heart rate mechanisms is needed, with particular focus in underlying differences between men and women and sex-adjusted medication treatments, in addition to a more focused approach towards patients with atrial fibrillation and early stages and heart failure development.

7. Methodology of a clinical biobanked cohort (4C study)

7.1. Abstract

Background

Consented cohorts recruited in clinical settings make important contributions towards addressing translational research questions in prognosis research. Few large, well-characterised cohorts that collect genetic material, imaging diagnostics and quality of life data are available to support research in people with suspected or confirmed coronary artery disease.

Objectives

The general objective of 4C was to establish a contemporary, prospective clinical cohort of patients with linked phenotypic, genetic and biomarker data as a resource. The individual objectives set initially for the purposes of this PhD were to explore heart rate associations with i) diagnoses based on functional imaging and invasive coronary angiography results, e.g. number of diseased vessels, ii) Quality of life parameters and mental health, iii) Single nucleotide polymorphisms (SNPs) that are related to coronary heart disease.

Methods

Consecutive patients undergoing investigation for new-onset, non-acute chest pain were recruited between 2009-2014 from four UK NHS hospitals. Participants provided blood samples for biomarker and DNA analysis and completed a health questionnaire at baseline. Detailed clinical information was manually extracted from hospital electronic databases. Participants are being followed-up for CVD events, and health-related quality of life was assessed using a postal questionnaire (mean follow-up 469 days).

Results

3345 consecutive patients (63.1% men; mean age±SD 58.0±12.5 years) were enrolled. Blood samples were collected for 84%, baseline questionnaire data for 89% and clinical data for 99% of patients. Heart rate was recorded for 83.3% of patients of which 20% of people belonged to the lowest heart rate range (<60bpm) and 12% to the highest (>90bpm). So far, during a median follow-up of 326 days, 839 patients were sent for matching and finally were matched to a record. Total number of deaths coming from ONS are 110 (3.2%). These low numbers of events that have been recorded so far render the exploration of associations between heart rate and CAD prognosis unfeasible in the current period of follow-up.

Conclusions

The Clinical Cohorts in Coronary disease Collaboration (4C) is a contemporary consented DNA bio-resource linked to hospital electronic health records (EHRs), questionnaire data and health

outcomes. Significant challenges remain for automatically extracting the entire patient EHR from health information systems and as a result a wealth of data remains inaccessible for research. The design, development and provision of common infrastructure, data standards and services that will allow researchers to access and exploit such data are crucial for expanding 4C in the future. Related initiatives such as the NIHR Health Informatics Collaborative will provide best practices and guidelines for doing so.

This chapter will describe the design and methodology of a clinical cohort (4C) of patients with coronary artery disease and chest pain symptoms that I recruited from a clinical settings in UK (The Heart Hospital London). This prospective cohort was assembled from 4 different hospitals in UK and was conducted to establish a resource of genetic, clinical and biomarker data that are associated with the onset of stable angina pectoris and its progression to acute fatal/non-fatal events.

7.2. Introduction

In the previous chapter it was noted that linked electronic health records fail to capture in depth parameters of the patients' perceptions on their health such the implementation of quality of life scales to assess psychological or behavioural functioning, or diagnostic imaging tests and other visual tools. Their observational nature and subsequently their confinement to associations or correlation pathways that are not causal was further pinpointed. As a consequence, the need for a consented cohort to yield both clinical and genetic information to address translational research questions in prognosis was crucial. High quality prognosis research in clinical populations can improve understanding of how biomarkers or genes interact with environmental factors associated with disease by linking imaging, genomic and bespoke phenotypic data with rich clinical information held in the patients EHR. However, despite their potential advantages, large, prospective clinical cohorts are lacking across all disease areas, with a limited number focused on coronary artery disease (CAD).[5-8]

For this purpose, a new clinical cohort of people with suspected or established coronary artery disease was designed and launched in 2009 as a resource in which DNA and biomarker samples were obtained at time of presentation with chest pain linked to detailed phenotypic data obtained from EHRs and participant self-completed questionnaires. This new cohort which aimed at finding new ways of diagnosing symptoms, offers information related to specific chest pain symptoms and the well-being of patients using self-reported questionnaires and vital genetic information through the use of biobanked data that would enable me to explore new perspectives of heart rate and coronary artery disease. The study recruitment phase finished in 2014 and its follow-up is ongoing.

The initial purpose of this PhD study was to explore further associations of heart rate with the prognosis of cardiovascular diseases in people with CAD and chest pain. It has been previously shown that chest pain is a more frequent initial presentation of CAD than an unheralded AMI[11] thus new-onset chest pain may represent a potential intervention point that could facilitate the identification of those at risk of acute cardiac events. Links between heart rate and chest pain have not yet to be examined and studies looking into associations of heart rate with CAD need to be updated and focused on clinically relevant endpoints that would further inform clinical practice and large trial investigations. However, the low number of events did not allow for associations between heart rate and chest pain and/or symptomatic coronary artery disease exploration.

A further initial objective of this PhD was to use the genetic pool accrued from the recruitment of patients' biological specimens to assess genetic variants role on the association between heart rate and CAD prognosis. Genome-wide association studies (GWAS) have failed to identify associations of heart rate loci with coronary artery disease or MI.[140] Furthermore, despite markedly different underlying pathophysiology, symptomatic presentation, clinical management and prognosis, most genetic case collections measure CAD and AMI in aggregate. GWAS of CAD and AMI published to date use the same single nucleotide polymorphism (SNP) platform in multiple patient samples and suggest that there may be different associations for CAD-only versus CAD and AMI collectively.[286, 287] Hence, distinguishing specific coronary phenotypes may provide specific causal mechanistic insights relevant to public health. The high genetic resonance of this consented cohort would allow for the examination of the relationship of resting heart rate and the prevalence and prognosis of CAD. However, due to time limitations these explorations will not be performed within the time frame of this PhD.

A summary of my responsibilities during the first year of my PhD conducting field clinical research are presented in **Table 7.1** below.

7.3. Aims

The aim of the 4C study was to explore and assess the current potential of setting up a comparable consented research platform by collecting DNA samples and to quantify the extent to which diverse NHS hospital information systems are accessible for extracting secondary care data (structured and unstructured) for research purposes at scale. This pool of genetic and clinical information would then be used to identify and evaluate genetic and environmental factors associated with the onset of suspected or confirmed stable coronary artery disease, the stable angina pectoris syndrome and its progression to acute fatal and non-fatal events.

Table 7.1 Personal responsibilities during 4C field research

Study setup in Heart hospital
Contribution to study forms design and piloting
Organization of study's site and equipment
Liaison with different clinical professionals for more efficient study conduct
Patients' approach and recruitment
Consenting patients
Questionnaires administration
Blood samples collection
Bloods processing (centrifugation/ aliquoting)
Clinical data collection from referral and discharge letters
Diagnostic imaging collection using hospital electronic systems
Insert data to case record forms
Questionnaires coding and data transfer to excel and access databases
Training of new staff
Co-ordination of meetings at tended by all research teams based at Heart Hospital

7.4. Methods

7.4.1. Source population

The 4C study is an ongoing clinical prospective cohort which was set out to explore the prognosis of people with suspected or established CAD. Patients were recruited from four centres in England: the Bristol Royal Infirmary (Bristol Heart Institute, Bristol), Newham University hospital (London), the Heart hospital (London) and the London Chest hospital (London). I recruited and collected information from 600 patients attended the Heart Hospital in London. Overall, 3,345 patients were recruited from all the four 4C centres.

7.4.2. Inclusion and exclusion criteria

Since the aim of 4C study was to identify factors related to stable CAD phenotype, the appropriate eligibility criteria were applied to ensure good quality and representative data (**Figure 7.1-Appendix 7.4).** Consecutive patients undergoing evaluation for stable angina being assessed at the Rapid Access Chest Pain Clinics (RACPC) or undergoing coronary angiography within cardiac catheter laboratories at participating hospitals were approached for inclusion in the study. Patients were not eligible for inclusion if they were diagnosed with non-cardiac chest pain, previous history of admission with acute coronary syndrome (ACS), Q wave or left bundle branch block on resting electrocardiogram or previous coronary angiography. On the basis of age or coexisting conditions, no patients were excluded. Trained researchers

identified eligible patients by checking clinic appointment databases and angiogram procedure lists on a daily basis.

7.4.3. Participant consent

Patients were approached directly by a researcher at the hospital at the time of their clinic appointment. Informed consent was sought for: a) completion of a baseline health questionnaire; b) provision of a blood sample for long-term storage and analysis of DNA and biomarkers; c) extraction of patient hospital data; and d) linkage of patient data with national EHR data sources (e.g. coded hospitalizations and procedures, emergency admissions and cause-specific mortality). A sample of the consent form is in **Appendix 7.1**.

7.4.4. Patients referred for coronary angiogram to pre-assessment clinics

The study's target population was people referred by their GPs to angiogram clinics for coronary angiography or percutaneous coronary interventions. Prior to their admission to the angiogram wards, patients had to go through a process that included an appointment to a pre-assessment clinic for blood collection and a brief clinical interview. In addition to the pre-assessment clinics I was attending coronary angiogram wards daily to identify potentially suitable patients for the study on the day of their angiogram procedure. Where possible, potential participants were recruited to the study and the baseline assessment was carried out right before the time of their procedure or in rare cases after the angiogram as soon as the patient fully recovered. I was checking the clinic appointments database daily (Mon-Fri) for details of new referrals to identify potentially suitable patients for the study. As soon as the potential participants arrived for their appointment, I was approaching and inviting them to take part after screening for inclusion criteria. At the same time, an information sheet and a sample consent form was administered by me and a second research staff member. After a few minutes I was approaching them again to discuss the requirements of the study in detail, its significance and purpose and consented those who finally accepted to participate. Patients were given a minimum of 15 minutes to read through the consent and study information sheet (see Appendix) and consider whether to participate in the study and an extra 15-20 minutes to fill in the questionnaire. All patients had the opportunity to discuss the study and any concerns regarding the upcoming angiography process they had with me. In cases of language or other problems related to reading and understanding the questions, I was responsible to go through the forms and make the appropriate interpretations.

7.4.5. Patients undergoing coronary angiography

Where possible, potential participants were recruited to the study and the baseline assessment carried out at the time of their angiogram preadmission appointment. However, a significant number of patients were transferred as emergencies from different hospitals. In this event,

patients were recruited to the study on the day of their coronary angiogram and their approach, consent and baseline assessment were conducted before or after the procedure as appropriate. Patients were allowed a minimum of 15 minutes to consider their decision to consent to participate in the
study.

7.4.6. Baseline assessment

Measures were piloted and refined prior to commencement of the study. Three sources of risk factors were used during patients' scheduled hospital appointments. Research measures (biological specimens) included blood samples for DNA and biomarker analysis and a short health questionnaire completed by participants. Clinical measures obtained as part of the usual clinical investigation collected for research purposes constituted detailed clinical information extracted from the hospital EHR up to six months after the date of patients' attendance.

7.4.6.1. Baseline health questionnaire

The questionnaires captured detailed information at entry to the study on education, ethnicity, general health functioning (EQ-5D),[288] functional chest pain (Rose angina questionnaire),[289] angina severity (Canadian Cardiovascular Society classification (CCS class),[290] and symptoms of anxiety (Generalised Anxiety Disorder 7-item scale (GAD-7))[291] and depression (Patient Health Questionnaire (PHQ-9))[292] at baseline. A sample questionnaire is attached in **Appendix 7.2**.

7.4.6.2. Research blood sampling

In order to collect genetic information on heart rate loci and relevant SNPs that would allow me to investigate links of heart rate with CAD prognosis using an instrumental variable apporach, I collected research blood samples from the majotity of participants approached and consented within the study. I followed detailed operation protocols for sampling, processing, logging and storage of samples, including adverse event standard procedure and reporting. I obtained research bloods from all consented individuals, including those in whom a diagnosis of angina was subsequently ruled out. Afterwards, I was transferring and processing the collected samples in a different site (Centre for cardiovascular Biology and Medicine, UCL) by centrifuging and aliquoting them. All the blood cryovials then were stored in a secure location from where the samples were collected and transported for long term storage at a biobank. A summary of the blood processing procedure is provided in Figure II below (Figure 7.3.3.2.2). A total 20 ml of blood was drawn from the antecubital vein (vein of the inside elbow) into several vacutainers in the following order (2x 4.0ml EDTA, 1x 4.5ml PST, 1x 5.0ml STT/gel, 1x 2.5ml PAXgene for RNA) to enable a wide range of research measures to be obtained. into 0.5ml 2-D bar coded cryovials as follows: EDTA (plasma) to 9 cryovials, EDTA (white cells) to 2

cryovials, LH (PST) to 4 cryovials, SST to 4 cryovials, PAXgene RNA to 5 cryovials. I logged each cryovial individually into the sample logging database by using a single-tube bar-code reader and then I stored them in a secure location in the basement of the same centre within a 96 position rack in a -20oC freezer. Samples were collected on a quarterly basis by secure courier and transported on dry ice for long term storage at a biobank where they were stored at -80oC until they are retrieved for analysis, which may be up to 30 years after sampling (**Figure 7.2, Appendix 7.4**).

7.4.6.3. Extraction of data as part of standard clinical care

I reviewed hospital databases and recorded detailed clinical information onto standardized case report forms (**Appendix 7.3**). Depending on the clinic or hospital, different clinical systems were searched to manually extract data that could not be downloaded or exported as a data file (**Table 7.2-Appendix 7.4**). Information included reason(s) for referral, history of chest pain, physician-recorded risk factors for CAD, previously diagnosed medical history and test results. The resting ECG and exercise treadmill test had to be removed from the notes or ordered from medical records and photocopied. Manual extraction of clinical biochemistry results from the hospital systems proved burdensome and was abandoned. Data were then manually entered onto a research database at the study co-ordinating centre, cleaned and coded ready for analysis.

7.4.6.3.1. Routine biochemistry results

Previous blood results collected as part of routine hospital care are recorded on local hospital clinical systems. I carried out individual patient searches using the hospital system to which I had access after logging in with a secure password. I removed any patients identifiers and replaced them with the unique participant study identifier after I downloaded all the relevant data from the hospital electronic database and stored onto encrypted media. Additionally, Reports were anonymised at source.

7.4.6.3.2. Routine cardiac imaging results

I gathered all the available invasive, CT and MR angiography results (reports and raw data) from the hospital electronic record using the hospital program TOMCAT. Reports are anonymised at source. Digitised images were transferred to a core laboratory in the iMAC suite within the Advanced Centre for Cardiac Imaging at the London Chest hospital using the Image Exchange Portal (IEP) where they will be further anonymised. All the available information from every consented patient (biochemistry results and imaging) was recorded into specific forms, the case record forms, which they were then transferred back to the co-ordinating centre (See Appendix). Extraction of data from the Primary Care record. With appropriate permissions (e.g. from NHS Primary Care Trusts) I had access to the primary care records for consented participants to record data including risk factors, medication, previous medical investigations

and treatment and comorbid medical conditions. Data were downloaded onto an encrypted data stick and printed and after proper anonymization I transferred the complete patients files to the study coordinating centre.

7.4.7. Heart rate measurement sources

Baseline heart rate in 4C was obtained (in some of the centres) from resting ECGs performed on the day of the participants' appointment, while in the Heart hospital ECGs were collected from the angiography labs that had performed them at the time of patients' arrival at the day units of the labs. In case that patients' ECGs had been performed at a later than recruitment time, ECGs were sent to another UCL centre (Maple House) and then collected from there. In the 4C dataset, heart rate values are available for 67.5% of the participants. Women had a significantly higher heart than men (74.5±13.6 versus 71.6±14.6, $p<0.001$).

7.4.8. Pseudo-anonymization of patients records

Patient identifiable data or information refers to information that can be used to identify an individual either on its own or in combination with other sources of information. In the context of this study, patient identifiable data is defined as a participants name, date of birth, full address or postcode, other contact details including email address, NHS number and any hospital-specific identifiers such as hospital record number or hospital name. In addition, several fields are defined as sensitive and will only be disclosed to members of the research team if there is a valid reason to do so. Sensitive fields include ethnicity, employment status and referring GP name. A unique participant study identifier was assigned to individual participants at the point of enrolment to the study. Study IDs were generated by the data manager at the study coordinating centre, and were consist of a randomly generated ID (unique to each research site and patient). All electronic data and case record forms, apart from the participant consent form and study administration form (containing patient contact details for follow up purposes), were anonymised using the unique study ID number (i.e. for example setting the patient name to the pseudo-identifier in the software application that generates it). When this was not possible, anonymization was carried out by complete removal of identifiers by cutting identifiers out with scissors (preferred) or using a combination of the provided black permanent marker and provided stickers. This was done in a manner which ensures all affected areas are entirely covered without overrunning clinical information.

7.4.9. Participant follow-up

7.4.9.1. Clinical outcomes

The primary endpoint of interest in the larger concept of 4C was a pre-specified composite of cardiovascular mortality, non-fatal AMI, non-fatal stroke and peripheral arterial disease. The

secondary outcomes are angina status and general health functioning. Unlike CALIBER, the power that stems from this smaller dataset does not allow for disaggregation of CVDs.

7.4.9.2. Electronic Sources of data (EHR)

We linked consented individuals with secondary care data from Hospital Episode Statistics, a national data warehouse of administrative data containing ICD-10 coded hospital diagnoses and OPCS4-coded procedures. We additionally linked participants with mortality data from the Office of National Statistics that provided ICD10-coded cause-specific mortality data. The linkages were conducted via the NHS Health and Social Care Information Centre (formerly known as the NHS Information Centre) and patients were identified using their NHS number (a unique ten digit numeric identifier for the healthcare system), gender, date of birth and postcode. Unlike CALIBER, linkages were not performed by the mediation of a third trusted party, due to the direct consent practice (right from the source/patients). Notifications for admission to hospital and death and are downloaded onto a secure server via a secure web-link from the NHS Information Centre for Health and Social Care on a quarterly basis by the study coordinator. Data are anonymised by removing patient identifiers and replacing them with the participant unique study identifier. In the UK, there is currently no centralized conduit, with national coverage, for linking and extracting primary care data at scale for research. We attempted to link consented participants with primary care resources but that involved going to individual GP practices and performing manual queries and data extraction operations – a route that is both unscalable and cost inefficient. As a result, we were unable to obtain primary care EHR data in this study, although proposed substantial investment in this area (e.g. the Clinical Practice Research Datalink) will make this feasible in the future.

7.4.9.3. Questionnaires

A postal (or online) follow-up questionnaire was sent to study participants after recruitment (mean follow-up 469 days) to assess general health status, functional status, symptoms of depression and anxiety and use of nitrate medication, consistent to the first questionnaire that was administered to the participants' on the day of their clinic attendance. Details of participant survival will be checked against quarterly notifications for death before sending invitations for follow-up. Participants are also being invited to consent to being contacted some years in the future with a further short follow-up questionnaire to determine their health status.

7.5. Results

7.5.1. Baseline data (Table 7.3-Appendix 7.4)

Between 9 July 2009 and 9 January 2014, 3345 participants (63.1% men; mean±SD age 58.0±12.5 years) were enrolled in the study. Detailed clinical information was manually extracted from hospital EHRs six months after the baseline assessment, to allow time for procedure and test results to be uploaded. Approximately half (52%) were recruited from RACPCs and 48% from angiography pre-assessment clinics and cardiac catheter laboratories. Heart rate was available in 2,841 patients (83.3%). For clinical relevancy reasons, I present the baseline characteristics by heart rate of the following levels : <60bpm, 60-69bpm, 70-79bpm, 80-89bpm and >90bpm. 20% of people belonged to the lowest heart rate range (<60bpm) and 12% to the highest (>90bpm). People that belonged to the highest heart rate level were more commonly younger (mean age= 56.8 years compared to 62 years of age in people with <60bpm heart rate). They were also more commonly men, current smokers and with lower diabetes type II proportions. They also had lower beta-blockers, blood pressure medication, statins and antiplatelet prescriptions. Of the 3345 participants recruited into the study, 99.1% granted full access to their medical records.

7.5.2. Diagnoses and angiography findings

The initial diagnosis provided by the clinician or nurse assigned to the patient was stable angina in 51.5% of the cohort for which this information was recorded. Surprisingly, of the total 4C population, 41.4% of the participants were initially diagnosed as non-CAD chest pain, of which a higher percentage were women (51.7% versus 36.0% for men). However, only 56.1% of our cohort had information available on initial diagnosis. The overall assessment, obtained for 61.3% of the total cohort, was based on the description of severity or percentage of luminal diameter stenosis made available on the angiogram report (coronary angiogram or coronary CT angiogram), with number of diseased vessels classified according to vascular territory of the three major coronaries. The following criteria were then applied: (1) no evidence of disease in any of the territories was classified as normal; (2) some evidence of disease (e.g. mild disease or irregularities, “no significant disease”, “no flow limiting disease”) classified as less than moderate (obstruction ≤50%) in severity, was considered non-obstructive CAD; (3) evidence of moderate (50-69%) or worse (severe: ≥70%) disease in any one of the three territories was classified as 1 diseased vessels; (4) evidence of moderate or worse disease in any 2 territories or the left main stem (LMS) was classified as 2 diseased vessels; (5) evidence of moderate or worse in all 3 territories was classified as 3 diseased vessels. Applying these criteria, 12.4% of our cohort was classified as having a normal angiogram, 28.1% as non-obstructive CAD, 21.2% as 1 diseased vessel, 23.4% as 2 diseased vessels and 14.9% as 3 diseased vessels. Of people with higher heart rate (>90bpm) only 19.6% had an ischaemic or CAD history and 6.92% of a previous acute MI event, compared to patients with heart rate <60bpm that had 37.5% and 21.4% respectively. Additionally, people with heart rate >90bpm reported more often shortness of breath (37.3% vs 30.5% in people with <60bpm heart rate. Finally, people with >90bpm rate had less often a normal angiogram (14.5%), whereas were

more often diagnosed with 3 diseased vessels (66.6% vs 41.1% in people with <60bpm). These diagnoses are presented in **Table 7.4-A7.4.**

7.5.3. Symptoms and quality of life (Table 7.5-A7.4)

Three-quarters (76.4%) of participants reported pain/discomfort problems (73.6% men versus 81.3% women), and nearly half (45.6%) reported problems with anxiety/depression (42.3% men versus 51.6% women). However, only 14.4% of participants reported problems with self-care (14.5% men versus % 16% women). People with heart rate >90bpm consistently reported more often problems with mobility, self-care, performing usual activities, pain and anxiety or depression. They also reported higher in the Canadian Cardiovascular Society (CCS) (class IV) which corresponds to severe limitation in performing any activity without angina or angina at rest. In the PHQ-9 scale of mental health they also reported slightly higher percentages of depression (6.92%).

7.5.4. Interim follow-up data for hospital admissions and procedures and mortality

A high proportion of consented participants were successfully linked to hospital admission and procedure data in HES (96.7% of patients sent for matching to date). Additionally, 99% of participants were linked successfully with the ONS national death registry and 110 incident deaths were recorded (with 25 recorded as CHD-related deaths (ICD-10 codes I20-25) as the underlying cause of death) (**Table 7.6-A7.4**). The nature of population (CAD patients) as well as the sample size restricts our power to explore specific subsequent cardiovascular events.

7.6. Strengths and weaknesses of a consented clinical cohort

4C principle strengths consist of:

- Research measures systematically recorded, on information that is virtually never available in the EHR, including quality of life, DNA, biomarkers.
- Direct generation of research ready data
- Higher quality information and research reinforcement
- Qualitative factors recorded such as quality of life, psychological symptoms and diagnostic imaging
- A pool of genetic information

4C principal weaknesses:

- Manually performed data collection processes and personal time investment for recruitment
- Difficulties in consenting

- Findings have limited applicability and are restricted to populations that resembles the clinical characteristics of cohort participants
- Small sample size

7.6.1. Strengths of 4C

7.6.1.1. Systematic way of data collection

The 4C study is an example of a clinical cohort that consists of 4 different individual cohorts representing 4 socioeconomically diverse areas of UK. Since it seeks to explore potential risk factors associated with the onset of stable coronary artery disease (angina pectoris) and chest pain, it has clear strategy and protocol to collect it according to the study needs. It is a research question driven cohort with a structured protocol and clear guidelines for conducting research in a standard and rigorous way. All the necessary data is collected in a clear and systematic way while we were able to adjust the techniques we used for its collection according to data nature or population characteristics, visiting back and revising our information gathering tools. The systematic way of data recording is also reflected on the clear accounts we have concerning biomarkers data collection, such as the one investigated in the PhD at hand. Heart rate measurements (recorded for 67.5% of participants) were collected through ECGs. The contribution of the systematic way followed by the researchers, had an additional benefit. Common problems in linked electronic health records stemming from the diverse sources recording such as data duplication or mislinkage, are not present in this clinical cohort. Each patient is recruited once by each centre and after regular communication with the other centres we made sure that the same patient would not be recruited twice or more.

7.6.1.2. Generation of research-ready data

Compared to the CALIBER platform and linked electronic data in general, one great advantage stands out. After the data collection and a brief process and cleaning that it might need depending to its nature, it is in a readily accessible form. As a result, the investigator could analyse the data without the need of extensive data manipulation.

7.6.1.3. Research methods reinforcement

A significant strength of 4C is the nature of data collected. Since the recruitment and data collection process required direct involvement of the investigator with patients and their data, I had the opportunity to thoroughly explain the needs and characteristics of the study to eligible participants and yield more accurate responses on the questions included in the questionnaires. Additionally, my personal time and involvement resulted to a better control of the responses rates (approximately 95% at Heart Hospital). Another benefit coming out of it is the low missing

values that is a result of the persistence and thoroughness of the researcher-recruiter. With my personal approach to the patients, I made sure that no question (hence variable) is left blank.

7.6.1.4. Qualitative parameters

Without questionnaires, parameters such as quality of life, psychological symptoms and specific chest pain descriptions wouldn't be measurable, unlike primary care practice and linked electronic health records that this information is not usually recorded. Having access to the hospitals electronic systems, offered as a wide pool of diagnostic imaging data necessary for in depth recording of patients procedures, findings and diagnoses.

7.6.1.5. Genetic information

However, the main indisputable advantage of 4C cohort remains the collection and linkage with genetic data of the participants. For reliable assessment of parameters relevant to diagnostics and therapy a study's subjects must be characterized both with respect to phenotype and genotype. The incorporation of genome parameter in clinical data will shed light into the complex nature of cardiovascular diseases causal pathways.

7.6.2. Limitations of 4C study

7.6.2.1. Manual processes

The main weakness of field research while I participated in 4C was the manual component that prevails in all clinical cohorts and surveys gathered for research purposes. From daily preparation of biomarkers collection equipment, collecting anthropometric measurements, processing blood samples (centrifugation, aliquoting) and preparing them for transference to Biobank, to collection of clinical information using different hospital systems, manual anonymization, data manually entered in different programs and coding, as well as manually entered in clinical information forms, etc. Data in the hospital systems were often missing or were incomplete requiring further manual adjudication and validation by the researchers and that translated into a significant investment of qualitative and quantitative sources.

7.6.2.2. Consent obstacles

A great part of this time spent in hospital and recruiting was taken up by the fact that recruitment relied exclusively on a voluntary basis, with eligible participants derived from diverse socioeconomic backgrounds. The language barriers that we had to overcome, along with the hesitant attitude of patients towards researchers enhanced by their concern about their health and the imminent angiographic procedures, made the process extremely challenging. One half

of patients approached between all 4 centres for inclusion in the study were either ineligible or declined to participate, and low response rates were more marked in hospitals serving an ethnically diverse population, so selection bias is likely. Continuous direct contact with different gatekeepers to ensure access to participants' medical records was further required, or to gain permission to approach patients and collect their biomarkers, without hinder their daily clinical routine.

7.6.2.3. Generalisability

A further weakness of 4C concerns the nature of population recruited. Since the aim was a cohort of CAD people with angina symptoms and chest pain, specifically recruited for research purposes, the generalisability of the findings is limited. Due to restricted representativeness of the CAD subjects into a general population, the inferences could not be interpreted in a wider clinical or epidemiological context.

7.6.2.4. Small sample size

Additional limitations that stemming from the nature of the study design, is the small sample size and hence the limited potential number of exposures and event types. The main outcome that will be explored to serve the main 4C purpose is a composite of cardiovascular mortality, non-fatal AMI, non-fatal stroke and peripheral arterial disease, while the investigation of more specific cardiac endpoints in relation to resting heart rate, was unfeasible.

7.7. Conclusions

4C is a resource of genetic, biomarker, clinical and questionnaire data among patients with new-onset established or suspected stable CAD. This source of genetic and clinical information, can be used to identify and evaluate genetic and environmental factors associated with the onset of a specific expression of stable coronary artery disease, the stable angina pectoris syndrome and its progression to acute fatal and non-fatal events. Despite the fact that its limited sample size does not allow for specific cardiovascular phenotypes investigation, the highly consistent clinical data collection with the large completeness along with the valuable genomics pool will provide insights to the links between clinical biomarkers such as heart rate and genetic variance in CAD populations using an instrumental variable approach.

8. A comparison of clinical cohort methods: conventional consented study (4C study) vs Linked electronic health records (CALIBER)

As presented in chapters 3 and 7, this PhD illustrates two alternative approaches to establishing clinical cohorts: the first, a conventional clinical research study involved consenting patients and manually extracting data from chart review, and obtaining and processing research blood samples (4C). The second, involved linked electronically recorded linked health records (CALIBER). Each of these two approaches offers methodological strengths and limitation:

CALIBER

Strengths

- Large sample size, hence great resolution in exposures
- Clinical phenotypes resolution
- Data readily updateable- Absence of any manual effort of investigators spanning from recruitment process to data recording
- Efficiency- Recruitment, baseline and follow up phenotypic assessment zero cost to research funder
- Flexible opportunities to define disease follow-up (start point and endpoints), based on availability in the clinical record of 'Phenome wide' information
- Flexibility in cohorts definition
- Flexibility in inclusion criteria of individual cohorts-diverse population that allows for investigation of various research questions applicable to different populations

Weaknesses:

- Missing information at a practice, patient and data level
- Linkage process difficulties
- Difficult to handle and curate, demand high degree of expertise-large datasets to handle.

4C

Strengths

- Research measures systematically recorded, on information that is virtually never available in the EHR, including quality of life, DNA, biomarkers.
- Direct generation of research ready data
- Higher quality information and research reinforcement
- Qualitative factors recorded such as quality of life, psychological symptoms and diagnostic imaging
- A pool of genetic information

Weaknesses:

- Manually performed data collection processes and personal time investment for recruitment
- Difficulties in consenting
- Findings have limited applicability and are restricted to populations that resembles the clinical characteristics of cohort participants
- Small sample size

This chapter highlights the main differences concerning information governance, study design (population and data), follow-up techniques and practical data linkage issues between CALIBER linked electronic health records study and the conventional clinical cohort 4C. Those differences are summarized in **Table 8.1**.

8.1. Information governance

A medical record (in paper or electronic format) provides a written account of a patient's medical history, containing information about diagnosis, treatment, chronological progress notes and discharge recommendations. A whole raft of legislation, standards and guidance on what has become known as 'Information Governance' has been produced in the last few years to cover issues of access, confidentiality and disclosure[293] The legal framework governing the use of personal confidential data in health care is complex. It includes the NHS Act 2006, the Health and Social Care Act 2012, the Data Protection Act, and the Human Rights Act. This framework allows personal data to be shared between those offering care directly to patients but it protects patients' confidentiality when data about them are used for other purposes, for instance improving the quality of care provided, planning and commissioning public health services, research purposes, etc. CALIBER complies to 251 of the NHS Act 2006. Section 251 allows the Secretary of State for Health to make regulations to lift temporarily the common law duty of confidentiality for defined medical purposes and is a result of the realization that certain NHS activities and important medical research could be conducted through the use of identifiable patient information. In CALIBER similarly to other linked electronic health record databases, individual patients' consent was not feasible to obtain for the collection of sensitive confidential information. Therefore, section 251 secured the law basis of the disclosure of confidential information that was not easily anonymized and consent seeking was unpractical in terms of cost, technology and other sources. In 4C study, on the other hand, a smaller scale clinical hospital-based cohort that required genetic material collection, this act was not necessary. Study's participants were individually approached and consented and permission to provide personal and clinical information, blood samples and future contact for follow-up purposes was asked.

The manual dimension of 600 patients approach and consent that I personally did, made the process particularly tedious and time-consuming, something that CALIBER and linked electronic health records conducted automatically within a trivial amount of time to around 5 million patients of GP practices. These practices participated by giving consent for inclusion in the study without individual consent having been seeking. Anonymization of sensitive confidential information was also made manually in 4C. Important identifiers were stripped manually during a pseudo-anonymization process (individual records could be identified by the researcher). These identifiers that were present at all stages of data collection, from patients clinical records collection (GP referrals, hospital discharge letters, blood samples collection and electronic databases creation for genetic material recording and storage to the Biobank, were removed and replaced with a unique participant study number assigned at the point of enrolment to the study.

8.2. Populations synthesis

4C study was created to "serve" a specific clinical purpose. To explore patients with suspected or established coronary artery disease. The very nature of this purpose implies a specific high amount of rigidness regarding the cohort synthesis and the population that is under examination. Hence, the structure of 4C cohort is fixed as opposed to the CALIBER cohort that due to the wide coverage of population and the lack of specificity in terms of the research purposes that enables a wide range of research questions explored, render the cohort more flexible and adjustable to researchers' specific scientific questions.

This lack of flexibility of 4C population is also reflected on the health status of the participants. To answer the specific research question posed at the conception and design of the cohort, patients suffering from specific disease or symptomatic of coronary artery disease were requited. In contrast to that, CALIBER population that was collected from GP practices that people attended for various reasons did not necessarily mean that they are diagnosed with a disorder or disease and a large part of this population did not provide evidence for a past cardiovascular disease event, that allowed the exploration of CVDs incidence in the present PhD. Healthy population was used in chapter 4 to explore associations of resting heart rate with CVDs onset that could not be conducted using data from a coronary disease registry similar to 4C cohort.

Since the aim of 4C study was to identify factors related to stable CAD and especially angina pectoris phenotype, the appropriate eligibility criteria were applied to ensure good quality and representative data. Therefore, patients were not eligible for inclusion if they were diagnosed with structural heart disease, cardiomyopathy or arrhythmia or were referred for ablation or placement of devices (e.g. pacemaker). On the basis of age or coexisting conditions, no patients were excluded. On the other hand, CALIBER study, which majorly focuses on an

advanced quality database of various clinical data sources and not on specific populations, set three main inclusion criteria; age <30 years at study entry, with at least 1 year registration prior to entry, during which up-to-standard quality data has been collected. The wide inclusion of eligible patients without any clinical restriction allows for various research questions' investigations that the results can be applicable and representative of different populations.

An additional difference lies on the magnitude of the sample sizes. CALIBER cohort, by consenting 225 GP practices with the subsequent linkage of additional sources yielded > 10^6 cohort sample size making it one of the biggest clinical information sources of real world data worldwide. This enables an in depth exploration of a massive pool of diverse risk factors and clinical phenotypes, but also a high degree of resolution which covers the detection of an array of specific, severe and non-severe, fatal and non-fatal diseases. In contrast to CALIBER, 4C cohort has a limited sample size that is sufficient for the examination of a specific research question but does not provide the degree of resolution or the coverage of a large amount of information that could extend further outside the narrow path of coronary artery disease patients with chest pain symptoms.

Finally, an important difference between CALIBER and 4C is the nature of patients' participation approach and response rates. 4C study relied exclusively on a voluntary participation approach that resulted to a response rate of 47% when compared to CALIBER that by design the patients participated automatically (after application of relevant quality criteria explicitly presented in Chapter 3) after their registration to GP practices without giving individual consents (response rate 100%).

8.3. Baseline data

4C cohort in reality is a combination of 4 different clinical cohorts, each of them derived from a different hospital setting in UK. Data was collected from rapid access chest pain clinics, cardiac catheter laboratories and coronary angiogram pre-assessment clinics in four ethnically diverse UK National Health Service (NHS) hospitals (**see chapter 7**), all parts of the secondary care setting in UK, that required direct access from the investigators. CALIBER baseline data on the other hand, was derived mainly from primary care system that was 225 GP practices consenting to data linkage in UK, while secondary health care data provided follow-up data and diagnoses information. The primary care system of GP practices contribution was one major difference between the clinical cohort and the linked electronic records data that used this linkage of GP to provide baseline risk factor and clinical variables information in contrast to 4C which required anthropometric characteristics measured by researchers and questionnaires administration in addition to hospital records and procedures on the day of clinic attendance manual recording and file. In UK, there is currently no centralized conduit, with national coverage, for linking and extracting primary care data at scale for research. The secondary care information coming from

the clinics in 4C consisted of discharge letters, and procedure on the day of attendance results, while in CALIBER, the linkage of MINAP, HES and ONS data provided a wealth of secondary care information.

However time-consuming the manual collection of 4C data was, offered access to information difficult to retrieve when you deal with linked health records, such as diagnostic imaging information. A major contribution of 4C was the blood samples and genetic information collection that made the cohort valuable as acts as a pool of genetic and clinical information, that could then enable it to identify and evaluate genetic and environmental factors associated with the onset of a specific expression of stable coronary artery disease. The lack of genetic information in CALIBER however, can be overcome by the linkage of external electronic datasets such as UK Biobank. To maximise the utility of this DNA collection bank, marrying the DNA to the electronic health records is essential. The United Kingdom is unique in maintaining a single set of primary care-based medical records containing all medical interactions involving a patient, whether in primary, secondary or tertiary care. Apart from CALIBER, there are further electronic databases that enrich the landscape of studies focused on cardiovascular diseases and more such as the Secure Anonymised Information Linkage (SAIL) database that uses ICD-10 secondary care diagnoses of CAD linked to primary care datasets. Future work on validation of associations of heart rate with CVDs by these initiatives will offer insights into the clinical marker of millions of patients registered in primary care, have large geographical coverage and good quality of records.

Additionally, behavioural and psychological information such as quality of life parameters were more thoroughly explored in 4C after the incorporation of well-being assessment scales (e.g. EQ-5D scale) in the questionnaires.

The flexibility of data recordings that differs among the data collection tools varies between the two studies. 4C on the one hand through the use of adjustable clinical case record forms for data collection, offers flexibility to ensure the highest efficiency and to match pre-specified research needs unlike CALIBER that data collection and nature varies uncontrollably depending the GP (free text use, etc.), which is another difference that contrasts with the investigator personal involvement in data collection process of 4C.

The number of risk factors and outcomes differs largely between the two studies with CALIBER being able to offer massive numbers of potentially available exposures collected without knowledge of research hypothesis tested as opposed to the limited number of risk factors that 4C collects after a purposively designed protocol. The form of variables however in 4C is a readily usable type of information that needs no further process to use, unlike CALIBER that the variables need to be curated by developing and using established meta-data standards.

Finally, heart rate measurements differ in regards to the way of recording, or more precisely to the information that we have on how the marker was recorded. ECGs were the main source of heart rate recordings in 4C that were performed on the day of patients' angiography clinic attendance. Heart rate is one of the most widely observed measurements in hospitals and is included in early warning scores and risk prediction for standard observations made by every nurse. However, currently hospitals still are at an early stage of digitisation (low HIMS score) and such data are commonly not available electronically, only on paper. In some individual hospitals (e.g. University Hospitals Birmingham) heart rate might be recorded electronically, but these data have not yet been combined across hospitals or linked to national primary care datasets, although this is feasible and undoubtedly will happen in the near future. The critical care theme of the NIHR Health Informatics Collaboration is collecting detailed clinical information including heart rate from patients admitted to critical care units in 5 hospitals. Hence, in CALIBER this kind of information is absent with the only information available being the value of heart rate and the date of measurement by the GP in primary care recorded used Read codes (see Chapter 3 for coding details) without specific reporting of the technique or device of measurement, while heart rate data from secondary care (HES/ONS) is entirely missing. I will present the main descriptive statistics of people with coronary artery disease recruited in 4C and those retrieved by CALIBER linkage. Their comparison is presented in Figure 8.3.1 and Table 8.3.2.

A higher percentage of men were recruited in 4C, raising questions on whether there are gender differences on health seeking behaviour that could partially account for more severe obstructive sCAD cases among men or if there are in fact underlying differences in aetiology, diagnosis, management and treatment of CAD between men and women that are not yet fully understood. 4C heart rate data has a skewness of 0.6 and a kurtosis of 3.8. The mean is 71.7 (±14.2) and median is 70 bpm. Heart rate shows a more symmetrical, less skewed shape, without rough peaks (**Fig 8.1 (a)).** Differences between men and women are smoother than in CALIBER data with a mean heart rate difference of 3bpm (**Figure 8.1 (a)** and **Table 8.2**. People with higher heart rate (>90bpm) tended to have higher blood pressure, less likely to be women or of white ethnicity (data not shown).

In CALIBER, heart rate is skewed right (skewness=1.0), a peaked distribution with a 6.4 kurtosis with heavier tails. The distribution is relatively symmetrical with moderate skewness and kurtosis. The mean is 72.2 (±14.5) and median 71. Men have rougher peaks (kurtosis=7.1 vs 5.8 in women) and their distributions are more skewed to the right (**Fig 8.1 (b)**). Mean heart rate of women is 4bpm higher than men (74.4 vs 70.5). Overall, in 4C dataset, heart rate was recorded in 64.7% of participants, while in CALIBER in only 11.9%.

8.4. Follow-up and outcomes

Follow up in 4C is being conducted using a two-step approach. A postal follow-up questionnaire (Chapter 7) was sent to study participants 2 years after recruitment to assess health status. The subsequent linkage of the consented patients to data from HES and ONS, will yield important information on potential future diagnoses and procedures they might undertake, or even death events respectively. However, no primary care data have been linked in 4C, therefore any future GP visit is not recorded in contrast to CALIBER that the linkage with GP practices and myocardial infarction registry in addition to HES and ONS provide a complete picture of a patient's clinical course.

The follow-up in CALIBER is performed automatically and exclusively using electronic methods, by linking secondary care, disease registry and ONS data, while the manual aspect is still involved in the follow-up process with questionnaires sent, recorded and coded by researchers.

Follow-up duration is a parameter highly different between the 4C clinical cohort and linked electronic health records. The median observation time from study entry date in CALIBER is 5.5 years in the study assessed in the present PhD, while for 4C it is just 469 days, with implications on methodological and analytical aspects.

Differences further lie on the outcomes of the studies. The primary endpoint of interest in 4C was pre-specified at baseline stage and aimed at a composite of cardiovascular mortality, non-fatal AMI, non-fatal stroke and peripheral arterial disease assessment. CALIBER endpoints on the other hand, due to various reasons such as the statistical power to handle individual specific cardiovascular endpoints, or the high degree of resolution that is provided by the wide coverage of primary and secondary care sources are numerous and flexible, with different outcomes explored by different studies depending on the research question or researcher's preferences.

Due to the short follow-up duration in 4C that resulted in a limited number of events, longitudinal analysis was not advisable, nor feasible. Cross-sectional analyses was exclusively the only robust methodological pathway that would lead to reliable inferences between risk factors and the composite outcome, compared to CALIBER and its large follow-up duration that allowed for risk factors effects on incidence and prognosis of future cardiovascular events (chapters 4, 5, 6).

Finally, interpretation and dissemination of results of 4C should be done cautiously as the findings due to the highly specific population might not representative on the general population and hence with limited generalizability. CALIBER on the other hand, produces results and presents findings applicable to various populations, regardless the severity of diseases, including healthy population without a history of a cardiovascular disease.

8.5. Generating research ready data

Data linkage is a crucial part of the studies design and performance. In 4C all participants' records and data are linked through a sequence number assigned by the investigator to every patient, hence the investigator has direct access to participants' identifiers (pseudo-anonymization) before the anonymization process. In CALIBER, the linkage is performed through NHS, date of birth, sex and post code by a third party, which prevents investigators from any kind of control over data identifiers.

Since 4C study recruits patients and collects data guided by a more specific research idea and a targeted population in addition to the personal direct involvement of the investigator during the data collection process, the data completeness is quite high at baseline. In contrast to linked electronic data that the data gathering relies on GP data collection preferences at every visit, the reason of practice attendance, etc. that produce high missing numbers. The fact that different sources and not a single researcher collect the data, as well as the fact that patients can be captured more than once by different source, leads apart from a partial completeness to data inconsistencies such as duplication of data by patients registered in several practices, inconsistencies in diagnoses or data recording dates or values. Therefore, the need for good documentation of decisions during data preparation and specification of relevant sensitivity analyses to test the robustness of the definitions is of utmost importance in CALIBER. However, the recruitment of participants only once by investigators in 4C has an important drawback that is eliminated in CALIBER. Data validation in 4C is not easily performed, since the lack of repetitive patients' recruitment and further information recorded by more than one source does not allow for crosschecks in contrast to linked records that provide extra information beneficial for data comparisons.

Table 8.1. Comparison of a consented clinical cohort (4C) and EHR cohort (CALIBER)

Research stage	Clinical cohort (4C study)	Linked Electronic Health Records (CALIBER)
Information Governance		
Legal and ethical basis	London City Road & Hampstead National Research Ethics Committee, local NHS Research & Development committees	General and PIAG (Patient Information Advisory Group) approvals for use of CALIBER: Compliance to section 251 of the NHS Act 2006 (which allows medical research, when individual patient consent not feasible) For CPRD access: Study specific approvals of the protocols from ISAC (Independent Scientific Advisory Committee) A signed licence outlining scope and data confidentiality of use of CPRD data For MINAP, HES, ONS data: Applications are made to the MINAP Academics Group, and to the NHS Information Centre
Identification of participants	Patients identified manually using daily appointment lists at the pre-assessment clinics and schedules for angiogram procedures. Patients' history files in pre-	Inclusion of all patients attended the consented GPs

		assessment clinics were available for a screening prior to approach to assess eligibility		
Written informed patient consent		Research staff seek consent from each patient individually		N/A
Practitioner consent		N/A		Yes and All patients of a GP practice are included in consenting practices
Confidentiality measures: handling of strong identifiers (NHS no, name, dob, address, postcode)		Retained by data manager and study co-ordinator only. Identifiers manually removed by researchers from all sources and replaced with a unique participant study number assigned at the point of enrolment		None released to research team Data are anonymized and all personal identifiers are removed by the data provider.
Population				
Cohort structure		Fixed		Flexible
Population selection		Selection for research specific purposes		All patients attended GP practices in UK from 1997-2010
Population health status		Diseased or symptomatic		General populations (healthy included)
Population inclusion criteria		Specific common criteria on population health status and symptoms		No health status restrictions for entry to the general CALIBER cohort
Population exclusion criteria		Diagnosed with heart disease, cardiomyopathy or arrhythmia or were referred for ablation or placement of devices (e.g. pacemaker)		Age <30 years at study entry, with <1 year registration prior to the study entry (depending on study requirements)
Sample size		Limited (N=3,345 patients)		Large (N=~2M patients without prior CVDs)

Patients participation	Voluntary participation. Lower response rates (47%)	All patients included given they are registered with a GP consented practice (100% response rate at patients level)
Populations' generalisability of findings	Might not be representative of the general population*	Data dissemination and findings can be applicable to various populations regardless severity of disease, etc.
Baseline data		
Patients recruitment sites	Rapid access chest pain clinics, cardiac catheter laboratories and coronary angiogram pre-assessment clinics in four ethnically diverse UK National Health Service (NHS) hospitals	225 GP practices consenting to data linkage in UK
Baseline risk factor sources	Anthropometric characteristics measured by researchers, questionnaires	Linkage of primary care records
Baseline risk factor sources (e.g. behavioural, environmental)	Questionnaires, GP referral letters	CPRD data
Baseline clinical variables' sources (e.g. heart rate, BP, etc.)	Hospital records, Patients' files on the day of the procedure, measurements by investigators	Linkage of CPRD, HES records
Baseline clinical variables *sources*	Hospital records and procedures on the day of clinic attendance and recruitment	Linkage of primary care records
Primary Care sources	Not able to link-scarce evidence from GP referrals	GP practices linkage
Secondary Care sources	Discharge Letters, Hospital attendance	Linkage with HES, MINAP and ONS
Data extraction ways	Data recorded both electronically and in paper and collected for research purposes	Electronically recorded for clinical purposes.

Clinical notes		Behavioural/environmental factors, prior procedures and medication		Biomarkers, environmental/behavioural factors
Imaging reports		Clinical characteristics such as heart rate, N of diseased vessels, biomarkers		N/A
Blood samples		Genetic info		No genetic material collected
Data collection protocols		Standardized data collection and recording with definitions and reporting commonly used by recruiters		Codified using standardised classifications systems (Read codes, ICD10, OPCS). Information also entered as free text but not available for research, No protocol
Data collection tools		Flexibility provided by clinical case record forms adjustable to ensure the highest efficiency and to match pre-specified research needs		Data collection and nature varies uncontrollably depending the GP (free text use, etc.)
Data collectors		Research staff (directly or through extraction from GP referrals letters or hospital records)		GPs
Biomarkers collection		Bloods, saliva (buccal swabs) specimens collected from all subjects at specified times (RACPC visits)		No biomarkers collection
Biomarkers processing		Centrifugation, aliquoting, transfer and storage as per protocol		Non applicable
Self-reported variables (chest pain description, quality of life and psychological parameters) and symptoms		Questionnaires standardized		Self-reported symptoms not standardised (not known if information was prompted by GP, what was recorded from what patient reported)

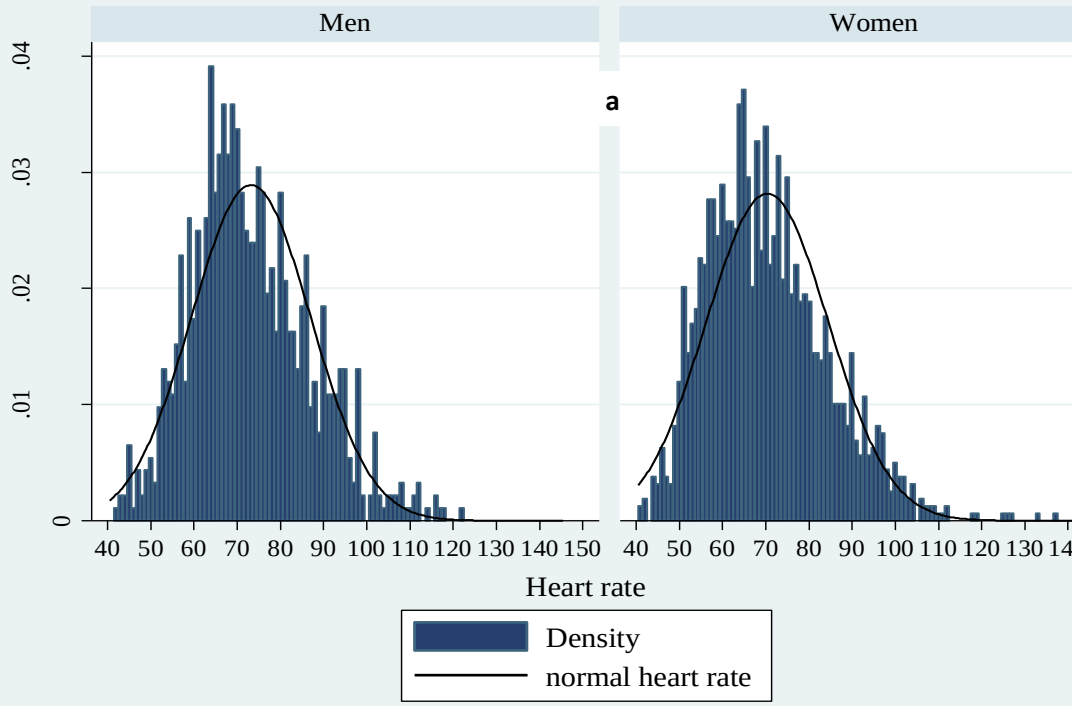
Mode of heart rate measurement	Resting ECGs, computed from R-R intervals	Usually not recorded, includes palpation, BP monitor and ECG
Exposures (risk factors) numbers	Limited number of exposures pre-defined in protocol	Large numbers of potentially available exposures collected without knowledge of research hypothesis tested
Variable responses	Standardised and pre-defined	Response categories wide and merged accordingly
Diagnostic imaging tests(e.g. angiograms, echocardiograms)	Available but unstructured, recorded in a text and imaging form, manually extracted information	Inconsistently recorded. Sometimes test recorded but not result. Multiple coding of results frequently available
Electrocardiograms	Extraction of heart rate, QT wave, PR intervals, QRS axis, etc.	Read codes for heart rate no further characteristics of pulse
Coronary angiography	Extraction of number of diseased vessel, arterial heart rate (used as substitute when heart rate missing), number of previous stents/grafts (history contribution), diseased territory or proximity to heart, LVEF	Poorly recorded LVEF in HES, no recording of a large piece of information regarding clinical characteristics or coronary disease in primary care.
QoL	Quality of life assessment using standardised scales (Euro QOL)	Rarely administered in clinical practice, and thus are not available in the HER. In case of recording QoL data, difficult curation, or identification of relevant codes time consuming
Follow-up and outcomes		
Follow-up data sources	HES/ONS data linkage. Not primary care	Primary care, HES, ONS, MINAP. Longitudinal to identify endpoints.
Follow-up duration	Limited by re-application for refresh of follow up data to HES, ONS	Potentially long follow up duration (e.g. until death, practice deregistration or last collection date).

Endpoints		Limited to those which are hospitalised or deaths..	Large numbers of potential endpoints (e.g. recorded diagnoses including those in primary care)
Data Linkage and research ready data generation			
Data linkage method		Data linked through a sequence number assigned to every participant (prefix centre-specific) by investigators	Data linked through NHS number, date of birth, sex and post code by a third party, so no control by investigators
Data coding and transfer		Responses manually coded and entered into excel and access databases	Electronically coded, curated. Algorithms applied to form final form of variables
Variables form		Readily available	Variables curated developing and using established meta-data standards
Data duplication and inconsistencies		Limited inconsistencies if properly conducted. Each patient recruited once. Rare data duplication.	Potential for data duplication (e.g. patients registered in several practices), Inconsistencies across datasets (e.g. differences in dates or values). Need for good documentation of decisions during data preparation and specification of relevant sensitivity analyses to test the robustness of the definitions)
Data completeness		High completeness (at baseline): thus e.g. if smoking status missing in one part of the notes, researcher can search for in another part of notes, or ask the patient. Additionally, purposively collected variables recorded across patients by researchers	Recordings of information depending on GPs or reason for attendance. Low completeness on biomarkers
Data validation		Each patient recruited individually, hence no alternative source of information for each patient (e.g. by duplicated recordings) to validate and crosscheck.	Same patient recorded in different data sources- Allows longitudinal crosscheck, however no further access to patients' medical history.

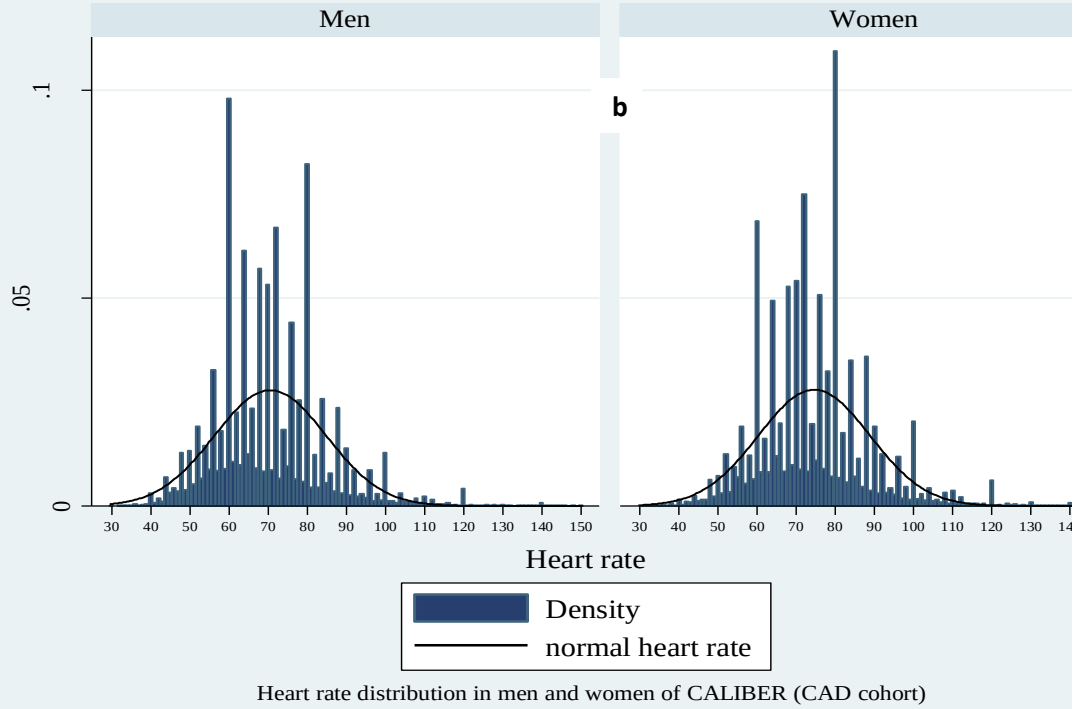
		However, information related to medication, prior diagnosis or procedures can be obtained and crosschecked via GP referral letters, angiography procedure results or patients' hospital files		

***Hospitals may admit patients with more comorbidities or be of different racial mix if they are located in areas that are systematically different from not participating hospitals. The degree to which a registry/study centre of a clinical cohort is representative of the general population will depend on the selection of enrolment sites and the use of consecutive or random sampling.**

Figure 8.1 Heart rate distributions in men and women of CALIBER and 4C data



Histogram of heart rate distribution in 4C men and women



Heart rate distribution in men and women of CALIBER (CAD cohort)

Table 8.2 Comparison of baseline characteristics of people with CAD using clinical cohort data or linked electronic health records

	4C research study (people with established CAD and HR measurement) (N=2,841)	CALIBER study (prognosis cohort) (N=51,703)
Baseline characteristics		
Clinical factors		
Heart rate (bpm)	71.7 (±14.3)	72.2 (±14.5)
Systolic blood pressure (mmHg)	135.4 (±24.1)	138.2(±19.9)
Hypercholesterolemia	52.5	22.7
Type 2 diabetes	22.4	11.7
BMI (kg/m^2)	29.5	28.2 (5.5)
Smoking status		
Current smoker	19.1	11.9
Ex-smoker	26.0	43.8
Non-smoker	28.9	38.13
Demographic characteristics		
Age	58.6(±12.6)	72.2(±11.4)
Female	36.9	44.1
White ethnicity	45.8	73.4
Education (finished at 15yo)	31.4	-
Medication		
Beta-blockers	14.5	50.7
Aspirin/antiplatelet	19.8	67.6
ACE-inhibitors	12.6	39.5
Nitrates	6.2	47.6
Statins	23.2	63.0
Endpoints		
Primary 4C composite endpoint (cardiovascular mortality, non-fatal AMI, non-fatal stroke and	27	

peripheral arterial disease) (HES)			
CVD death		-	1,642
Heart failure		-	3,947
Myocardial infarction		-	1,241
Stroke		-	2,375
Peripheral arterial disease		-	1,181

Note: Means for continuous variables (SD), (%) for categorical; cohorts total population after exclusion of those without heart rate measurements

8.6. Conclusions

In this chapter I tried to point out the dual nature of this PhD, compares the two largely different studies and their data that I used to explore my research questions. Overall, CALIBER platform provides a knowledge pool of large sample size that can be variously used depending on gaps identified in clinical research, flexible enough to investigate questions from different clinical backgrounds, whereas 4C cohort, aims specifically to a coronary artery disease population investigation, gathering data from a research (diseased) population that serves that particular purpose, while its findings will be applicable only to a population with similar characteristics. The manual nature of processes in 4C made the participants' recruitment stage and the data collection handling time-consuming, however it provided a high completeness of data among which genetic information valuable for mendelian associations exploration. Finally, CALIBER cohort that was designed and created using electronic techniques and automatic methodologies, saved valuable time but required a higher degree of expertise.

9. Conclusions

9.1. Introduction

Summary of thesis

In this thesis, I have described the clinical marker of heart rate and the factors that affect or are affected by higher values (Chapter 1). I then went on to explore published literature on resting heart rate and adverse cardiovascular outcomes association (Chapter 2). In Chapter 3 I briefly described the field of electronic health record (EHR) research and I specifically focused on the research platform CALIBER that I used to assess potential associations of heart rate with cardiovascular diseases. In chapter 4, using the aforementioned platform's data, I examined the onset of specific fatal and non-fatal cardiovascular diseases with regards to resting heart rate of healthy individuals (free from atherosclerotic diseases) that attended GP practices. In chapter 5 my aim was to explore similar associations as in chapter 4, in a coronary heart diseased population using CALIBER data. Chapter 6 aimed at the assessment of the initial presentation of atrial fibrillation in a healthy population. However this time, people that eventually experienced an atrial fibrillation event were followed for subsequent cardiovascular events associated with the patients' heart rate levels. In chapters 7 and 8, I presented the methodology used in a consented cohort study of patients with established or suspected coronary heart disease (4C), that I participated in recruiting from clinical settings in UK and then compared and contrasted the weaknesses and advantages offered by CALIBER platform which represented digital era and various automatic processes, with the consented cohort 4C that is characterized by manual components and personal involvement with data collection. In this chapter I will give a summary of the findings of this PhD, describe the implications of these findings in a broader clinical, research and public health context and finally present the overall strengths and limitations of the cohorts produced and analysed by this PhD followed by recommendations for future research.

Research context

In the literature search, we observed that the whole literature body is derived by population surveys, clinical trials or registries, that their common characteristic is the research specific purpose of their data collection. Among further weaknesses it was the limited sample sizes, the questionable generalizability of the findings or the representativeness. We also found that their findings are mostly related to mortality endpoints or composite phenotypes. Finally, clinically relevant heart rate ranges are often ignored from an analytical perspective. No previous study used linked electronic records to assess associations between heart rate data yielded by primary care and cardiovascular events experience. This is the first attempt to explore these associations using EHR, since the large sample size and resolution they offer, enable the design and perform of large scale analyses allowing for investigation of heart rate associations

across a wide range of individual phenotypes. To that effect, the present PhD had the following objectives:

i) Explore published literature on resting heart rate and adverse cardiovascular outcomes association.
ii) Examine the onset of specific fatal and non-fatal cardiovascular diseases with regards to resting heart rate of healthy individuals using linked electronic health records (EHR)
iii) Examine associations of heart rate with the prognosis of specific CVDs in people with coronary artery disease (CAD) using EHR
iv) Assess the association of HR with the onset and prognosis of atrial fibrillation using HER
v) Describe a consented clinical cohort of patients with CAD (4C) and explore associations of resting heart rate with parameters not recorded by primary care and EHR, such as genetic variants and quality of life
vi) Compare EHR processes and data with the 4C consented clinical cohort (4C)

9.2. Major findings

This PhD set out to explore associations between resting heart rate and incidence and prognosis of cardiovascular diseases in healthy, coronary artery diseased and atrial fibrillation populations. Of eminent position in this thesis that largely contributed to address and answer of the research questions posed, has been EHR and particularly the CALIBER platform that was developed by colleagues at Farr (prev. The Clinical Epidemiology Group at UCL). CALIBER links primary care data from GP practices, hospital and registry data and data from ONS that provide the mortality parameters of the studies. Using these data, I constructed and analysed two different cohorts, one included healthy population (N=233,970) and one patients with stable coronary artery disease (SCAD) (N=51,703). The former cohort was also used to explore the onset of atrial fibrillation in a healthy population that subsequently led to cardiovascular events.
The major findings observed from these 3 cohorts were:

- *Study of resting heart rate and incidence of CVDs in healthy individuals*
  - Resting heart rate showed specific associations with myocardial and arrhythmic disorders, but not with coronary disease, stroke or PAD.
  - Average resting heart rate of >70bpm in the general population is associated with increased hazard of specific cardiovascular diseases and mortality particularly in men and should not be considered as normal.

- Women and men differed in their heart rate-CVD associations, with associations being weaker or absent in women

➢ *Resting heart rate and prognosis of patients with CAD*

- Increased resting heart rate (RHR) was strongly associated with higher risk of cardiovascular outcomes not included so far in the primary endpoints of trials such as heart failure. Additionally, RHR was not found to be associated with outcomes commonly used by trials as main endpoint or a part of composite primary endpoints such as myocardial infarction.
- Higher resting heart rates above 70bpm increase the hazard of heart failure events, stroke in women, and atrial fibrillation, without substantially affecting the hazard of events in the coronary arterial beds.

➢ *Resting heart rate and atrial fibrillation onset with subsequent CVD events*

- Higher heart rate is strongly associated with atrial fibrillation in men
- This association in women was not found.
- Cardiovascular event rates across heart rate levels show a constant increase of hazard of subsequent heart failure events compared to low heart rate values (<60bpm) in people with diagnosed atrial fibrillation.

9.2.1. Heart rate and CVDs in men and women

In the present PhD, we found an increased hazard of heart failure that was greater in healthy men and evident at heart rates >70bpm compared with healthy women in whom the hazard was confined to heart rates >90bpm. Epidemiological studies on resting heart rate and heart failure have shown weaker associations in women and in other smaller studies it was confined to men perhaps reflecting under-powering rather than a true gender difference. Average heart rate of 70-79bpm, showed strong associations with unheralded coronary death but only men, whereas for women the risk was not present. Finally, associations with stable angina showed a protective effect in 60-69bpm, 70-79bpm and >90bpm in women, whereas in men associations were of the opposite direction, however imperceptible and insignificant.

A strong association between heart rate >90bpm (vs 70-79bpm) and atrial fibrillation onset was observed in both healthy men (HR=1.50, 95% CI: 1.33-1.68) and women (HR=1.40, 95% CI: 1.27-1.54). The associations were particularly strong in cases that no CVD event preceded that of atrial fibrillation in men and women (HR=1.65, 95% CI: 1.45-1.87 and HR=1.45, 95% CI: 1.30-1.62, respectively). Risk of AF at lower heart rate range (<60bpm vs 70-79bpm) was found to be strong in women (HR=1.35, 95% CI: (1.18-1.54) but not significant in men. Compared to men, heart rate range of 70-90bpm vs <60bpm showed a protective effect for atrial fibrillation

in women. Finally, atrial fibrillation risk was higher in people aged >80 that belonged to the >90bpm heart rate range (HR=1.32, 95% CI: 1.10-1.59).

Finally, I found a slightly higher increase in risk of stroke in women with CAD in heart rate >90bpm (HR: 1.47, 95% CI: 1.15-1.88) compared to men (HR: 1.09, 95% CI: 0.83-1.42), while a higher risk for atrial fibrillation was found in men with CAD in 70-79bpm, 80-89bpm and >90bpm compared to women that the risk was restricted to heart rate values >80bpm. Gender-related difference in the association between heart rate and mortality was also found in some studies conducted in subjects in patients with MI. In particular, in most studies high heart rate appeared to be a weak predictor of death from coronary artery disease in the female gender, which indicated that tachycardia can be deleterious also in women.

9.2.2. Shapes of associations between heart rate and CVDs

This PhD also provides evidence for a steep increase in risk for heart failure and cardiovascular mortality above 70bpm, a threshold significantly lower than the majority of the available studies. Quite steep is also the increase to atrial fibrillation events above 70bpm, while the risk of sudden cardiac death shows a steep increase at higher heart rate values above 90bpm in both men and women. Published studies have suggested a threshold effect of heart rate >77bpm on mortality outcomes, above which the risk for all-cause mortality increases steeply and for CV death at a heart rate >83 beats/min. In contrast, other studies have found a slightly lower threshold of >70 beats/min while others have demonstrated an increased risk at relatively low heart rates, suggesting a J-shaped, rather than a linear, relation. In line with our findings, data from the BEAUTIFUL study, which suggested that the increase in death and heart failure outcomes rose continuously for values of ≥70 bpm, whereas the relationship was less pronounced for MI and revascularization. I also showed that atrial fibrillation risk has a U shape and increases steeply above 74bpm. This shape was particularly pronounced in women that their lower levels of heart rate showed a high increase of AF incidence. In follow-up of people that subsequently experienced an atrial fibrillation event we showed an increase in risk of heart failure above 70bpm, similar to the one we previously showed in people with CHD whereas in healthy population this risk is more obvious in heart rates above 75bpm.

9.2.3. Heart rate monitoring-challenges

Apart from the measurement during clinical routine by medical professionals, heart rate is now also recorded by individuals, athletes or people trying to measure their fitness levels and are interested in monitoring their heart rate to gain maximum efficiency from their training, using various devices such as activity trackers (fitbits), smartphones, pedometers, accelerometers, etc. The ubiquity of cheap technology and an attendant abundance of phone applications now allow a growing number of people to track their heart beat in a 24/7 basis. Large health

databases such as UK BIOBANK, invite participants to wear a wrist worn activity monitor, and have already undertaken repeated measures on 20,000 participants.

Limitations

A key challenge for this is that a huge amount of personal data can be collected from many of these devices. The aforementioned health and fitness gadgets can capture sensitive details about a person's markers and consequently health, and send it automatically for processing to tech vendors, who may then wish to share it with third parties for 'big data' profiling. Organizations and companies will soon start offering wearables to employees aiming at improving productivity. Although the size of data yielded particularly on markers such as heart rate will be vast, individuals must be given clear and transparent information about what data is collected about them and how it will be used, in addition to rights to manage their personal data. Additionally, data security is another important issue. Without the proper security and precaution measures, some wearables could expose a huge amount of intimate and extensive personal health data (not only limited to health) about an individual. Urgent reforms that give wearers of fitness devices the right to have all personal data erased, and in case these personal data are given for processing by private companies and industry, a consent before that should be required and obtained.

9.2.4. Mechanistic implications

An important finding in the present study were the relatively trivial associations of heart rate with acute myocardial infarction, intracerebral haemorrhage and peripheral arterial disease, the lower confidence intervals for increased risk of these outcomes never exceeding 10% in adjusted >90bpm versus <60bpm comparisons. Moreover, there was no association of heart rate with the other manifestations of coronary or cerebrovascular disease or with abdominal aortic aneurysm. These observations may have mechanistic implications, and suggest that tachycardia and its autonomic drivers are more damaging to the myocardium and the electrical stability of the conduction system than to disease progression in the arterial wall, despite trial data relating increased heart rates to endothelial dysfunction and accelerated atherosclerosis.[238] However, an alternative explanation could be the longer atherosclerotic process that leads to delayed clinical manifestations, hence studies with longer follow-up might be potentially more appropriate to capture these effects.

Additionally, Genome Wide Association Studies (GWAS), failed to identify associations of heart rate loci with coronary artery disease (CAD) or MI.[140] Consistent to these findings our study enhances the theory of lack of atherogenic and endothelial dysfunction mechanisms behind increased heart rate effect. Certainly, adjustment for conventional atherogenic risk factors had little effect on our risk estimates and there are now clinical data from the Study Assessing the Morbidity-Mortality Benefits of the If Inhibitor Ivabradine in Patients with Coronary Artery

Disease (SIGNIFY) trial showing that heart rate reduction with ivabradine does not affect the risk of myocardial infarction in patients with stable coronary artery disease.[128] The association between sustained tachycardia and cardiomyopathy, however, is well established based on experimental studies of rapid cardiac pacing and on clinical presentations of patients with tachyarrhythmias. The potential for complete reversal of LV dysfunction following correction of the arrhythmia emphasizes the central role of heart rate in generating these disorders. Associations of heart rate with sudden cardiac death 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. Further evidence of a mechanistic link of heart rate with cardiomyopathy and sudden death comes from genome-wide association studies that have identified single nucleotide polymorphisms influencing heart rate regulation in genes also involved in the pathophysiology of dilated cardiomyopathy, congestive heart failure and sudden cardiac death.[233]

9.2.5. Clinical implications

9.2.5.1. People with normal heart rates at risk

Heart rate is one of the most ubiquitous clinical measurements and is increasingly recorded by healthy people monitoring personal fitness with mobile devices and phone applications. The findings of this PhD can be used to help establish normal values for men and women. Approximately 74% of women and 63% of men have heart rates >70bpm and are at increased risk of cardiac events, with a risk for heart failure, unheralded coronary death, CVD mortality and all-cause death more pronounced in men. In other words, average heart rate values particularly in men, cannot be considered normal and further attention should be given even to those males with heart rates lower than those so far considered as “normal” rhythm values. Trials are required of heart rate lowering in high risk groups, e.g. in patients with resting tachycardia (≥90bpm) present in 17% of women and 13% in men. Remarkably there are no guidelines to inform clinical decision-making regarding behavioural, pharmacological, etc. for these patients. Heart rate may contribute to the identification of patients at high risk of severe outcomes such as sudden cardiac and unheralded coronary death.

9.2.5.2. Risk prediction

Finally, our findings require re-evaluation of the contribution that heart rate makes to risk prediction, taking account specific outcomes of interest 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. Common CHD risk scores are not effective at predicting AF risk. CHD and AF share some common risk factors, such as hypertension, diabetes, and obesity, but heart rate has been shown to be a risk factor of development of AF only and not of

CHD. This highlights the importance of a separate risk score to predict AF, and potentially, the need to develop different preventive interventions by incorporation of heart rate in such scores.

9.2.5.3. Patient management and guidelines

We showed differences between genders with a focus in lower heart rates and hence potential differences in pathophysiologies of AF that should lead to a personalized clinical care. Additionally, targeting of drug interventions in routine clinical practice should be examined with caution. In a recent meta-analysis it was found that ivabradine has not been shown to limit the ventricular rate in patients in AF, and so authors concluded that those patients who develop AF are likely to have higher heart rates, thus negating any benefits of ivabradine as a rate-lowering therapy in treating either angina or heart failure. Our findings support that the increase of AF incidence is more prominent among men and women with higher baseline heart rate, as well as in women with low heart rate. This raises the possibility that the contribution of ivabradine in these patient groups could be possibly proved to be trivial if not adverse. In another clinical trial, it was provided solid preclinical evidence that ivabradine and ranolazine, alone or in combination, have roles in AF rate control. Therefore, clinical practice professionals should be targeting to medications for AF prevention and treatment as well as for its prognosis with a personalized health care perspective and communicating of risk for individuals cautiously.

9.2.6. Research implications

Heart rate is one of the most easily accessible biomarkers that recent studies have given impetus to its examination. Private companies and academic institutes have invested significant amount of financial, scientific and infrastructural sources to design and conduct clinical trials investigating the effect of heart rate lowering medication such as ivabradine or beta-blockers on specific coronary disease phenotypes such as MI that as showed by our study are not linked. These quantitative (money) and qualitative (investigators' or patients' time) investments could have been avoided if the application of linked electronic health records had preceded the actual trial, while these sources could have been allocated towards investigation of heart rate links with other cardiac diseases such as people at early stages of heart failure and resting tachycardia. The design of such trials should take into account of the selective associations of heart rate with the non-vascular disease presentations identified in this PhD.

9.2.7. Heart rate in 4C

As we noticed, the linked electronic health records fail to capture in depth parameters of the patients' perceptions on their health such the implementation of quality of life scales to assess psychological or behavioural functioning, or diagnostic imaging tests and other visual tools. Their observational nature and subsequently their confinement to associations or correlation

pathways that are not causal was further pinpointed. Consequence a consented cohort to yield both clinical and genetic information to address translational research questions in prognosis was required. Therefore, the 4C clinical cohort of people with suspected or established coronary artery disease was launched in 2009 as a resource in which DNA and biomarker samples were obtained at time of presentation with chest pain linked to detailed phenotypic data obtained from EHRs and participant self-completed questionnaires.

I personally recruited and consented 600 patients from a single centre (overall cohort including the other centres was 3,345), collected and processed their blood samples in addition to questionnaires that yielded important information related to specific chest pain symptoms and their well-being. People that belonged to the highest heart rate level were more commonly younger (mean age= 56.8 years compared to 62 years of age in people with <60bpm heart rate). They were also more commonly men, current smokers and with lower diabetes type II proportions. They also had lower beta-blockers, blood pressure medication, statins and antiplatelet prescriptions. Of the 3345 participants recruited into the study, 99.1% granted full access to their medical records.

Among my initial objectives were to explore associations of heart rate with i) diagnoses based on functional imaging and invasive coronary angiography results, e.g. number of diseased vessels, ii) Quality of life parameters and mental health, iii) Single nucleotide polymorphisms (SNPs) that are related to coronary heart disease. However, due to time limitations and significant lack of cardiovascular events due to limited follow-up time as this is still in an on-going process, I was unable to pursuit these aims.

9.3. Conclusion

With the use of heart rate data recorded in clinical care by general practitioners or other clinical professionals, this PhD sought to examine associations of resting heart rate and incidence and prognosis of CVD events in healthy and CAD populations. This is the first time that that primary care data is used to provide answers related to heart rate links with cardiovascular diseases and by the large number and high resolution information I was able to shed light into these links. These complex relationships are hard to disentangle in terms of direction and causality. Further work on the true causality of these associations is needed where the accuracy of mendelian randomization studies combined with the specificity and clinical wealth of linked electronic health records data will yield more scientifically robust answers on underlying mechanisms and causal effects. Nowadays, this will be soon feasible through the linkage of CALIBER datasets with UK Biobank, a major national health resource of 500,000 people recruited across UK that will complete the translational route of research in linked electronic health records.

10. Appendix 3[§]

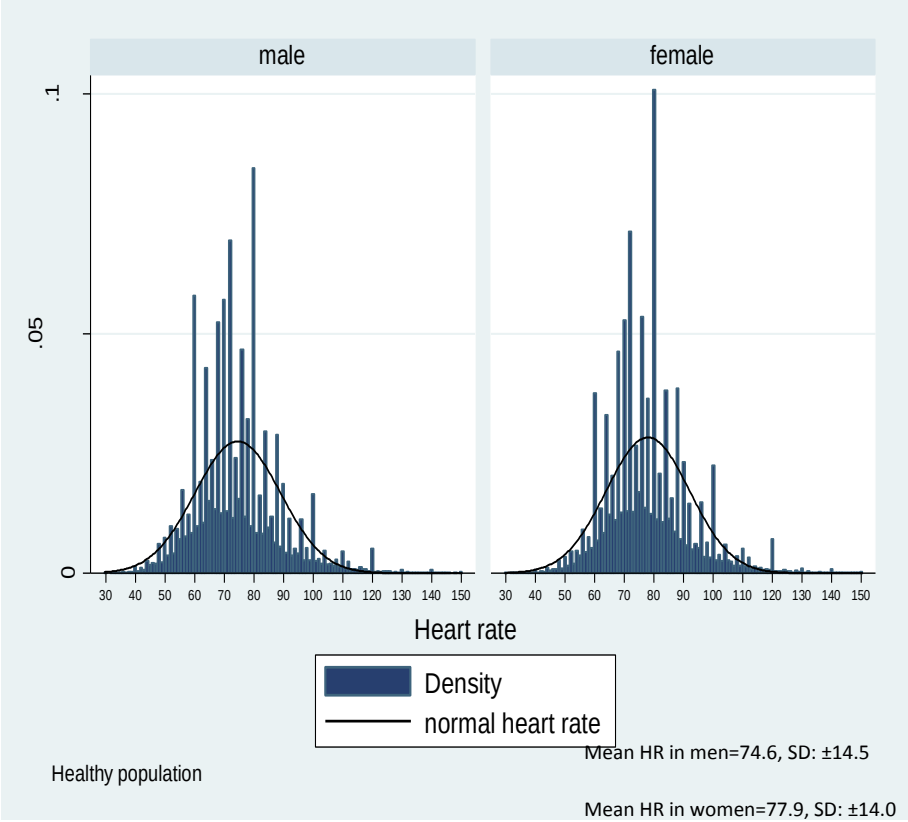
Table A3.3 Selected constituent data files used for PhD, † including description and number of rows in full CALIBER research platform Constituent Data files[193]

	Description	Records	Used for
CPRD files			
Heart rate	Record of heart rate measurement, patient identifier, heart rate value	751,165	Main PhD exposure
Patient	Year of birth, gender, marital status, registration details and other administrative information	5,372,790	Demographic co-variates
Practice	Region of practice, date practice met data quality standards and last data collection date	226	Modelling data clustered at general practice level
Clinical	Record of each consultation including practice, patient and consultation identifiers, date of data entry, date of consultation, and medcode (CPRD synonym for Read codes)	356,446,923	Specifying cohort, and defining ethnicity, clinical co-variates, and endpoints
Additional	Information, such as measurements (e.g. blood pressure measurement or BMI) or categories (e.g. smoking status – current, ex, non) which are not captured by Read code.	97,244,627	Defining clinical co-variates
Test	Type of test performed, values, units of measure and normal range for laboratory.	227,075,743	Defining clinical co-variates

[§] Appendices numbering correspond to chapter numbers and start from the chapter that we encounter an appendix reference for the first time

Therapy	Prescriptions issued included British National Formula (BNF) code, CPRD product code, total quantity prescribed, pack type, number of packs, numeric daily dose, total quantity and number of repeats.	400,859,645	Defining clinical co-variates and specifying endpoints (stable angina)
HES files			
Patient	Patient identifier, birthyear, gender, ethnicity, ethnicity, HES data collection start and end, and matching quality data	2,026,520	Defining demographic co-variate (ethnicity only)
Diagnosis (Admissions)	Patient identifier, admission identifier, date of discharge, ICD10 code, primary diagnosis flag	7,983,022	Specifying cohort, and defining clinical co-variates and endpoints
ONS files			
Mortality	Patient identifier, date of death, under-lying cause of death, cause of death (1-10)	278,088	Specifying cohort and defining endpoints

Figure A3.3. Histograms of heart rate in, healthy and CAD cohorts (by sex)



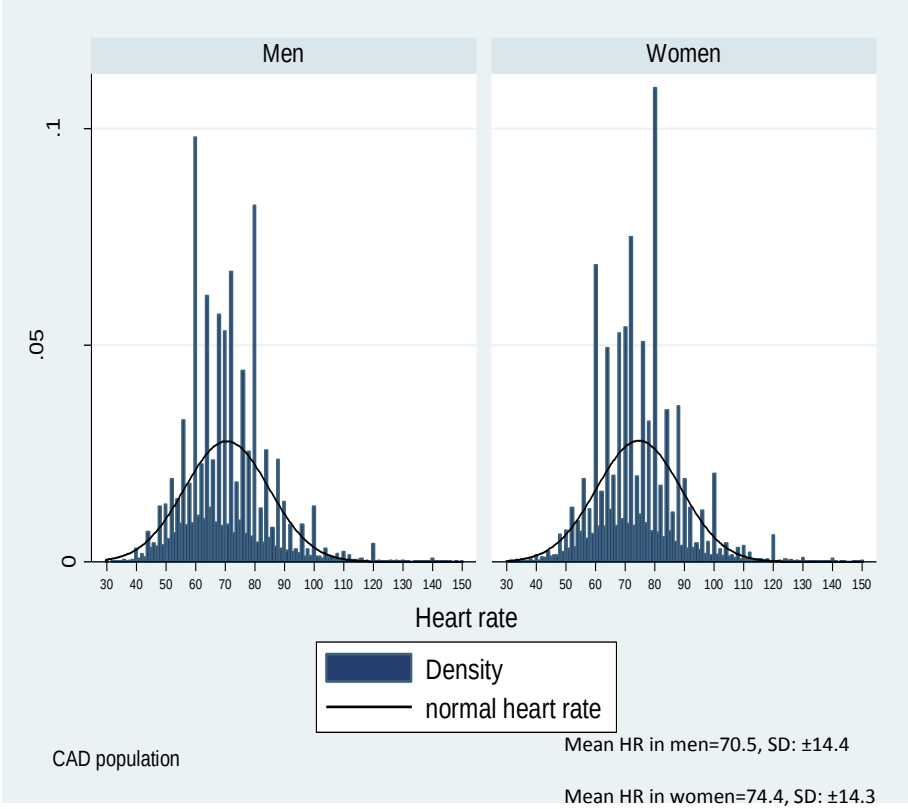


Figure A3.4. Boxplots of mean heart rate in healthy populations identified in literature (by sex)

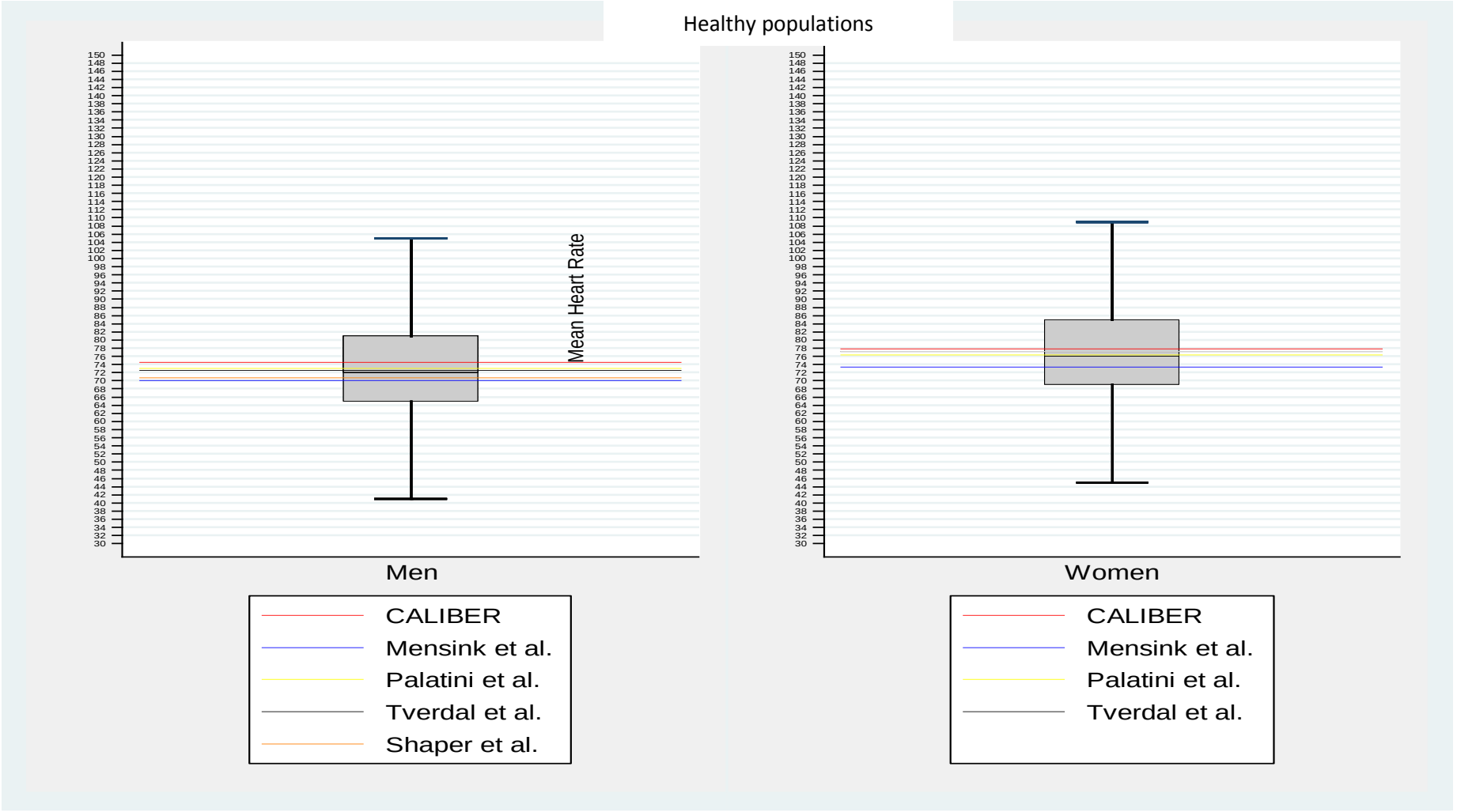


Table A3.7. Digit preference exploration in heart rate data in both healthy and CAD population of CALIBER

	Healthy individuals		CAD population	
Heart rate (bpm)	**Frequency**	**Percent**	**Frequency**	**Percent**
30	11	0.00	3	0.01
32	11	0.00	2	0.00
33	7	0.00	3	0.01
34	11	0.00	6	0.01
35	23	0.01	6	0.01
36	42	0.02	10	0.02
37	22	0.01	23	0.04
38	35	0.01	5	0.01
39	38	0.02	25	0.05
40	238	0.10	14	0.03
41	71	0.03	117	0.23
42	168	0.07	32	0.06
43	114	0.05	79	0.15
44	404	0.17	41	0.08
45	252	0.11	212	0.41
46	319	0.14	127	0.25
47	313	0.13	147	0.28
48	968	0.41	122	0.24
49	356	0.15	2	0.00
50	1,189	0.51	163	0.32
51	582	0.25	583	1.13
52	1,573	0.67	220	0.43
53	694	0.30	815	1.58
54	1,553	0.66	259	0.50
55	1,207	0.52	675	1.31
56	2,947	1.26	433	0.84
57	1,352	0.58	1,337	2.59
58	2,232	0.95	425	0.82
59	1,546	0.66	869	1.68
60	10,769	4.61	413	0.80
61	1,887	0.81	4,461	8.64
62	3,711	1.59	491	0.95
63	2,183	0.93	1,044	2.02
64	8,674	3.71	498	0.96
65	3,138	1.34	2,910	5.63
66	5,074	2.17	701	1.36
67	2,822	1.21	1,196	2.32
68	11,422	4.89	483	0.94
69	2,950	1.26	2,863	5.54
70	12,759	5.46	471	0.91
71	3,032	1.30	2,879	5.57
72	16,479	7.05	447	0.87
73	2,873	1.23	3,467	6.71
74	5,965	2.55	376	0.73
75	3,821	1.63	975	1.89
76	11,846	5.07	558	1.08
77	3,018	1.29	2,360	4.57
78	8,103	3.47	404	0.78
79	2,653	1.13	1,525	2.95
80	21,983	9.40	357	0.69
81	2,364	1.01	4,774	9.24
82	4,419	1.89	292	0.57
83	2,251	0.96	770	1.49
84	8,080	3.46	265	0.51

85	2,482	1.06	1,523	2.95
86	3,282	1.40	341	0.66
87	1,804	0.77	490	0.95
88	8,062	3.45	215	0.42
89	1,508	0.65	1,465	2.84
90	4,980	2.13	190	0.37
91	1,209	0.52	822	1.59
92	3,086	1.32	133	0.26
93	1,046	0.45	494	0.96
94	1,343	0.57	131	0.25
95	1,123	0.48	195	0.38
96	3,105	1.33	118	0.23
97	718	0.31	470	0.91
98	1,392	0.60	82	0.16
99	715	0.31	200	0.39
100	4,664	1.99	69	0.13
101	615	0.26	745	1.44
102	819	0.35	70	0.14
103	552	0.24	102	0.20
104	1,277	0.55	62	0.12
105	550	0.24	169	0.33
106	532	0.23	64	0.12
107	380	0.16	66	0.13
108	777	0.33	45	0.09
109	360	0.15	123	0.24
110	1,132	0.48	33	0.06
111	296	0.13	163	0.32
112	699	0.30	26	0.05
113	213	0.09	80	0.15
114	274	0.12	23	0.04
115	201	0.09	29	0.06
116	284	0.12	28	0.05
117	184	0.08	29	0.06
118	194	0.08	18	0.03
119	136	0.06	25	0.05
120	1,477	0.63	10	0.02
121	78	0.03	229	0.44
122	105	0.04	7	0.01
123	83	0.04	14	0.03
124	138	0.06	5	0.01
125	106	0.05	16	0.03
126	99	0.04	15	0.03
127	47	0.02	16	0.03
128	118	0.05	7	0.01
129	50	0.02	14	0.03
130	211	0.09	3	0.01
131	36	0.02	26	0.05
132	99	0.04	4	0.01
133	33	0.01	13	0.03
134	32	0.01	1	0.00
135	42	0.02	2	0.00
136	55	0.02	10	0.02
137	15	0.01	8	0.02
138	22	0.01	3	0.01
139	8	0.00	3	0.01
140	191	0.08	3	0.01
141	10	0.00	34	0.07
142	16	0.01	3	0.01
143	7	0.00	1	0.00
144	34	0.01	6	0.01

145	22	0.01	2	0.00
146	19	0.01	2	0.00
147	3	0.00	2	0.00
148	24	0.01	2	0.00
149	1	0.00	1	0.00
150	61	0.03	16	0.03
Total	**233,790**	**100.00**	**51,703**	**100**

Table A3.8 **Digit preference exploration in heart rate data in measurements recorded on the same day as blood pressure and not recorded on the same day**

	HR measured on the same day as BP		HR not measured on the same day as BP	
Heart rate	Frequency	Percent	Frequency	Percent
30	7	0.00	11	0.00
31	0	0.00	0	0.00
32	3	0.00	11	0.00
33	2	0.00	7	0.00
34	5	0.00	11	0.00
35	14	0.01	23	0.01
36	26	0.02	42	0.02
37	15	0.01	22	0.01
38	19	0.01	35	0.02
39	18	0.01	38	0.02
40	122	0.08	237	0.10
41	48	0.03	69	0.03
42	95	0.06	167	0.07
43	78	0.05	112	0.05
44	236	0.15	401	0.17
45	148	0.09	252	0.11
46	192	0.12	319	0.14
47	227	0.14	309	0.13
48	594	0.37	964	0.42
49	234	0.14	352	0.15
50	747	0.46	1,182	0.51
51	401	0.25	576	0.25
52	1,005	0.62	1,561	0.67
53	485	0.30	688	0.30
54	1,009	0.62	1,544	0.67
55	822	0.51	1,200	0.52
56	1,909	1.18	2,928	1.26
57	996	0.61	1,342	0.58
58	1,511	0.93	2,222	0.96
59	1,129	0.70	1,536	0.66
60	6,606	4.07	10,700	4.61
61	1,370	0.84	1,871	0.81
62	2,600	1.60	3,674	1.58
63	1,617	1.00	2,165	0.93
64	5,743	3.54	8,608	3.71
65	2,285	1.41	3,112	1.34
66	3,591	2.21	5,040	2.17
67	2,177	1.34	2,789	1.20
68	7,993	4.92	11,309	4.87
69	2,277	1.40	2,929	1.26
70	8,673	5.34	12,653	5.45
71	2,306	1.42	3,011	1.30
72	11,124	6.85	16,355	7.05
73	2,199	1.35	2,848	1.23
74	4,355	2.68	5,910	2.55
75	2,894	1.78	3,787	1.63
76	8,375	5.16	11,765	5.07
77	2,316	1.43	2,996	1.29
78	5,733	3.53	8,059	3.47
79	2,050	1.26	2,632	1.13
80	14,336	8.83	21,826	9.41
81	1,805	1.11	2,350	1.01
82	3,195	1.97	4,391	1.89

83	1,739	1.07	2,229	0.96
84	5,523	3.40	8,024	3.46
85	1,837	1.13	2,456	1.06
86	2,362	1.45	3,257	1.40
87	1,375	0.85	1,787	0.77
88	5,489	3.38	7,999	3.45
89	1,157	0.71	1,498	0.65
90	3,364	2.07	4,941	2.13
91	928	0.57	1,198	0.52
92	2,182	1.34	3,066	1.32
93	804	0.49	1,036	0.45
94	991	0.61	1,333	0.57
95	846	0.52	1,113	0.48
96	2,073	1.28	3,079	1.33
97	548	0.34	713	0.31
98	1,006	0.62	1,379	0.59
99	550	0.34	712	0.31
100	3,004	1.85	4,634	2.00
101	481	0.30	613	0.26
102	598	0.37	814	0.35
103	430	0.26	550	0.24
104	897	0.55	1,267	0.55
105	397	0.24	547	0.24
106	396	0.24	526	0.23
107	285	0.18	380	0.16
108	524	0.32	766	0.33
109	283	0.17	357	0.15
110	750	0.46	1,125	0.48
111	229	0.14	291	0.13
112	467	0.29	693	0.30
113	165	0.10	212	0.09
114	208	0.13	271	0.12
115	146	0.09	201	0.09
116	217	0.13	282	0.12
117	144	0.09	184	0.08
118	144	0.09	193	0.08
119	110	0.07	133	0.06
120	902	0.56	1,468	0.63
121	56	0.03	77	0.03
122	76	0.05	104	0.04
123	62	0.04	82	0.04
124	101	0.06	137	0.06
125	66	0.04	106	0.05
126	70	0.04	97	0.04
127	34	0.02	47	0.02
128	79	0.05	117	0.05
129	40	0.02	50	0.02
130	125	0.08	210	0.09
131	34	0.02	35	0.02
132	64	0.04	99	0.04
133	21	0.01	32	0.01
134	23	0.01	32	0.01
135	26	0.02	42	0.02
136	31	0.02	55	0.02
137	13	0.01	15	0.01
138	13	0.01	22	0.01
139	7	0.00	8	0.00
140	115	0.07	191	0.08
141	7	0.00	10	0.00
142	11	0.01	16	0.01

143	2	0.00	7	0.00
144	19	0.01	34	0.01
145	12	0.01	22	0.01
146	12	0.01	19	0.01
147	2	0.00	3	0.00
148	17	0.01	24	0.01
149	0	0.00	1	0.00
150	34	0.02	61	0.03

Table A3.10. Overview of codes used to define each cardiovascular endpoints and data sources

Endpoint	CPRD – Read codes	MINAP – specific disease registry	HES – OPCS 4 hospital	HES – ICD 10 hospital diagnoses†	ONS – ICD 10 causes of death‡
Stable angina	G33..00: Stable Angina. G33z.00: Angina pectoris NOS + 25 other codes for diagnosis of stable angina pectoris. 30 codes for evidence of coronary artery disease at angiography (CT,MR, invasive or not specified). 151 Read codes for evidence of myocardial ischaemia (Resting ECG, exercise ECG, stress echo, radioisotope scan). Two or more successive prescriptions for anti-anginals.	nu	K40-K46: Coronary artery bypass graft. K49,K50 and K75: Percutaneous coronary intervention, not within 30 days of an acute coronary syndrome.	I20: Stable angina pectoris excluding unstable angina (I20.0).	nu

Unstable angina	G311.13/G311100: Unstable angina. G233200: Angina at rest. G311400: Worsening angina + 13 other codes.	Discharge diagnosis of unstable angina, no raised ST elevation. No raised troponin levels.	nu	I20.0: Unstable or worsening angina. I24: Acute ischaemic heart disease. I24.0: Coronary thrombosis not resulting in MI.	nu
Coronary heart disease not otherwise specified	G3…00: Ischaemic heart disease + 90 other codes including CHD NOS, chronic ischaemic heart disease, silent myocardial infarction.	nu	nu	CHD NOS, chronic ischaemic heart disease, silent MI (I25) excluding.I25.2, old MI.	nu
Acute Myocardial Infarction (MI)	G30X000: Acute ST segment elevation myocardial infarction. G307100: Acute non-ST segment elevation myocardial infarction. G30..14: Heart attack.	MI with or without ST elevation based on initial electrocardiogram findings, raised troponins and clinical diagnosis.	nu	I21: Acute myocardial infarction. I23: Current complications of acute MI.	nu
Unheralded coronary death	Any CVD excluded.	Any CVD excluded.	Any CVD excluded.	Any CVD excluded.	I20: Angina Pectoris. I21: Acute MI. I22: Subsequent MI. I23: Certain current complications following acute MI. I24: Other acute ischaemic

Heart failure	G58..00: Heart Failure + 92 other Read codes for heart failure diagnosis.	nu	Nu	I50: Heart failure. I11.0: Hypertensive heart disease with (congestive) heart failure. I13.0: Hypertensive heart and renal disease with (congestive) heart failure. I13.2: Hypertensive heart and renal disease with both	I50 Heart failure. I11.0 Hypertensive heart disease with (congestive) heart failure. I13.0: Hypertensive heart and renal disease with (congestive) heart failure. I13.2: Hypertensive heart and renal disease with both
Ventricular arrhythmias, cardiac arrest and sudden cardiac death	G574.00: Ventricular fibrillation and flutter. G757.00: Cardiac arrest + 35 other Read codes for ventricular fibrillation, asystole, cardiac arrest, cardiac resuscitation, electro-mechanical dissociation. G575100: Sudden cardiac death.	nu	X50: Implanted cardiac defibrillation device. K59: Implantation, revision and renewal of cardiac defibrillator.	I46: Cardiac arrest. I47.0: Re-entry ventricular arrhythmia. I47.2: Ventricular tachycardia.	I46: Cardiac arrest. I47.0: Re-entry ventricular arrhythmia. I47.2: Ventricular tachycardia.
Transient ischaemic attack	Fyu5500: [X]Other transient cerebral ischaemic attacks + related symptoms + 5 other Read codes.	nu	Nu	G458: Other transient cerebral ischaemic attacks and related syndromes. G459: Transient cerebral ischaemic attack, unspecified.	nu

Ischaemic stroke	G64..11: CVA – cerebral artery occlusion, G64..13 Stroke due to cerebral arterial occlusion. G6W..00: Cerebral infarction due to unspecified occlusion/stenosis of precerebral arteries. G6X..00: Cerebral infarction due to unspecified occlusion/stenosis of cerebral arteries plus 8 other codes.	nu	Stroke NOS with carotid endarterectomy or stenting within 90 days (OPCS codes L294, L295, L311, L314; Read codes 7A20300 + 4 others).	I63: Cerebral infarction.	I63: Cerebral infarction.
Subarachnoid haemorrhage	G601.00:Subarachnoid haemorrhage from carotid siphon and bifurcation. G602.00: Subarachnoid haemorrhage from middle cerebral artery. G60X.00: Subarachnoid haemorrhage from intracranial artery, unspecified.	nu		I60: Subarachnoid haemorrhage.	I60: Subarachnoid haemorrhage.
Intracerebralhaemorrhage	Gyu6F00: [x] Intracerebral haemorrhage in hemisphere, unspecified + 16 other codes.	nu		I61: Intracerebral haemorrhage.	I61: Intracerebral haemorrhage.

Stroke not otherwise specified	G66..11: Cerebrovascular accident unspecified + 14 other Read codes.	nu	U54.3: Delivery of rehabilitation for stroke.	I64: Stroke not specified as haemorrhage or infarction. G463-G467: Stroke syndromes.	I64: Stroke not specified as haemorrhage or infarction. I672: Cerebral atherosclerosis. I679: Cerebrovascular disease, unspecified.
Peripheral arterial disease	63 codes for lower limb peripheral arterial disease diagnosis (including diabetic PAD, gangrene, arterial thrombosis of the leg and intermittent claudication). Evidence of atherosclerosis of iliac and lower limb arteries based on angiography or Dopplers.	nu	L50-L54: Bypass, reconstruction and other open operations on iliac artery. L58-L60, L62: Bypass, reconstruction, transluminal operations or other open operations of femoral artery. L65: Revision of reconstruction of artery.	I70.2: atherosclerosis of arteries of extremities. I73.9: Peripheral vascular disease intermittent claudication E10.05,E11-E14: Peripheral complications of diabetes including gangrene, insulin dependent diabetes mellitus, non-insulin-dependent diabetes mellitus, malnutrition-related diabetes mellitus, other specified diabetes mellitus, unspecified diabetes mellitus.	I70.2: Atherosclerosis of arteries of extremities. I73.9: Peripheral vascular disease intermittent claudication. Peripheral complications of diabetes including gangrene 0.5 suffix of E10: Insulin dependent diabetes mellitus, E11: Non-insulin-dependent diabetes mellitus, E12: Malnutrition-related diabetes mellitus, E13: Other specified diabetes mellitus, E14: Unspecified diabetes mellitus

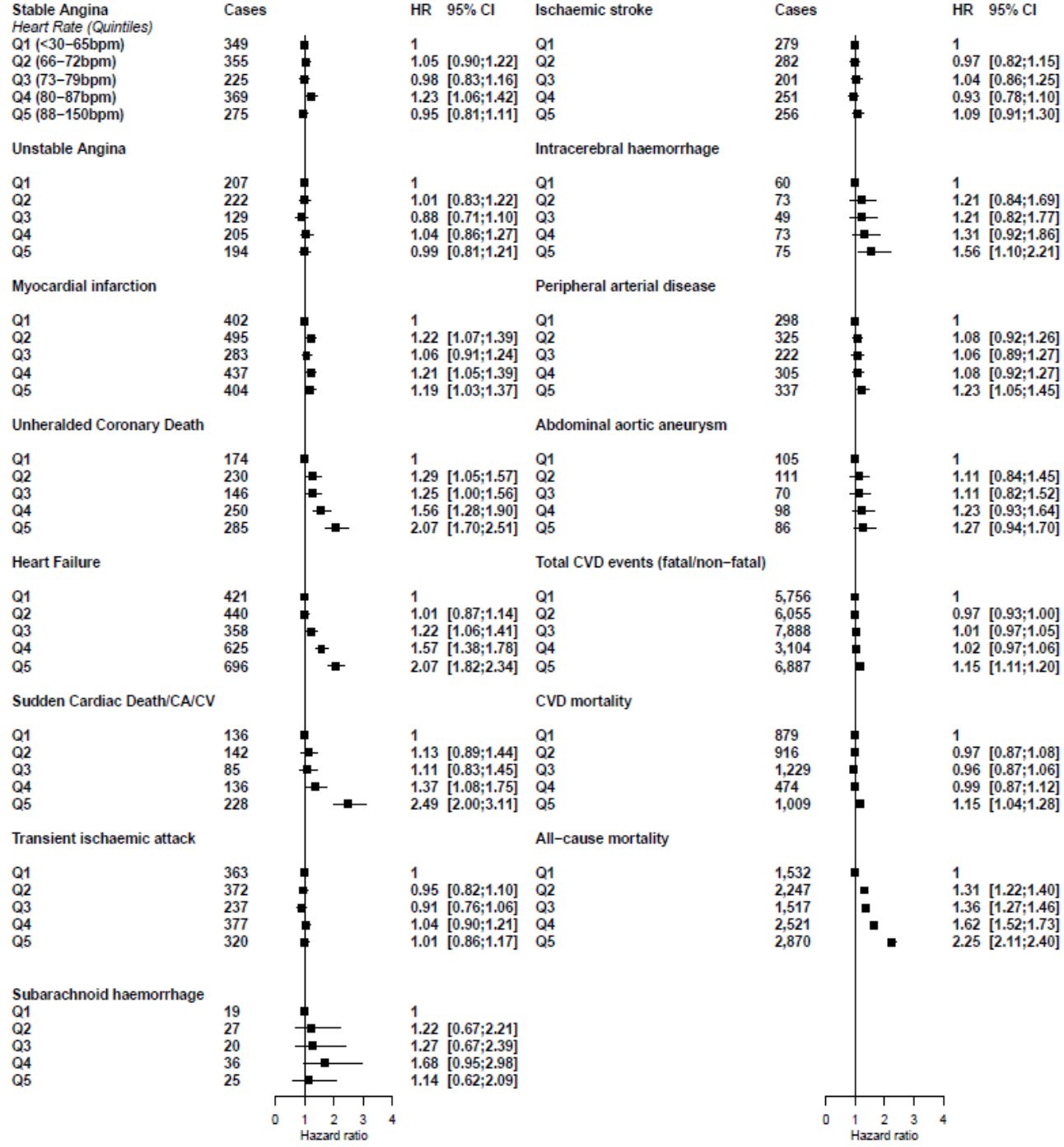
Abdominal aneurysm	**aortic**	G714.00: AAA without nu mention of rupture + 12 more codes for AAA diagnosis. 42 codes for AAA procedures.		L16: Extra anatomic bypass of aorta. L18-L23: Replacement of aneurysmal segment of aorta, bypass of segment of aorta, plastic repair of aorta. L25-L28: Transluminal or endovascular insertion of stent on aneurysmal segment of aorta.	I71.3: Ruptured AAA. 171.4: AAA without rupture. I71.5: Ruptured thoraco-abdominal aortic aneurysm. I71.6: Thoracoabdominal aortic aneurysm without mention of rupture. I71.8: Aortic aneurysm of unspecified site, ruptured. I71.9: Aortic aneurysm of unspecified site, without mention of rupture.	I71.3: Ruptured AAA. I71.4: AAA without rupture. I71.5: Ruptured thoraco-abdominal aortic aneurysm. I71.6: Thoracoabdominal aortic aneurysm without mention of rupture. I71.8: Aortic aneurysm of unspecified site, ruptured. I71.9: Aortic aneurysm of unspecified site, without mention of rupture.

11. Appendix 4

Table A4.1 Hierarchy of endpoints severeness

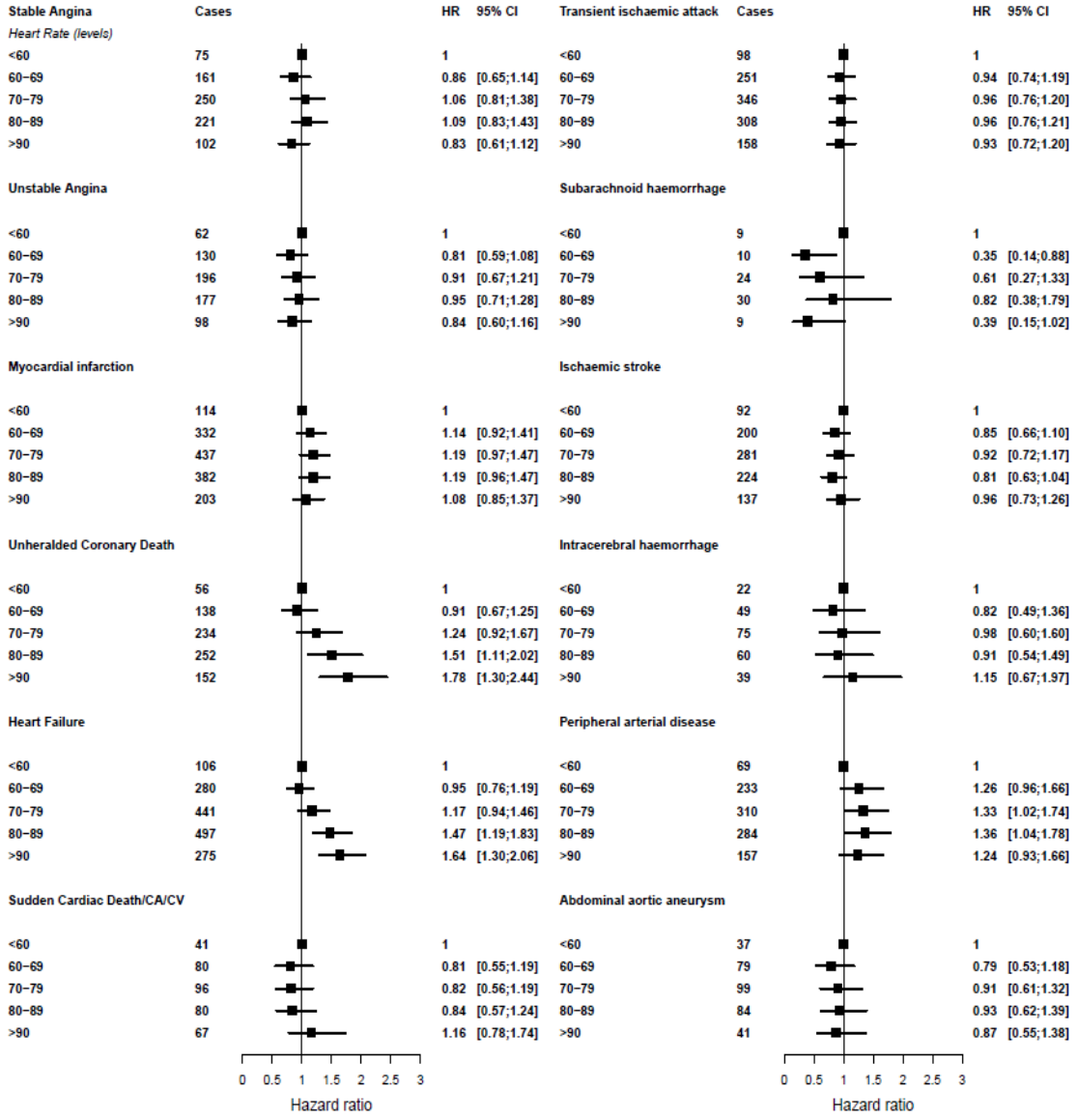
1	Sudden cardiac death / ventricular fibrillation / cardiac arrest
2	Heart failure
3	Unheralded coronary death
4	Myocardial infarction
5	Unstable angina
6	Stable angina
7	Coronary disease, not otherwise specified
8	Abdominal aortic aneurysm
9	Peripheral arterial disease
10	Subarachnoid haemorrhage
11	Haemorrhagic stroke
12	Ischaemic stroke
13	Transient Ischaemic Attack
14	Other deaths (Cancer, COPD, Liver disease)

Figure A4.2. Hazard ratios (95% CIs) for the association between heart rate quintiles (vs. reference 1st Q) in 12 cardiovascular diseases and mortality



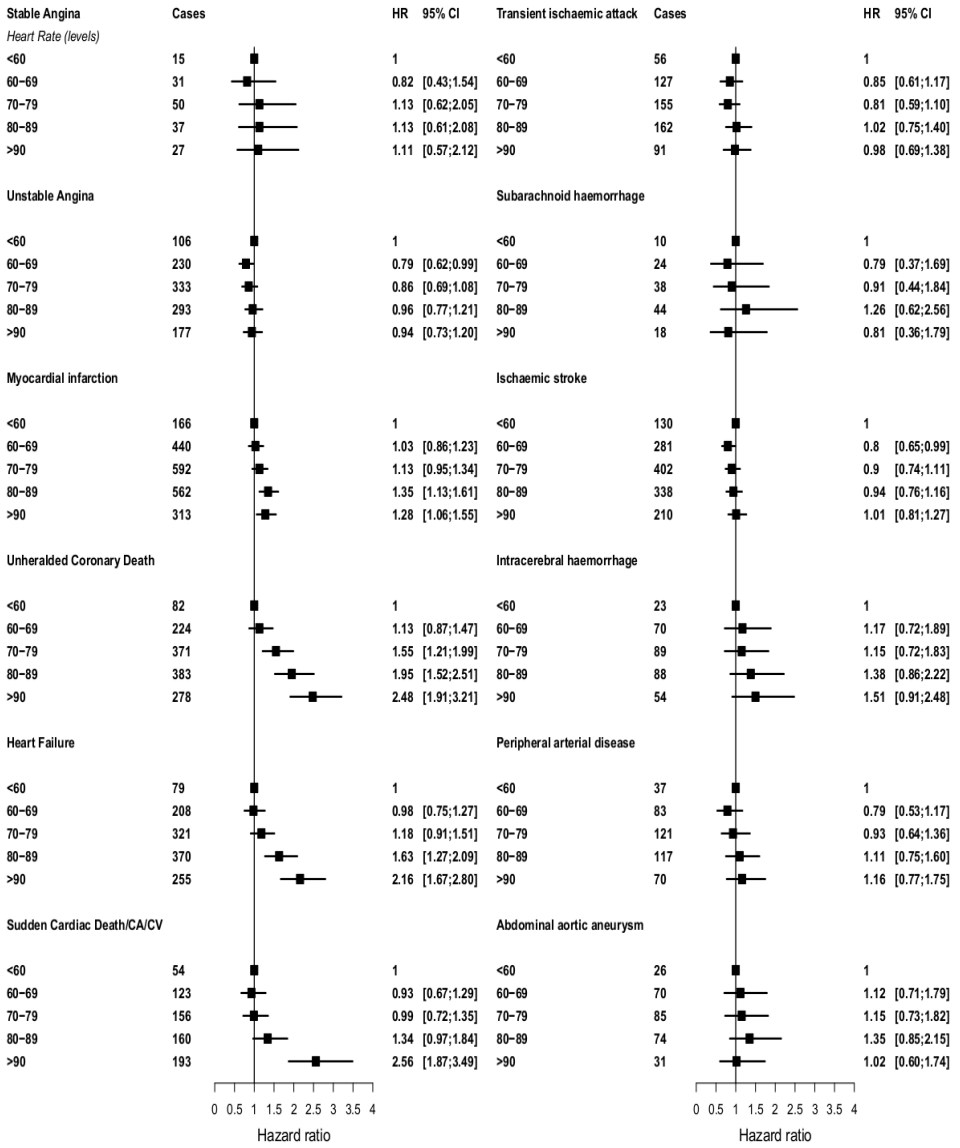
Note: Hazard ratios adjusted for sex, age, quadratic age, interaction between heart rate and sex, social deprivation, smoking, systolic blood pressure, BP medication, total cholesterol, HDL, LDL, diabetes II and BMI and stratification by primary care practice (data imputed); CI, confidence interval; HR, hazard ratios; CA, Cardiac Arrest; CV, Cardioversion

Figure A4.3 Multivariable ajusted hazard ratios between heart rate (top vs bottom level) and the initial presentation of 12 cardiovascular diseases after exclusion of cardiovascular events during the first year after heart rate measurement



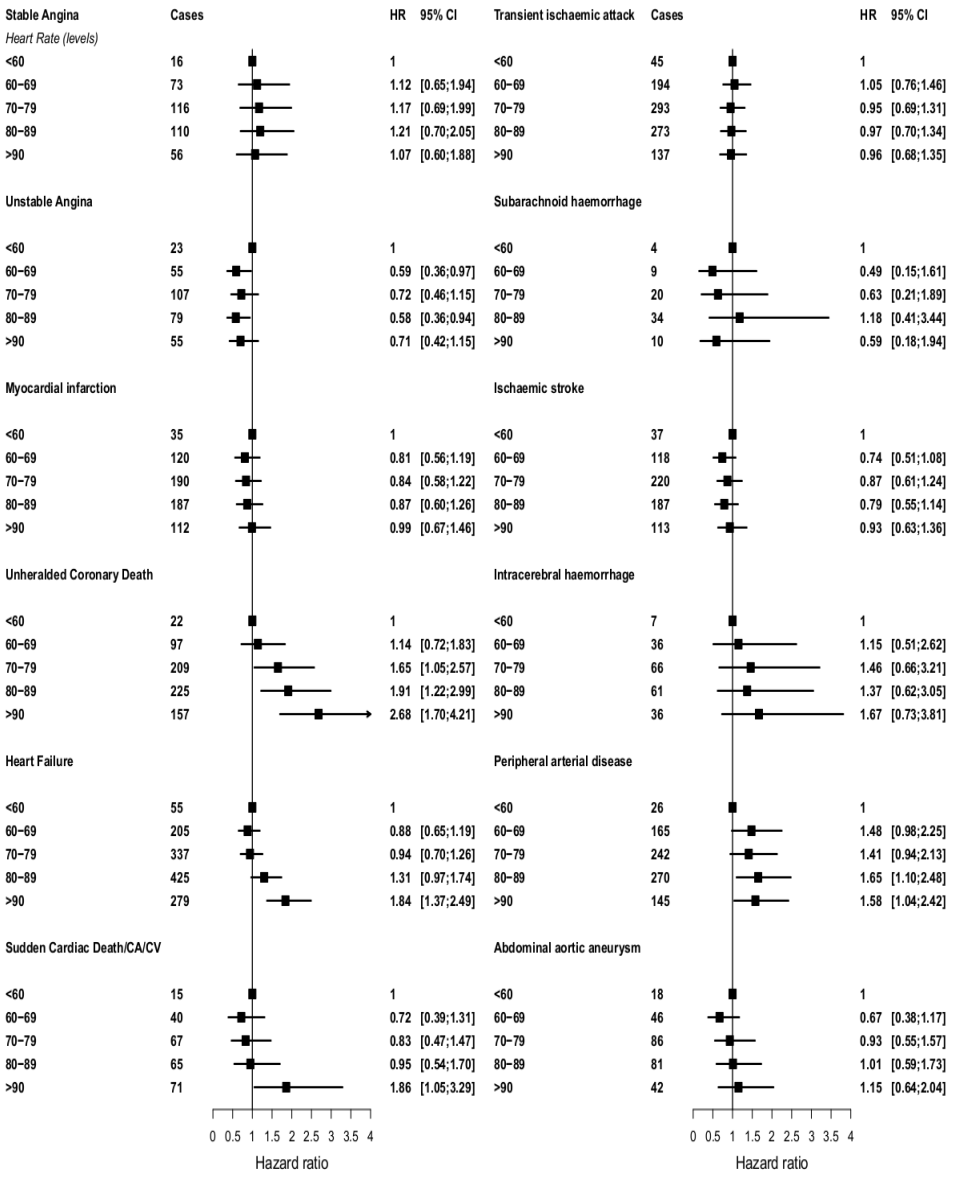
Note: Hazard ratios adjusted for sex, age, quadratic age, interaction between heart rate and sex, social deprivation, smoking, systolic blood pressure, BP medication, total cholesterol, HDL, LDL, diabetes II and BMI and stratification by primary care practice (data imputed); CI, confidence interval; HR, hazard ratios; CA, Cardiac Arrest; CV, Cardioversion

Figure A4.4 Hazard ratios for the association of heart rate with 12 CVDs using only secondary care data (after exclusion of CPRD data)



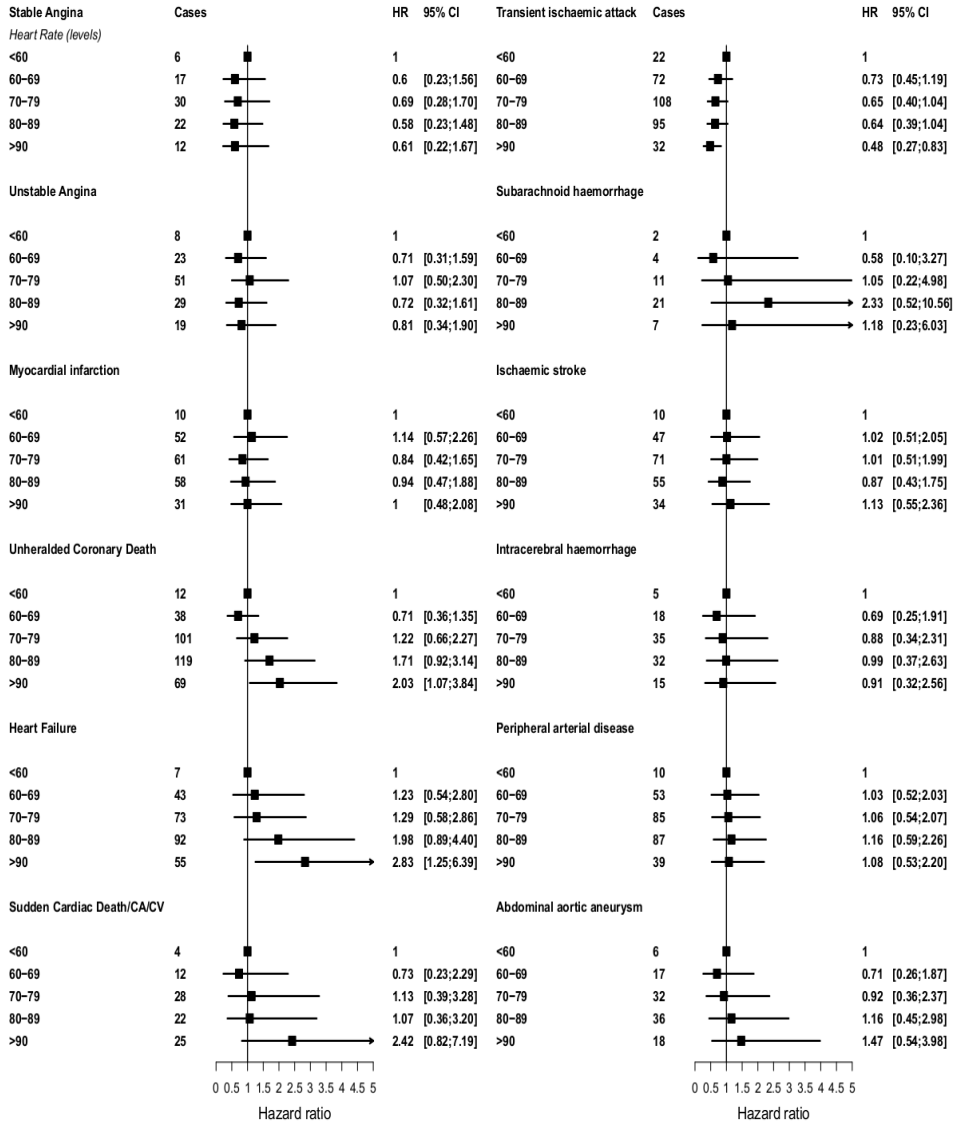
Note: Hazard ratios adjusted for sex, age, quadratic age, interaction between heart rate and sex, social deprivation, smoking, systolic blood pressure, BP medication, total cholesterol, HDL, LDL, diabetes II and BMI and stratification by primary care practice (data imputed); CI, confidence interval; HR, hazard ratios adjusted for sex and age; CA, Cardiac Arrest; CV, Cardioversion

Figure A4.5 Multivariable adjusted hazard ratios for the association between heart rate (top vs bottom quintile) and the initial presentation of 12 cardiovascular diseases in patients without beta-blockers intake reports



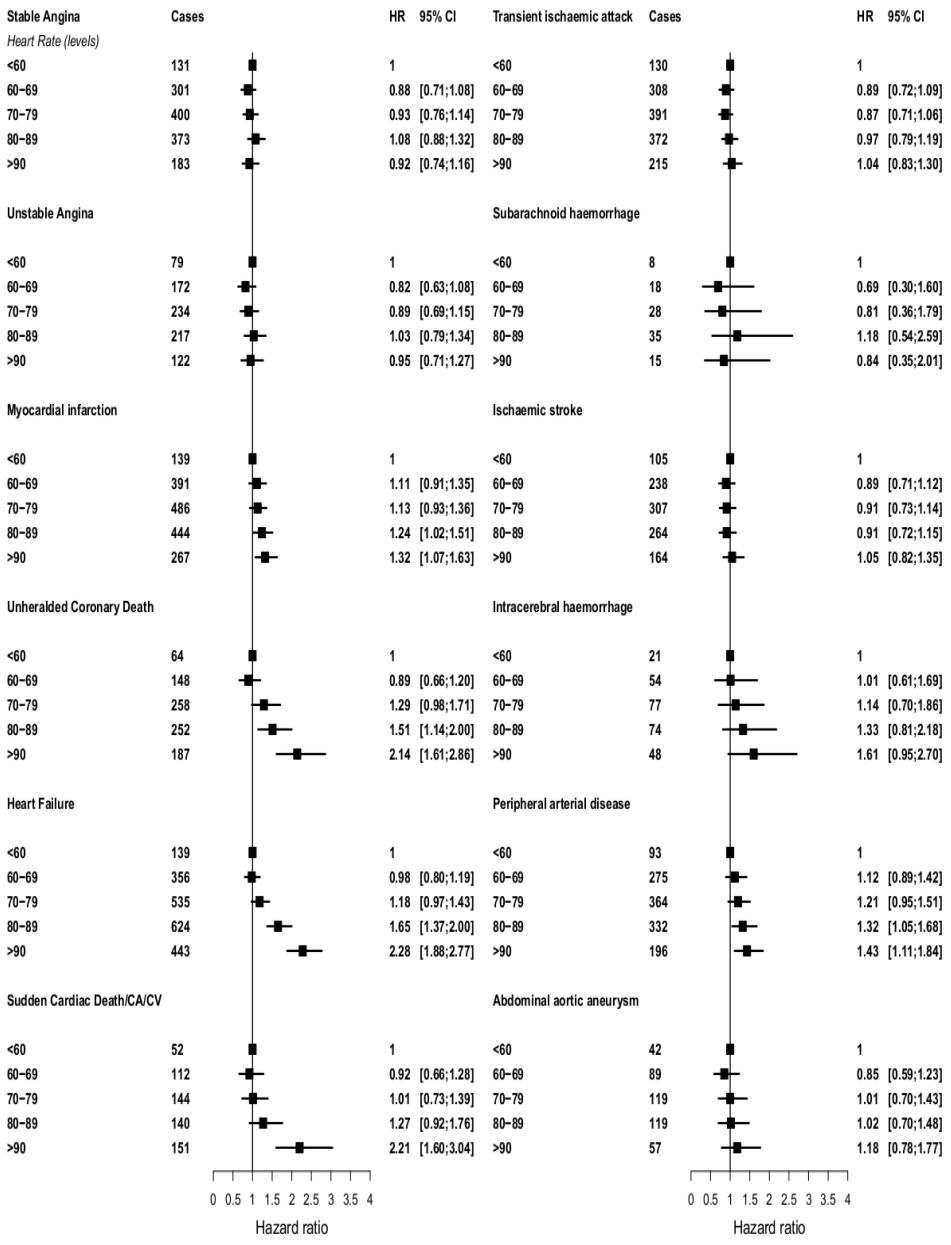
Note: Hazard ratios adjusted for sex, age, quadratic age, interaction between heart rate and sex, social deprivation, smoking, systolic blood pressure, BP medication, total cholesterol, HDL, LDL, diabetes II and BMI and stratification by primary care practice (data imputed); CI, confidence interval; HR, hazard ratios; CA, Cardiac Arrest; CV, Cardioversion

Figure A4.6 Multivariable adjusted hazard ratios for the association between heart rate (top vs bottom level) and the initial presentation of 12 cardiovascular diseases in patients without blood pressure medication intake reports



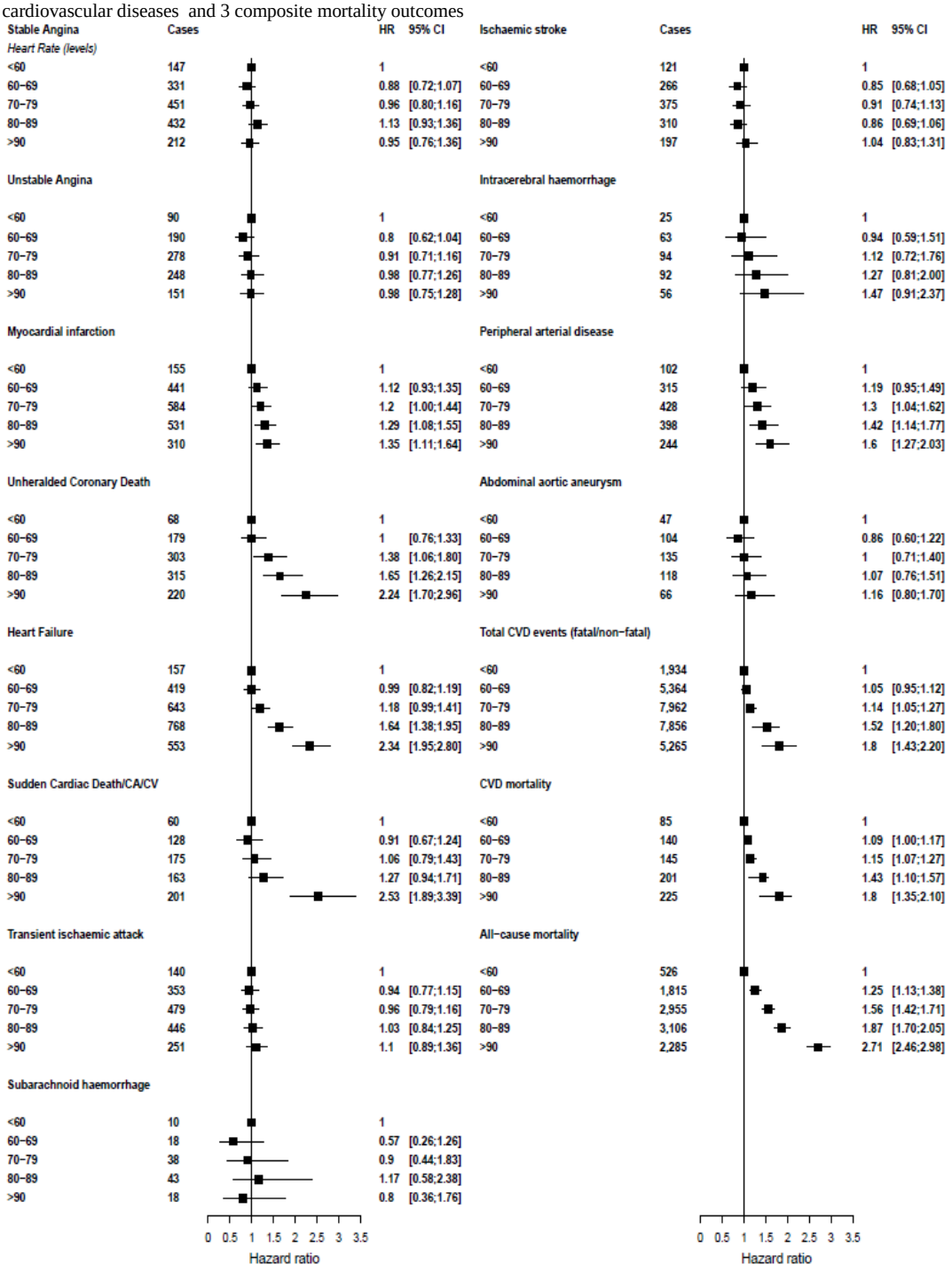
Note: Hazard ratios adjusted for sex, age, quadratic age, interaction between heart rate and sex, social deprivation, smoking, systolic blood pressure, BP medication, total cholesterol, HDL, LDL, diabetes II and BMI and stratification by primary care practice (data imputed); CI, confidence interval; HR, hazard ratios; CA, Cardiac Arrest; CV, Cardioversion

Figure A4.7 Hazard ratios for the association between heart rate (top vs bottom level) and the initial presentation of 12 cardiovascular diseases in patients with heart rate and systolic blood measurements reported on the same day



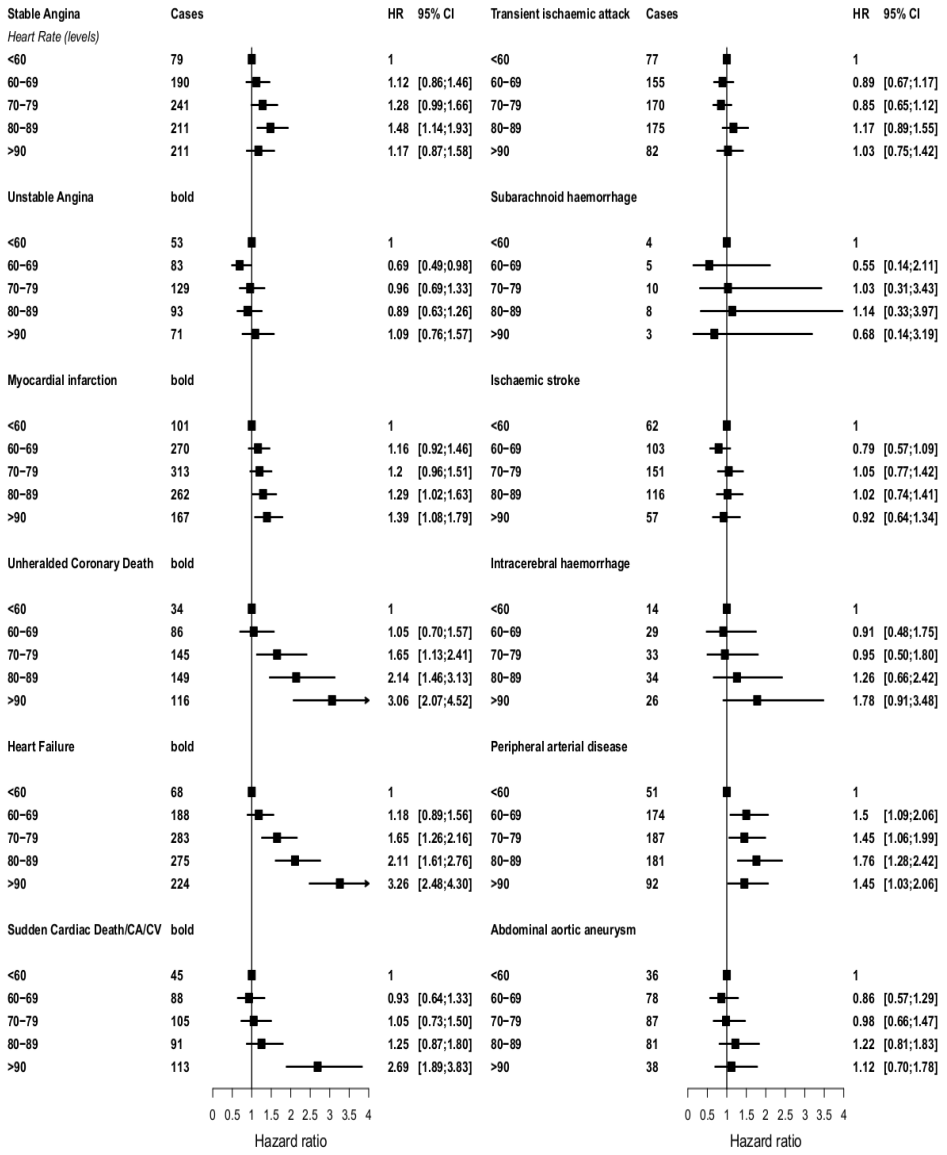
Note: Hazard ratios adjusted for sex, age and BP medication and stratification by primary care practice; CI, confidence interval; HR, hazard ratios; CA, Cardiac Arrest; CV, Cardioversion

Figure A4.8 Age and sex adjusted hazard ratios (95% CIs) for the association between heart rate and the initial presentation of 12 cardiovascular diseases and 3 composite mortality outcomes



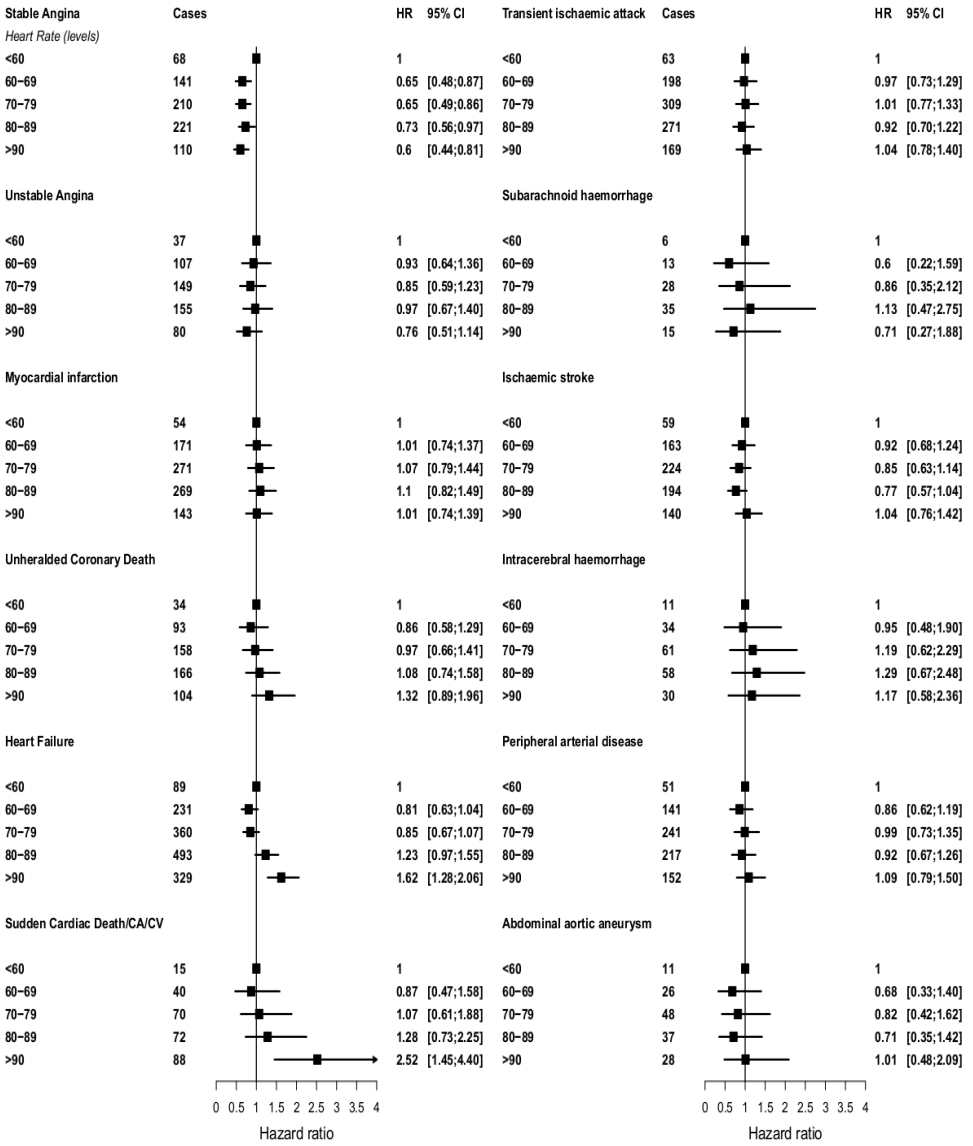
Note: CI, confidence interval; HR, hazard ratios adjusted for sex and age; CA, Cardiac Arrest; CV, Cardioversion

Figure A4.11 Multivariable ajsuted hazard ratios (95% CIs) for the association between heart rate levels (vs. reference L1) in 12 cardiovascular diseases in men



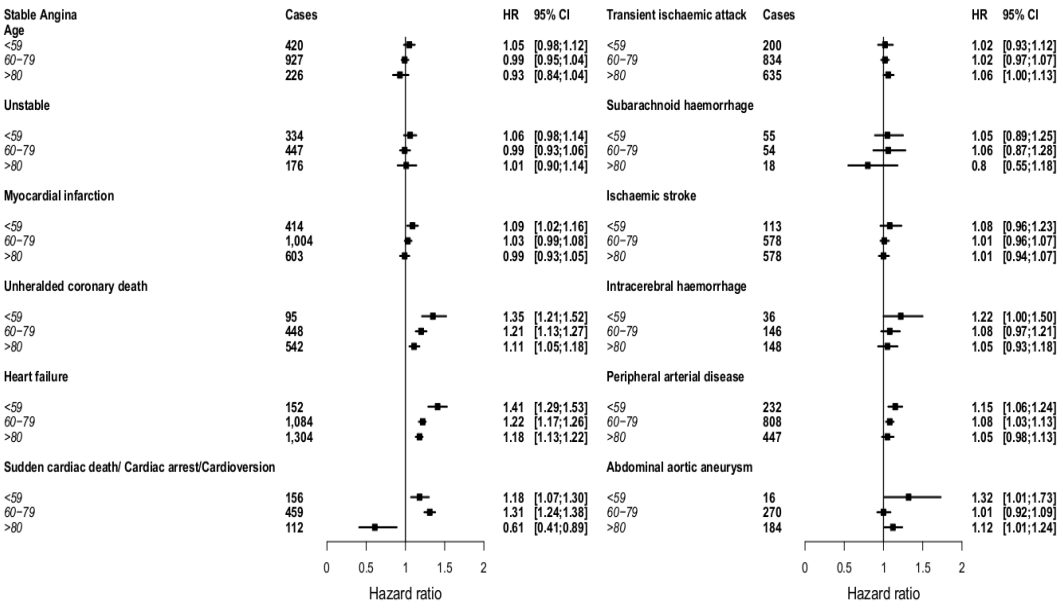
Note: Hazard ratios adjusted for sex, age, quadratic age, interaction between heart rate and sex, social deprivation, smoking, systolic blood pressure, BP medication, total cholesterol, HDL, LDL, diabetes II and BMI and stratification by primary care practice (data imputed); CI, confidence interval; HR, hazard ratios; CA, Cardiac Arrest; CV, Cardioversion

Figure A4.12 Multivariable ajsuted hazard ratios (95% CIs) for the association between heart rate levels (vs. reference L1) in 12 cardiovascular diseases in women



Note: Hazard ratios adjusted for sex, age, quadratic age, interaction between heart rate and sex, social deprivation, smoking, systolic blood pressure, BP medication, total cholesterol, HDL, LDL, diabetes II and BMI and stratification by primary care practice (data imputed); CI, confidence interval; HR, hazard ratios; CA, Cardiac Arrest; CV, Cardioversion

Figure A4.13. Multivariable ajsuted hazard ratios (95% CIs) for the for the association between heart rate and 12 cardiovascular diseases (by age group)



Note: Heart rate measured in 10 bpm increments. Hazard ratios adjusted for sex, interaction between heart rate and sex, social deprivation, smoking, systolic blood pressure, BP medication, total cholesterol, HDL, LDL, diabetes II and BMI and stratification by primary care practice (data imputed); CI, confidence interval; HR, hazard ratios; CA, Cardiac Arrest; CV, Cardioversion

12. Appendix 5

A5.1. Study Flow diagram

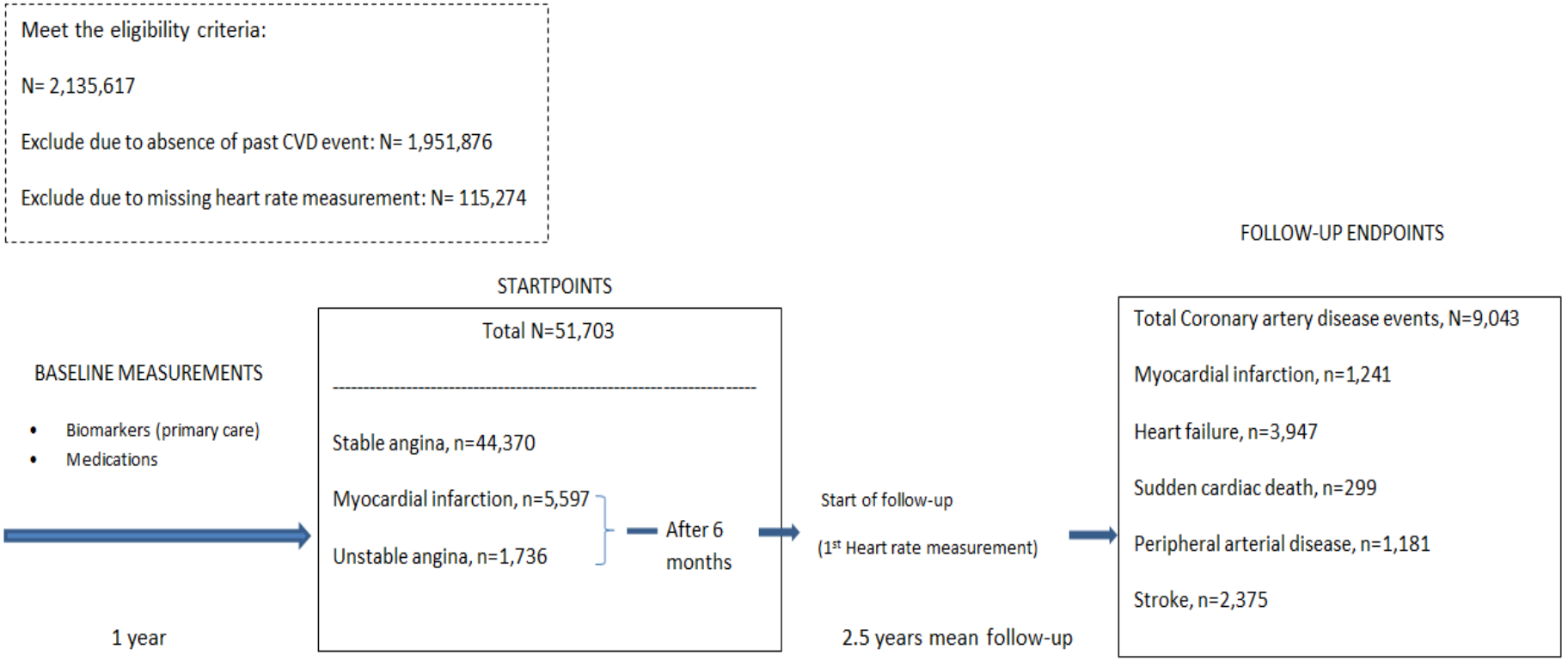


Table A5.2. Baseline characteristics of stable CAD patients by previous coronary artery disease event (cause of study entry)

	All stable patients (N=51,703)	Stable angina (N=44,370)	Stable after unstable angina (N=1,736)	Stable after MI (N=5,597)	% recorded
Demographic factors					
Age at entry (years)	72.3 (11.4)	72.1 (11.4)	71.5 (12.3)	73.6 (11.1)	100%
Female	22,809 (44.1%)	20,141 (45.39)	812 (46.7)	1,856 (33.2)	100 %
White Ethnicity	37,980 (80.1%)	32,529 (73.3)	1,369 (78.8)	4,082 (72.9)	91.66%
Deprivation (most deprived quintile)	10,300 (19.98%)	8,941 (20.1)	351 (20.2)	1,008 (18.0)	99.72%
Clinical factors					
Heart rate (continuous) (bpm)	72.2 (14.5)	72.2 (14.4)	72.7 (14.7)	71.6 (14.5)	100%
Systolic blood pressure, (mmHg)	138.3 (19.9)	138.5 (20.7)	136.7 (20.3)	137.2 (20.7)	85.6%
Diastolic blood pressure, (mmHg)	76.8 (10.8)	76.9 (10.7)	76.5 (11.4)	76.3 (11.1)	85.6%
High density lipoproteins, (mmol/L)	85.3 (40.0)	85.5 (40.1)	84.2 (38.7)	83.9 (39.8)	53.5%
Low density lipoproteins, (mmol/L)	2.5 (0.92)	2.50 (0.92)	2.43 (0.94)	2.44 (0.86)	41.3%
Total cholesterol (mmol/L)	44.7 (10.8)	44.9 (10.9)	43.6 (11.0)	43.9 (10.1)	71.0%
Triglycerides (mmol/L)	1.59 (1.04)	1.60 (1.05)	1.57 (0.90)	1.53 (0.95)	51.0%
Creatinine (μmol/L)	102.5 (64.8)	101.7 (67.3)	105.6 (59.8)	107.4 (41.5)	19.0%
Haemoglobin (g/dL)	13.5 (1.64)	13.5 (1.62)	13.3 (1.76)	13.5 (1.75)	54.3%
Lymphocytes (10^9 /L)	2.03 (1.26)	2.04 (1.26)	2.05 (1.08)	1.98 (1.29)	48.7%
Neutrophils (10^9 /L)	4.60 (1.89)	4.58 (1.87)	4.78 (2.14)	4.68 (1.98)	48.7%
Behavioural/Environmental factors					
Non-smokers	19,713 (38.1)	17,260 (40.8)	645 (38.8)	1,808 (34.0)	
Ex-smoker	22,670 (43.8)	19,260 (45.5)	778 (46.9)	2,632 (49.6)	95.2%
Current smoker	6,177 (11.9)	5,179 (12.2)	217 (13.0)	781 (14.7)	
BMI (kg/m^2)	28.2 (5.48)	28.3 (5.49)	28.8 (5.76)	27.3 (5.17)	46.3%
Family history of CHD	1,013 (1.96)	916 (2.06)	18 (1.04)	79 (1.41)	100%

Diabetes type II	6,087 (11.7)	5,190 (11.7)	230 (13.2)	667 (11.9)	100%
Current alcohol drinker	9,367 (18.1)	8,114 (18.3)	264 (15.2)	989 (17.7)	32.1%
Hypertensives	2,791 (6.30)	2,399 (5.41)	112 (6.45)	280 (5.00)	85.6%
Medication					
Beta-blockers	26,212 (50.7)	22,400 (50.5)	908 (52.3)	2,904 (51.8)	100%
Antianginal medication*	34,040 (65.8)	30,375 (68.5)	1,123 (64.7)	2,542 (45.4)	100%
BP medication	38,871 (75.2)	33,308 (75.1)	1,376 (79.3)	4,187 (74.8)	100%
Anti-arrhythmic medication	4,241 (8.20)	3,583 (8.08)	186 (10.7)	472 (8.43)	100%
Statins					
Aspirin					

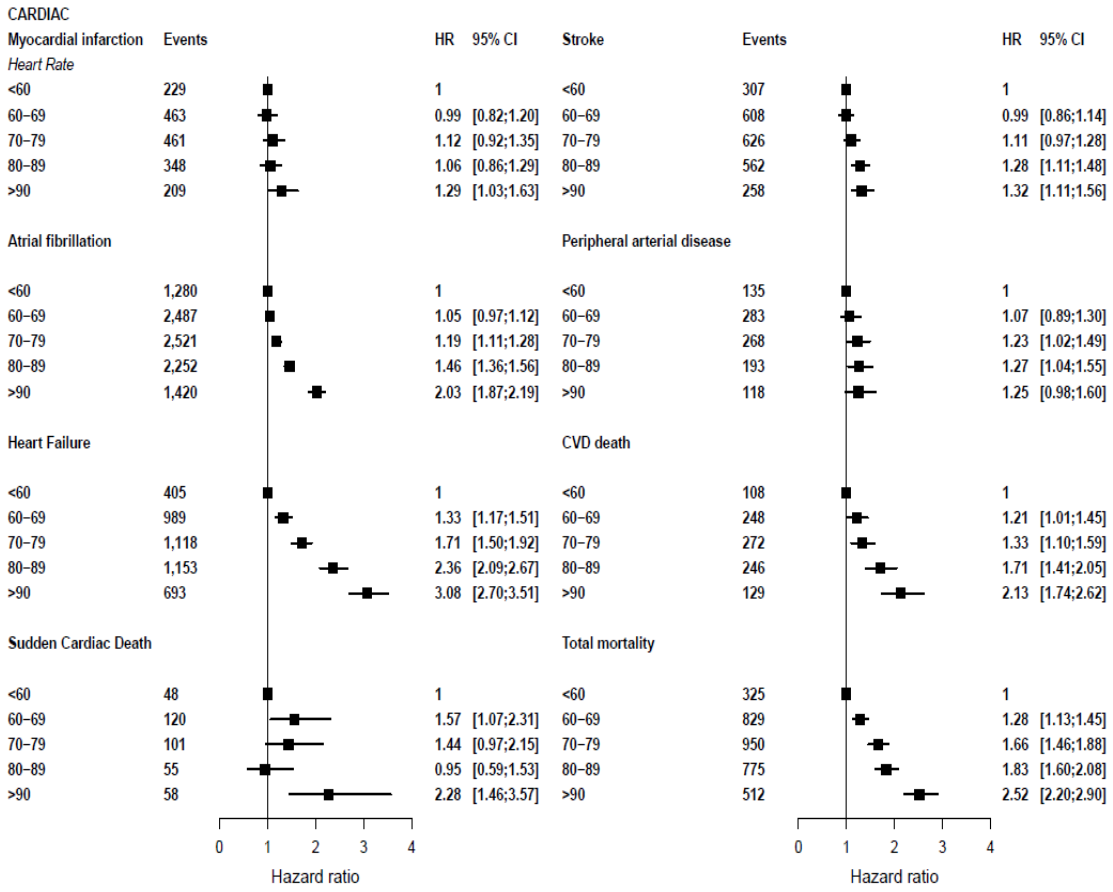
Note: Blood pressure (BP) medication consists of BNF codes that refer to diuretics, b-blockers, calcium channel blockers, hypertension and heart failure medication and ACE inhibitors intake.
For categorical variables the means represent % proportions. *Antianginal medication consists of: Ca channel blockers, nitrates, vasodilators and other angina medication. Mean (SD) for continuous measurements, N(%) for categorical data

Table A5.3 Multivariable adjusted hazard ratios for the association between heart rate levels and the subsequent fatal and non-fatal events among people with stable coronary artery disease (by coronary disease type at baseline)

Prior stable angina							
Primary outcomes							
Myocardial infarction	999	REF	0.98(0.79-1.21)	1.13(0.91-1.39)	1.06(0.84-1.33)	1.26(0.97-1.63)	1.04 (0.99-1.08)
Heart Failure	3,235	REF	1.29(1.13-1.49)	1.63(1.42-1.87)	2.32(2.02-2.66)	3.02(2.61-3.50)	1.22 (1.19-1.24)
SCD-CA	227	REF	1.21(0.79-1.86)	1.21(0.78-1.89)	0.94(0.56-1.56)	1.86(1.12-3.08)	1.08 (0.99-1.18)
Peripheral arterial disease	1,009	REF	1.08(0.88-1.33)	1.15(0.93-1.42)	1.18(0.95-1.47)	1.08(0.83-1.42)	1.02 (0.97-1.06)
All cause stroke	2,010	REF	1.02(0.87-1.19)	1.11(0.95-1.30)	1.29(1.10-1.52)	1.33(1.10-1.61)	1.07 (1.04-1.10)
CVD death	1,339	REF	1.16(0.94-1.41)	1.24(1.01-1.52)	1.62(1.31-1.99)	2.05(1.63-2.58)	1.14 (1.10-1.18)
Total mortality	2,940	REF	1.23(1.07-1.42)	1.52(1.32-1.74)	1.71(1.48-1.97)	2.26(1.94-2.63)	1.15 (1.12-1.18)
Secondary outcomes							
Atrial fibrillation	8,365	REF	1.04(0.97-1.12)	1.17(1.08-1.26)	1.45(1.34-1.57)	2.00(1.84-2.18)	1.15 (1.13-1.16)
Prior MI							
Primary outcomes							
Myocardial infarction	194	REF	1.05(0.66-1.65)	0.80(0.49-1.30)	0.91(0.54-1.52)	1.15(0.63-2.10)	1.01 (0.91-1.12)
Heart Failure	583	REF	1.32(0.95-1.81)	1.79(1.31-2.46)	2.17(1.56-3.00)	2.85(1.97-4.11)	1.19 (1.13-1.26)
SCD-CA	64	REF	7.75(1.91-31.46)	5.20(1.22-22.07)	1.55(0.28-8.61)	8.22(1.69-40.01)	0.97 (0.80-1.18)
Peripheral arterial disease	146	REF	0.82(0.46-1.47)	1.19(0.67-2.09)	1.26(0.69-2.32)	1.21(0.57-2.55)	1.10 (0.98-1.24)
All cause stroke	283	REF	1.02(0.67-1.53)	1.09(0.71-1.65)	1.30(0.84-2.00)	1.32(0.78-2.25)	1.04 (0.95-1.13)
CVD death	247	REF	1.26(0.79-2.01)	1.34(0.84-2.14)	1.55(0.96-2.51)	1.75(0.97-3.13)	1.12 (1.02-1.23)
Total mortality	465	REF	1.69(1.16-2.46)	2.09(1.44-3.04)	2.09(1.41-3.09)	2.84(1.83-4.38)	1.14 (1.07-1.21)
Secondary outcomes							
Atrial fibrillation	1,183	REF	1.03(0.83-1.27)	1.28(1.04-1.58)	1.42(1.14-1.76)	2.34(1.84-2.98)	1.13 (1.09-1.17)
Prior unstable angina							
Primary outcomes							
Myocardial infarction	48	REF	0.76(0.23-2.45)	1.04(0.35-3.06)	0.47(0.13-1.76)	0.32(0.05-1.85)	0.81 (0.61-1.08)
Heart Failure	129	REF	1.78(0.80-3.93)	1.78(0.79-3.96)	2.43(1.07-5.51)	3.30(1.37-7.95)	1.17 (1.03-1.33)
SCD-CA	8	REF	-	-	-	-	-
Peripheral arterial disease	26	REF	1.50(0.24-9.46)	2.64(0.43-16.24)	1.58(0.21-11.97)	2.21(0.31-16.02)	1.13 (0.85-1.49)
All cause stroke	82	REF	0.85(0.37-1.94)	1.03(0.46-2.31)	0.94(0.39-2.28)	0.67(0.21-2.20)	0.97 (0.81-1.18)
CVD death	56	REF	5.88(0.72-48.14)	11.05(1.32-92.50)	6.19(0.73-52.58)	11.62(1.26-107.25)	1.18 (0.95-1.46)
Total mortality	120	REF	0.81(0.38-1.70)	1.38(0.68-2.82)	0.62(0.27-1.42)	2.64(1.21-5.78)	1.14 (1.02-1.29)
Secondary outcomes							
Atrial fibrillation	412	REF	1.15(0.78-1.72)	1.19(0.80-1.79)	1.45(0.96-2.20)	2.02(1.27-3.20)	1.14 (1.06-1.23)

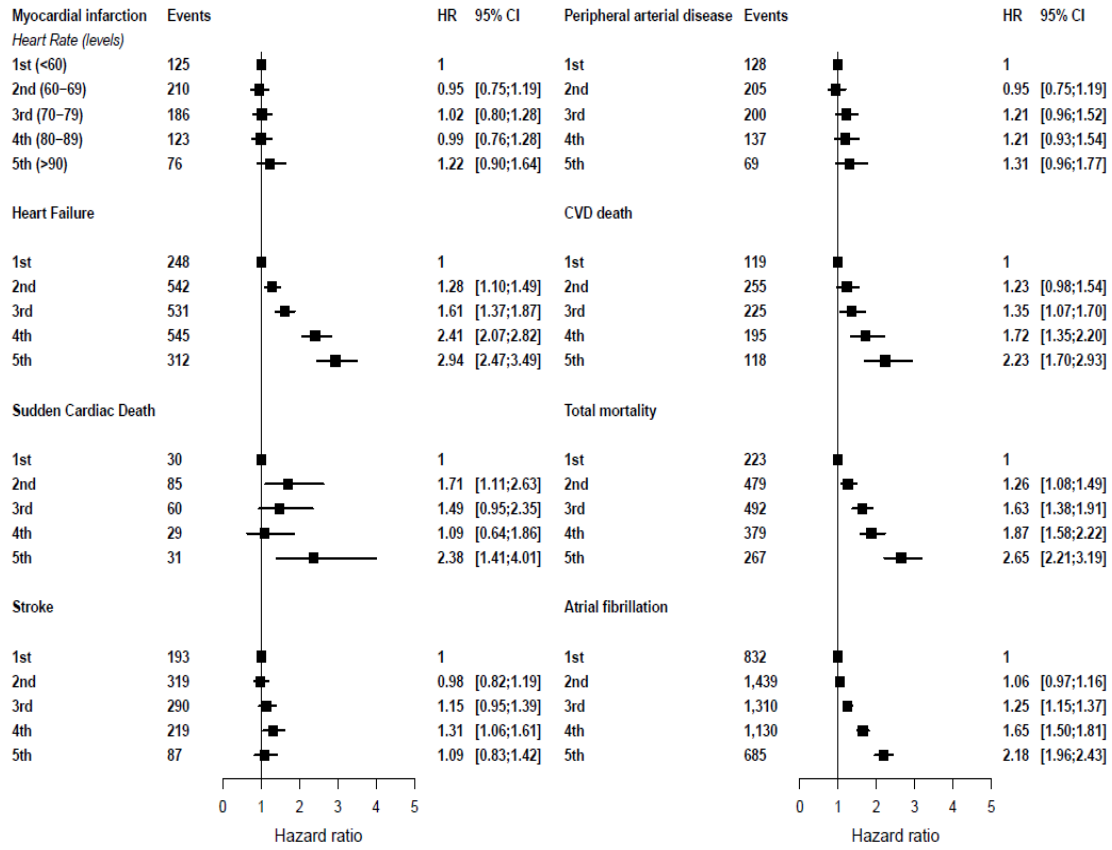
Note: CVD, cardiovascular; SCD-CA, Sudden cardiac death-Cardiac arrest; CI, confidence interval; HR, hazard ratios from Cox proportional hazard model stratified by general practice and adjusted for sex, age, index of multiple deprivation, smoking, systolic blood pressure, diabetes type II, total cholesterol, HDL cholesterol and body mass index

Figure A5.3. Age and sex adjusted hazard ratios for the association between heart rate (top vs bottom level) and the incidence of 7 cardiovascular diseases and mortality outcomes in people with sCAD



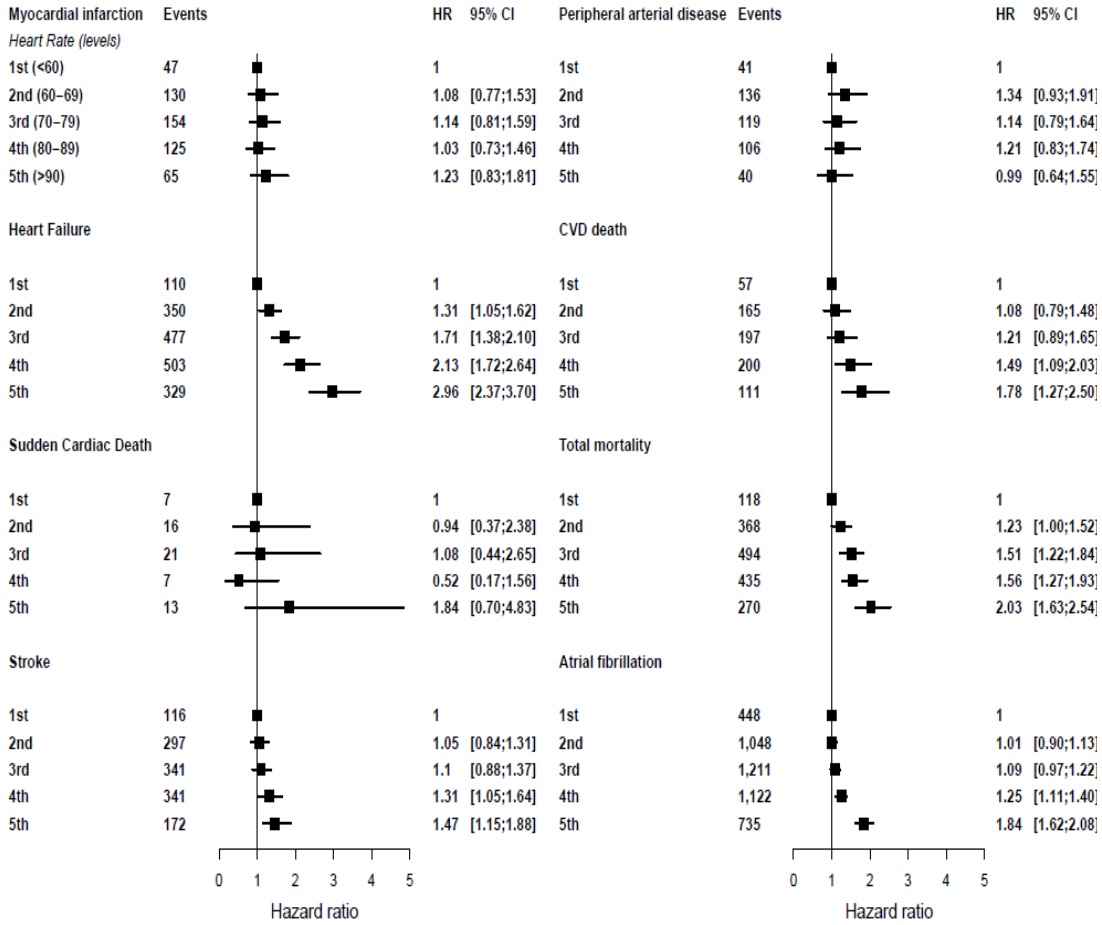
Note: CI, confidence interval; HR, hazard ratios from Cox proportional hazard model stratified by general practice and adjusted for sex and age

Figure A.5.4. Multivariable adjusted hazard ratios for the association between heart rate (top vs bottom level) and the subsequent fatal and non-fatal events among men with stable coronary artery disease



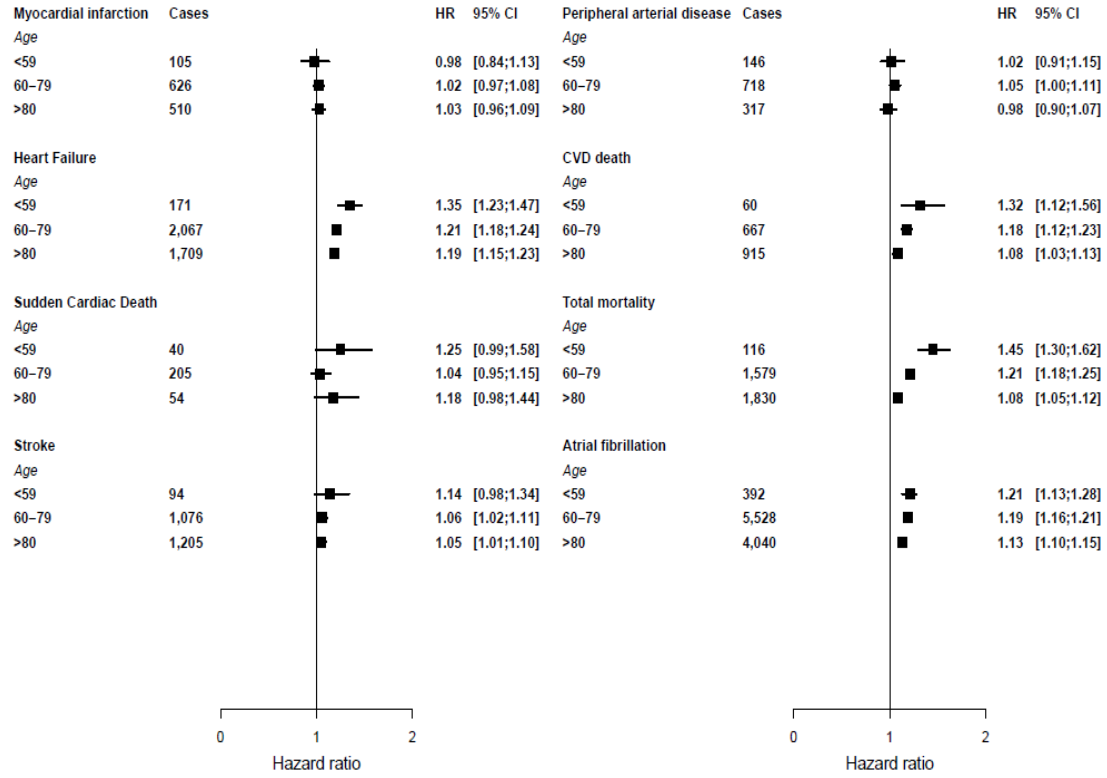
Note: CI, confidence interval; HR, hazard ratios from Cox proportional hazard model stratified by general practice and adjusted for sex, age, index of multiple deprivation, smoking, systolic blood pressure, diabetes type II, total cholesterol, HDL cholesterol and body mass index

Figure A5.5. Multivariable adjusted hazard ratios for the association between heart rate (top vs bottom level) and the subsequent fatal and non-fatal events among women with stable coronary artery disease



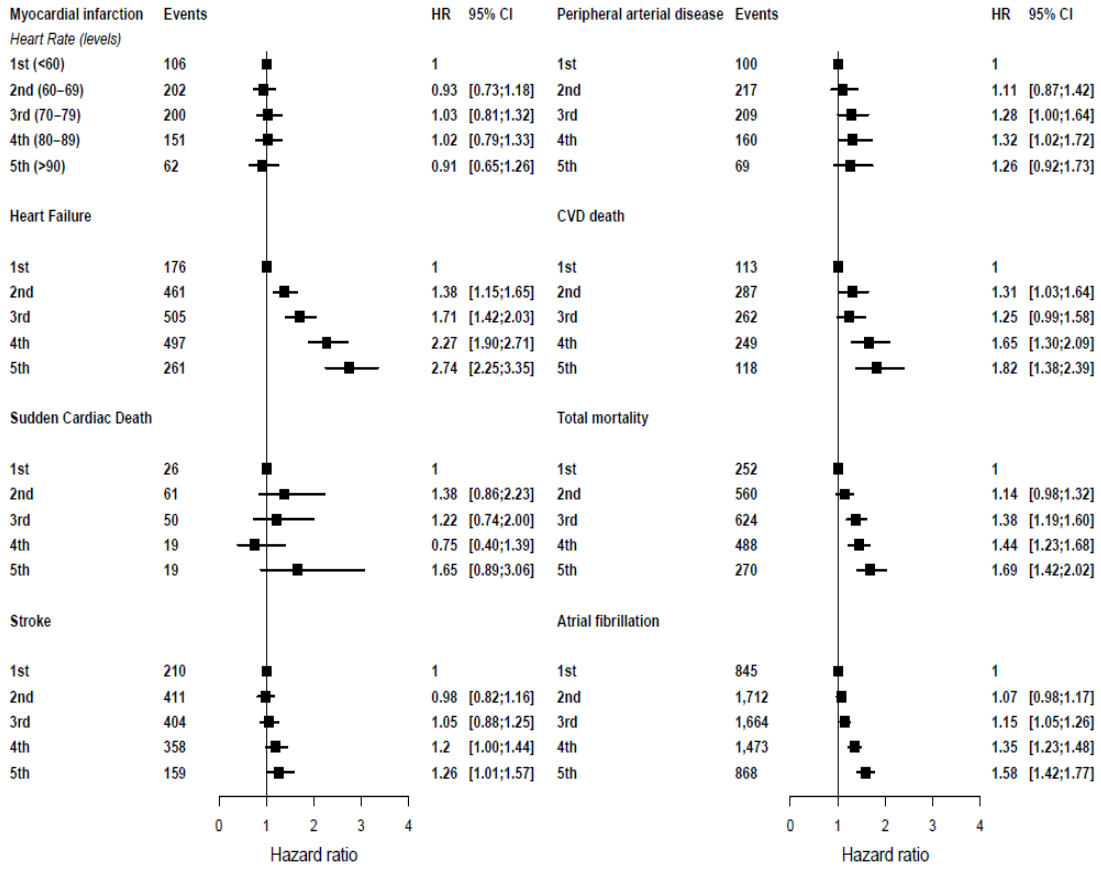
Note: CI, confidence interval; HR, hazard ratios from Cox proportional hazard model stratified by general practice and adjusted for sex, age, index of multiple deprivation, smoking, systolic blood pressure, diabetes type II, total cholesterol, HDL cholesterol and body mass index

Figure A5.6. Multivariable hazard ratios for the association between heart rate and the initial presentation of cardiovascular diseases in people with stable coronary artery disease stratified by age group



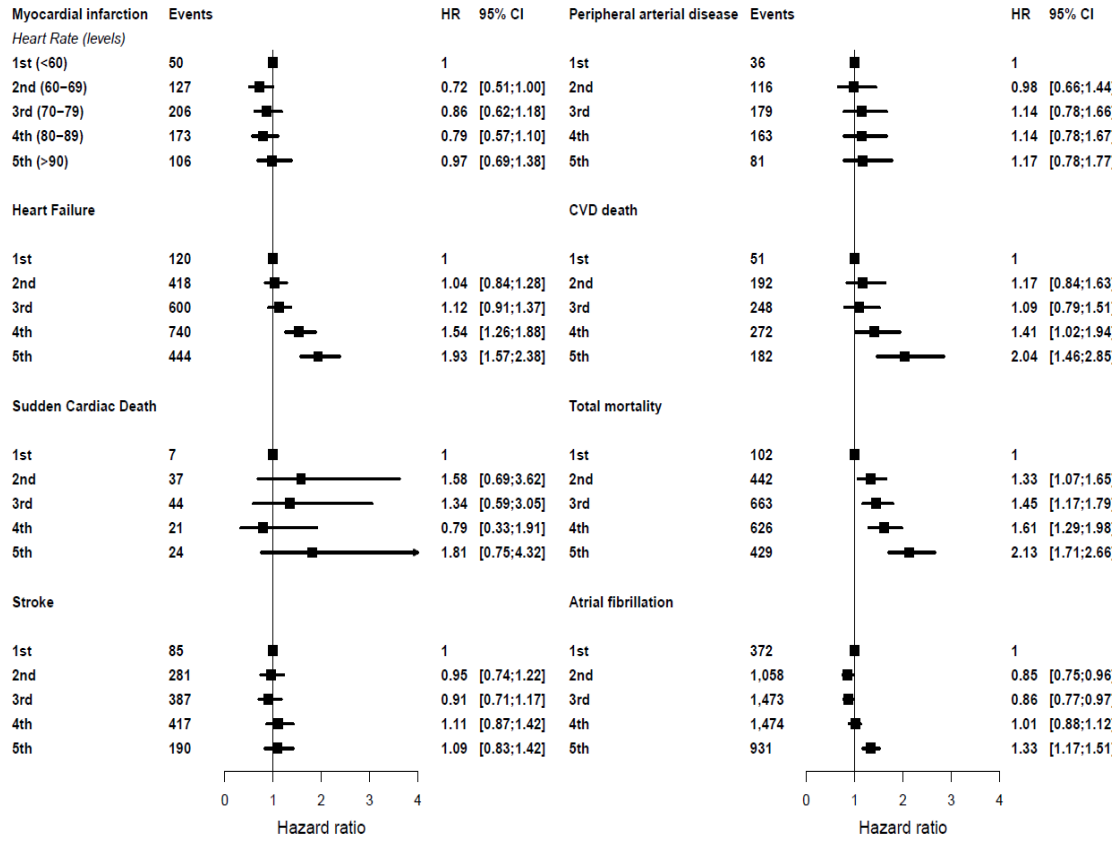
Note: Heart rate measured in 10 bpm increments. CI, confidence interval; HR, hazard ratios from Cox proportional hazard model stratified by general practice and adjusted for sex, age, index of multiple deprivation, smoking, systolic blood pressure, diabetes type II, total cholesterol, HDL cholesterol and body mass index

Figure A.5.7 Multivariable adjusted hazard ratios for the association between heart rate (5th vs 1st level) and the subsequent fatal and non-fatal events among people with corornary artery disease after exclusion of events occurring during the first year of study follow-up



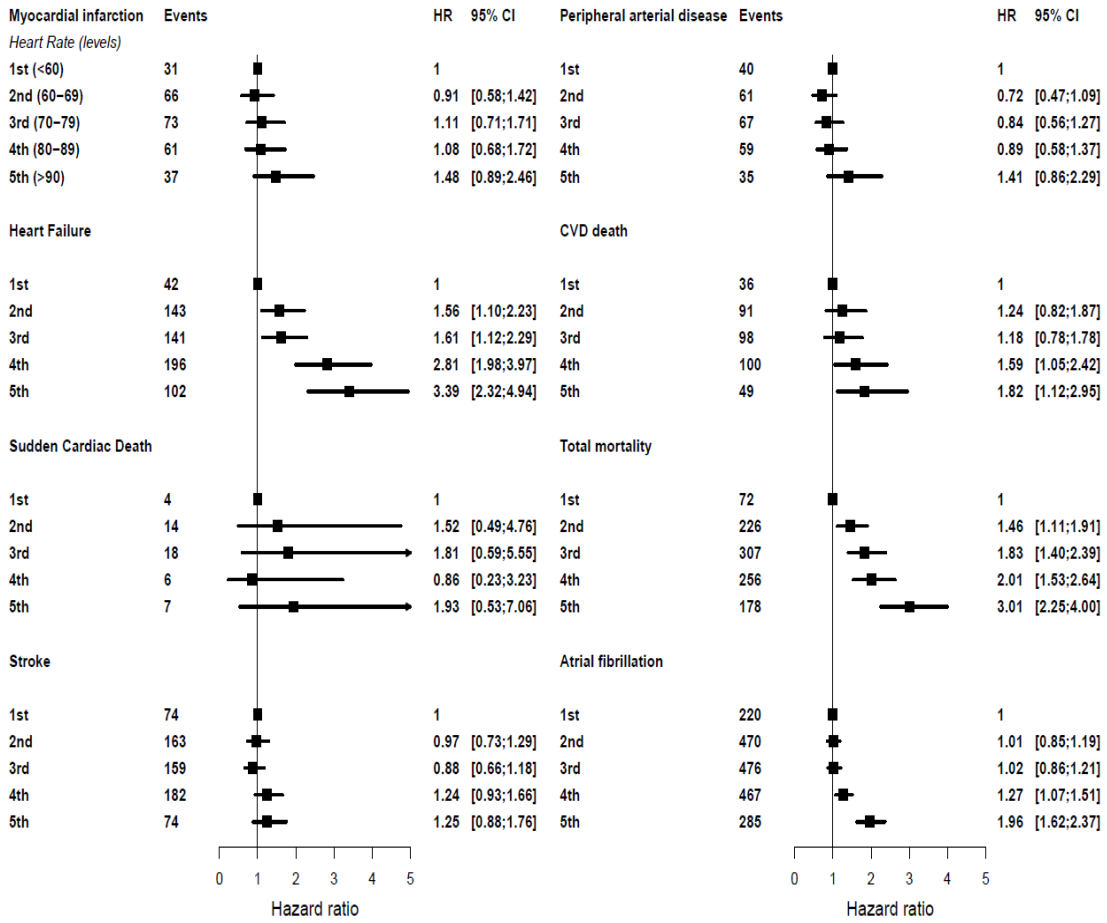
Note: CI, confidence interval; HR, hazard ratios from Cox proportional hazard model stratified by general practice and adjusted for sex, age, index of multiple deprivation, smoking, systolic blood pressure, diabetes type II, total cholesterol, HDL cholesterol and body mass index

Figure A5.8 Multivariable adjusted hazard ratios for the association between heart rate (5th vs 1st level) and the subsequent fatal and non-fatal events among people with stable corornary artery disease but no baseline beta-blockers prescription



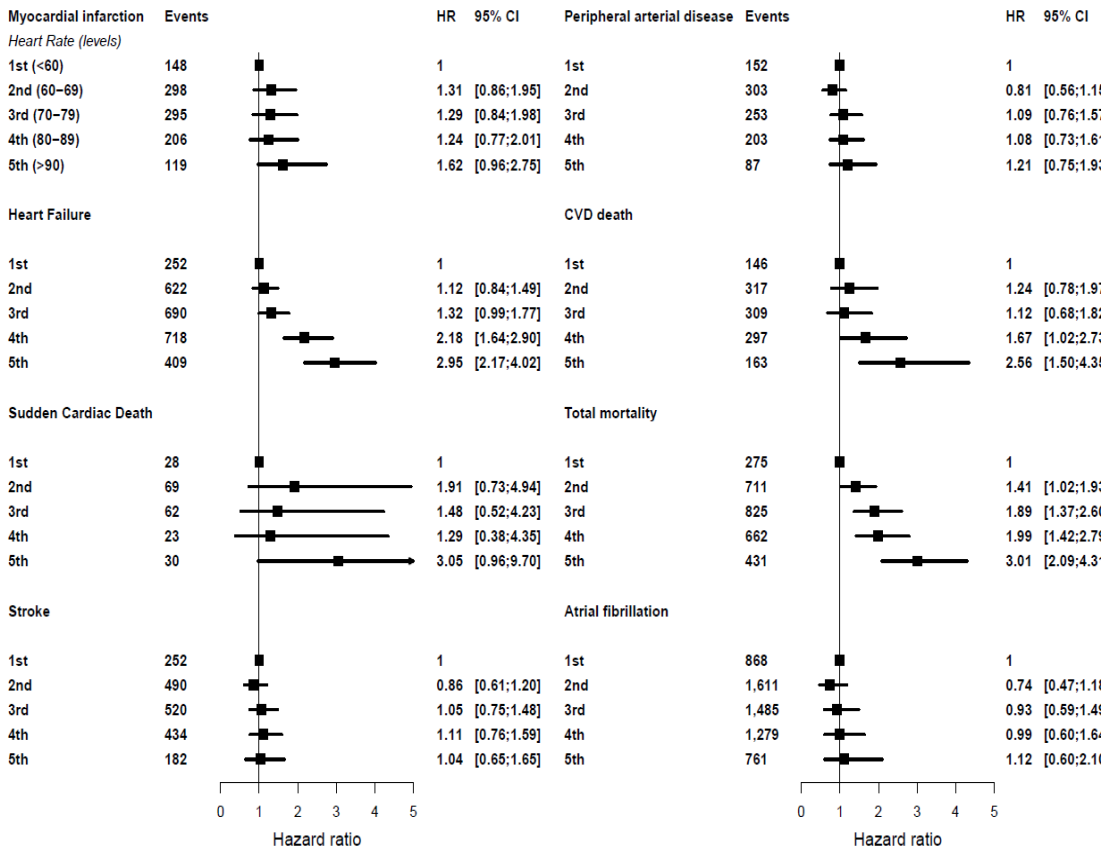
Note: CI, confidence interval; HR, hazard ratios from Cox proportional hazard model stratified by general practice and adjusted for sex, age, index of multiple deprivation, smoking, systolic blood pressure, diabetes type II, total cholesterol, HDL cholesterol and body mass index

Figure A5.9 Multivariable adjusted hazard ratios for the association between heart rate (5th vs 1st level) and the subsequent fatal and non-fatal events among people with stable corornary artery disease but no baseline blood pressure lowering medication prescription



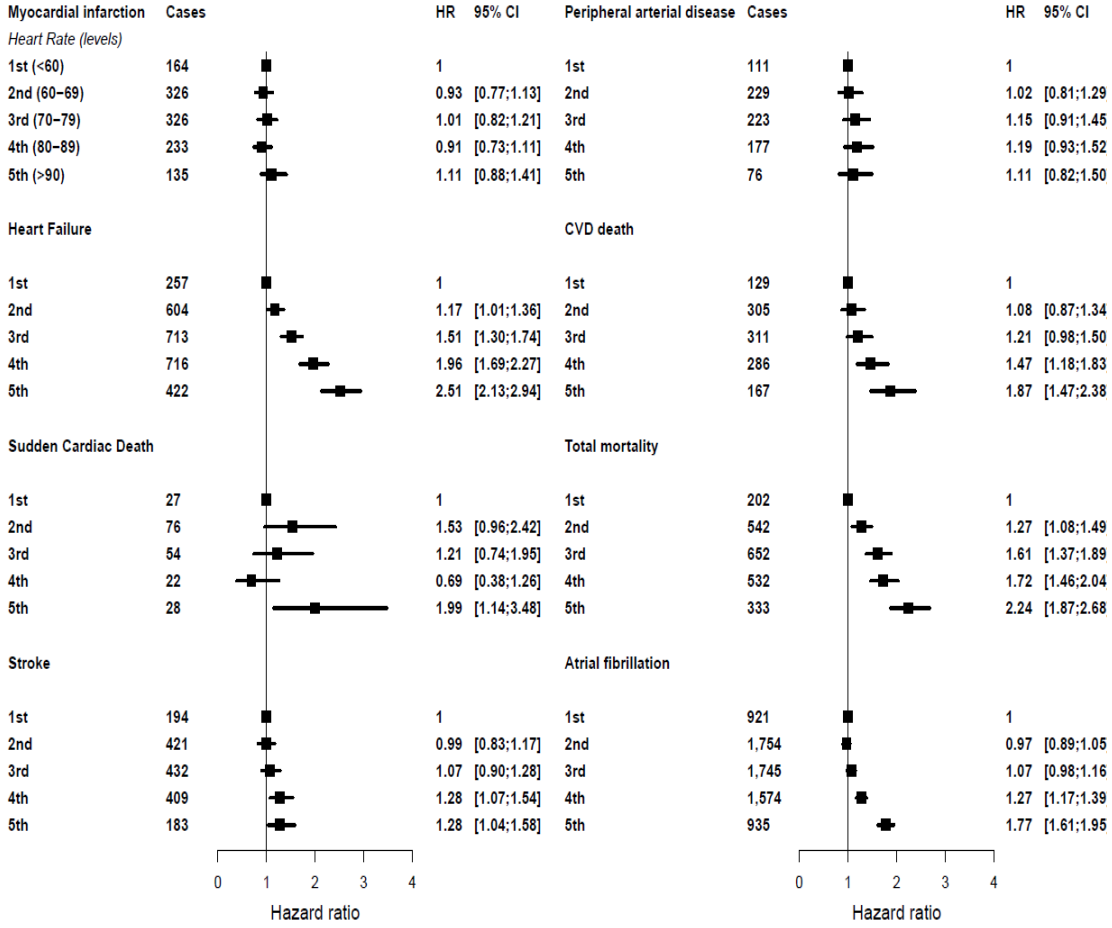
Note: CI, confidence interval; HR, hazard ratios from Cox proportional hazard model stratified by general practice and adjusted for sex, age, index of multiple deprivation, smoking, systolic blood pressure, diabetes type II, total cholesterol, HDL cholesterol and body mass index

Figure A5.10. Multivariable adjusted hazard ratios for the association between heart rate (5th vs 1st level) and the subsequent fatal and non-fatal events among people with stable corornary artery disease but no baseline warfarin/digoxin prescription



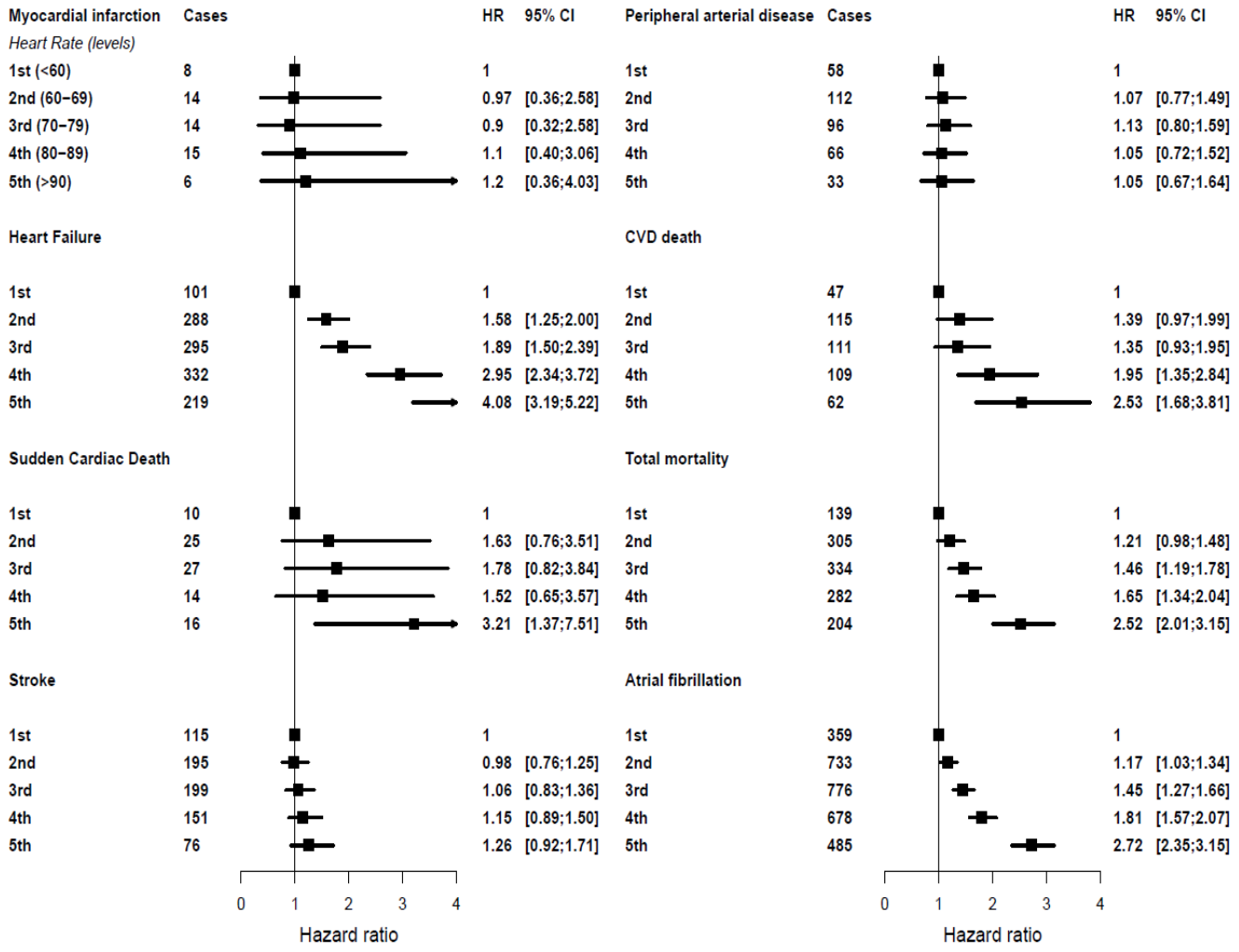
Note: CI, confidence interval; HR, hazard ratios from Cox proportional hazard model stratified by general practice and adjusted for sex, age, index of multiple deprivation, smoking, systolic blood pressure, diabetes type II, total cholesterol, HDL cholesterol and body mass index

Figure A5.11 Multivariable adjusted hazard ratios for the association between heart rate (5th vs 1st level) and the subsequent fatal and non-fatal events among people with coronary artery disease and the entry eligibility CVD event occurred prior to the date of entry in the study



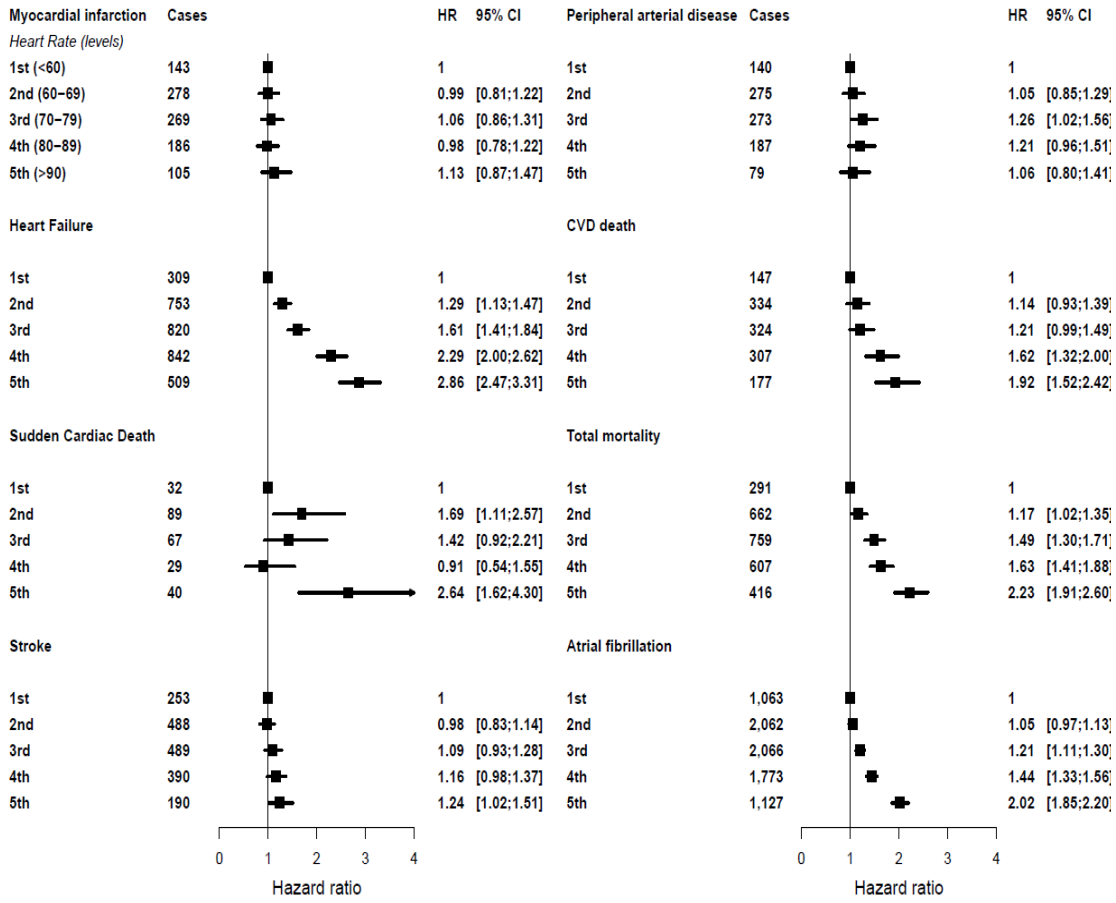
Note: CI, confidence interval; HR, hazard ratios from Cox proportional hazard model stratified by general practice and adjusted for sex, age, index of multiple deprivation, smoking, systolic blood pressure, diabetes type II, total cholesterol, HDL cholesterol and body mass index

Figure A5.12 Multivariable adjusted hazard ratios for the association between heart rate (5th vs 1st level) and the subsequent fatal and non-fatal events among people with coronary artery disease and the entry eligibility CVD event occurred after the date of entry in the study



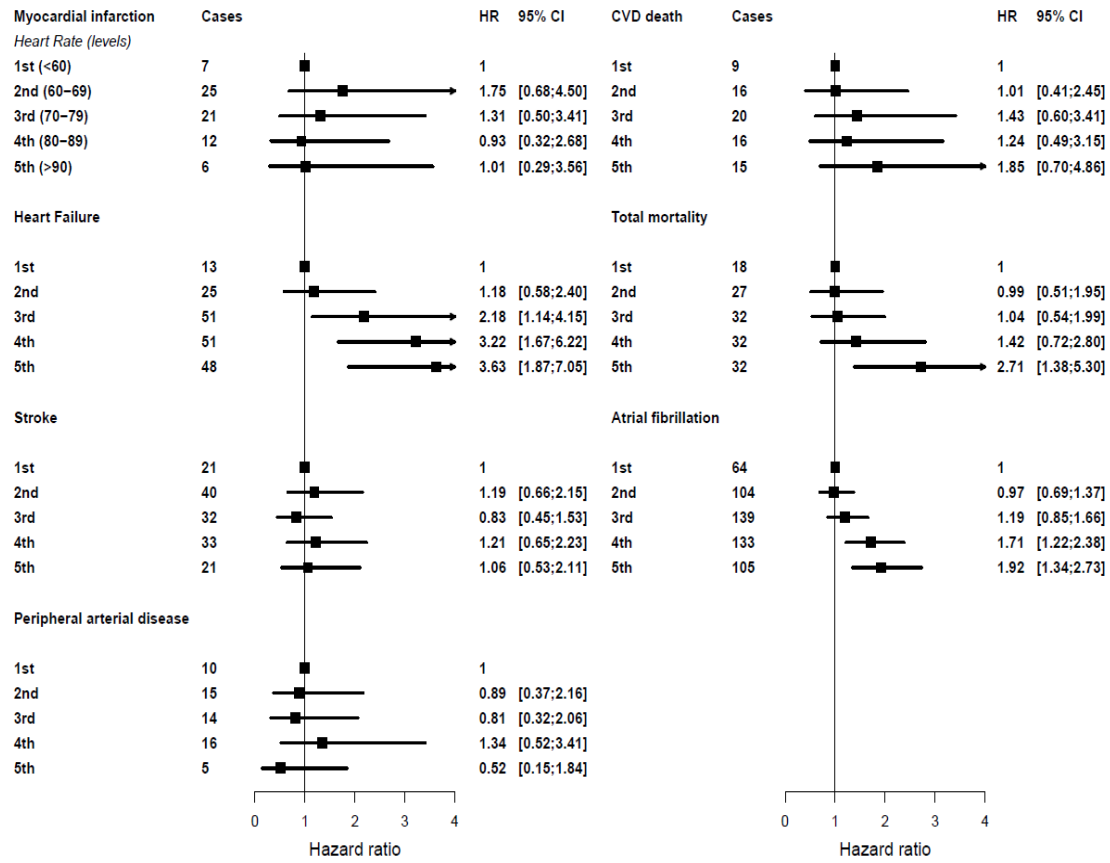
Note: CI, confidence interval; HR, hazard ratios from Cox proportional hazard model stratified by general practice and adjusted for sex, age, index of multiple deprivation, smoking, systolic blood pressure, diabetes type II, total cholesterol, HDL cholesterol and body mass index

Figure A5.13 Multivariable adjusted hazard ratios for the association between heart rate (5th vs 1st level) and the subsequent fatal and non-fatal events among people with stable coronary artery disease and baseline normal blood pressure values



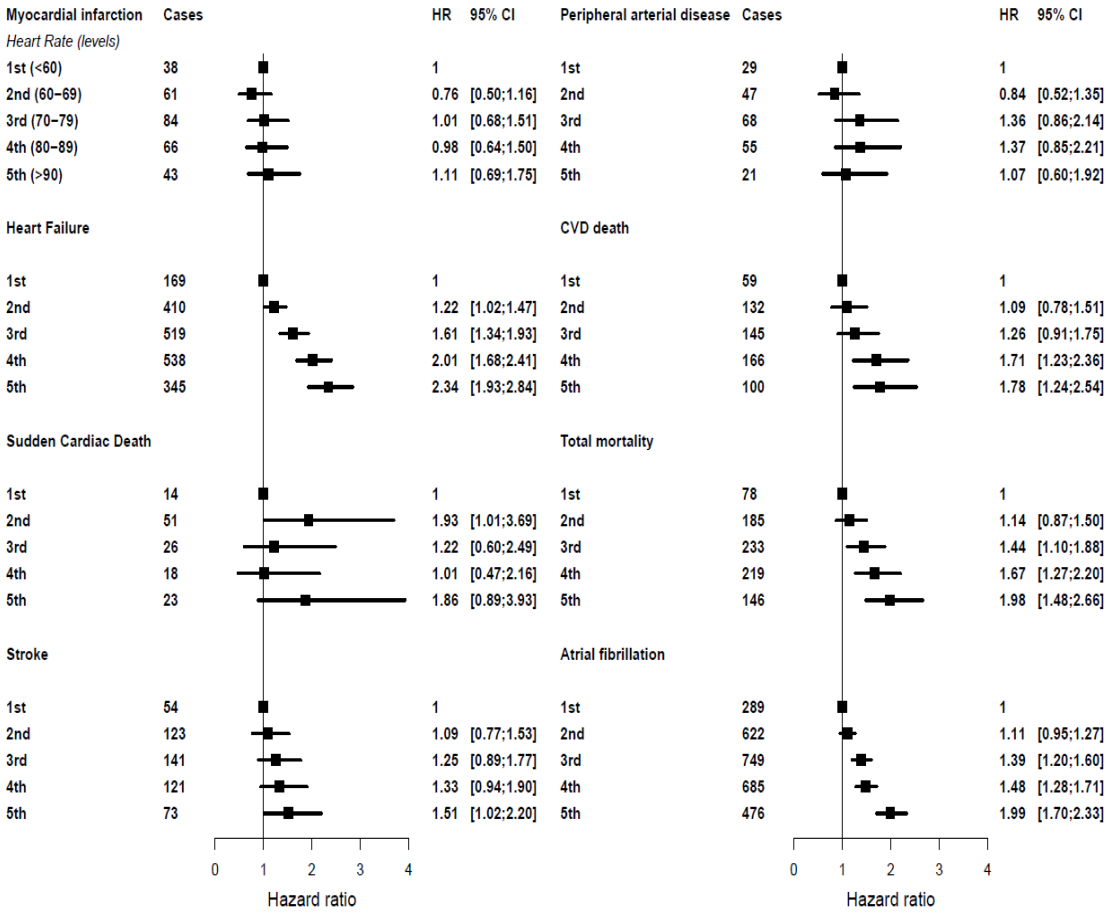
Note: CI, confidence interval; HR, hazard ratios from Cox proportional hazard model stratified by general practice and adjusted for sex, age, index of multiple deprivation, smoking, systolic blood pressure, diabetes type II, total cholesterol, HDL cholesterol and body mass index

Figure A5.14 Multivariable adjusted hazard ratios for the association between heart rate (5th vs 1st level) and the subsequent fatal and non-fatal events among people with hypertension



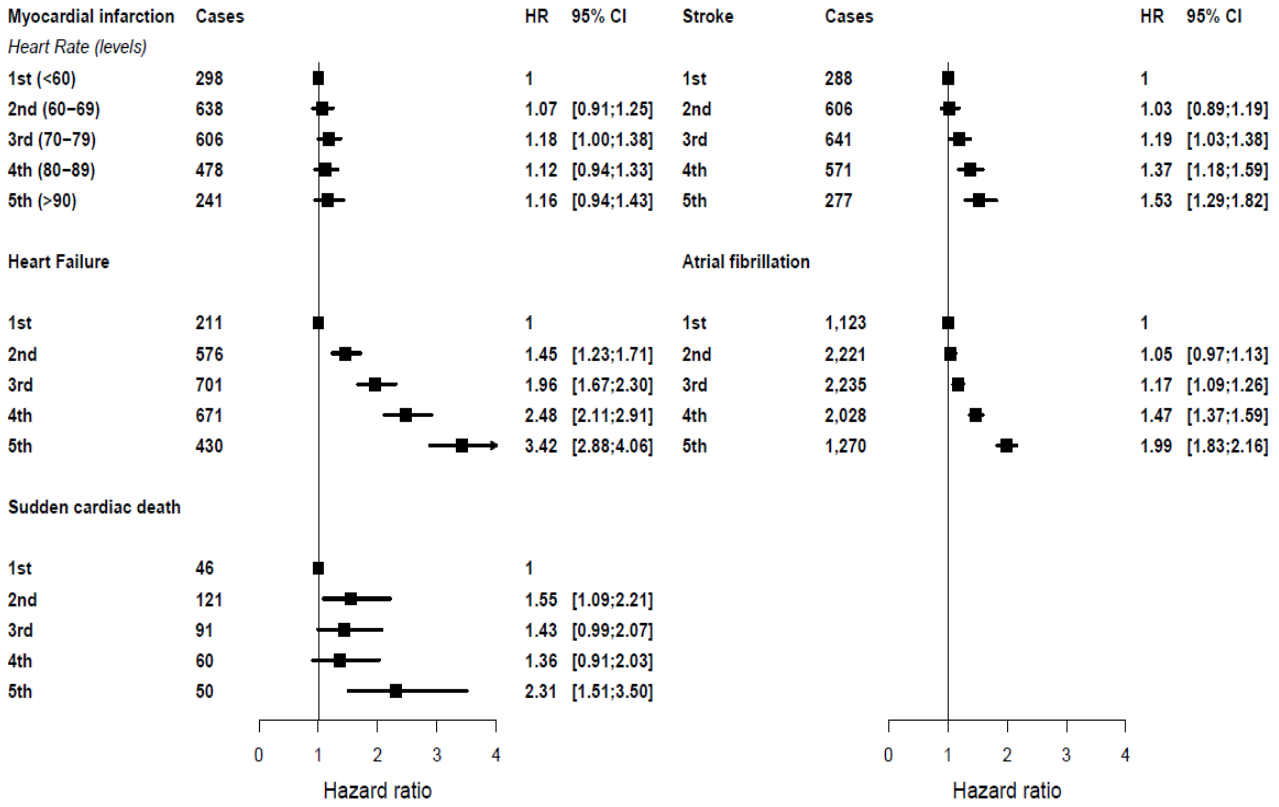
Note: CI, confidence interval; HR, hazard ratios from Cox proportional hazard model stratified by general practice and adjusted for sex, age, index of multiple deprivation, smoking, systolic blood pressure, diabetes type II, total cholesterol, HDL cholesterol and body mass index

Figure A5.15Multivariable adjusted hazard ratios for the association between heart rate (5th vs 1st level) and the subsequent fatal and non-fatal events among people with stable coronary artery disease after exclusion of patients with recorded heart failure before study entry



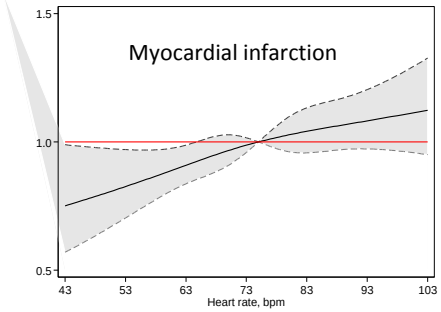
Note: CI, confidence interval; HR, hazard ratios from Cox proportional hazard model stratified by general practice and adjusted for sex, age, index of multiple deprivation, smoking, systolic blood pressure, diabetes type II, total cholesterol, HDL cholesterol and body mass index

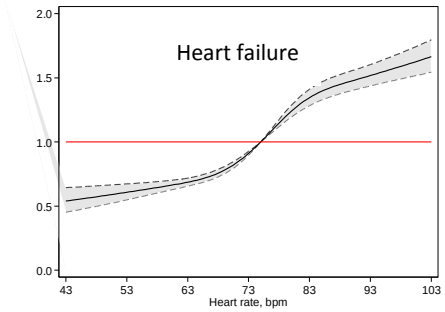
Figure A5.16 Age and sex adjusted hazard ratios for the association between heart rate (5th vs 1st level) and the subsequent fatal and non-fatal events among people with stable coronary artery disease after exclusion of primary care data

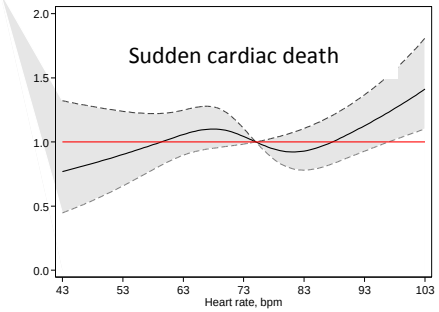


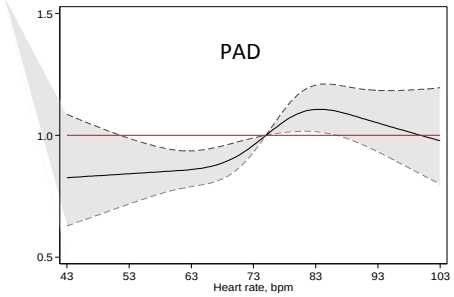
Note: CI, confidence interval; HR, hazard ratios from Cox proportional hazard model stratified by general practice and adjusted for sex and age

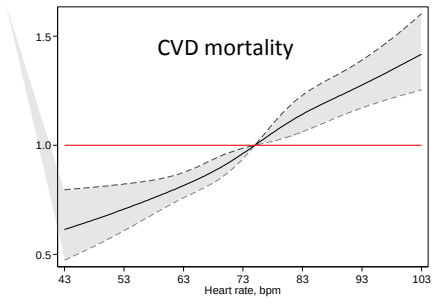
Figure A5.17 Restricted cubic splines of heart rate and CVD events in people with stable coronary artery disease

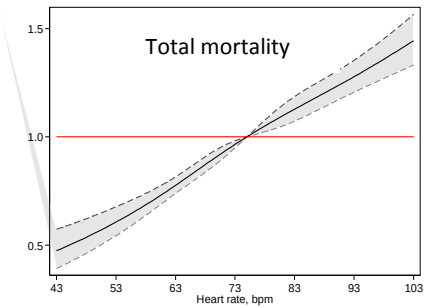


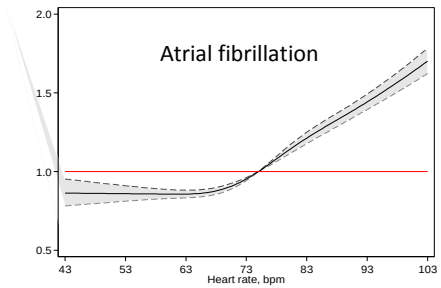


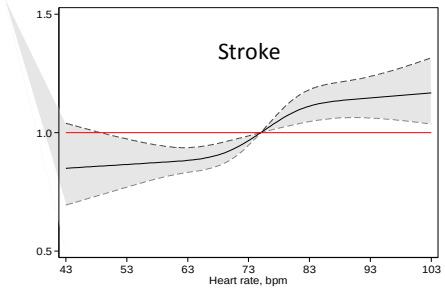






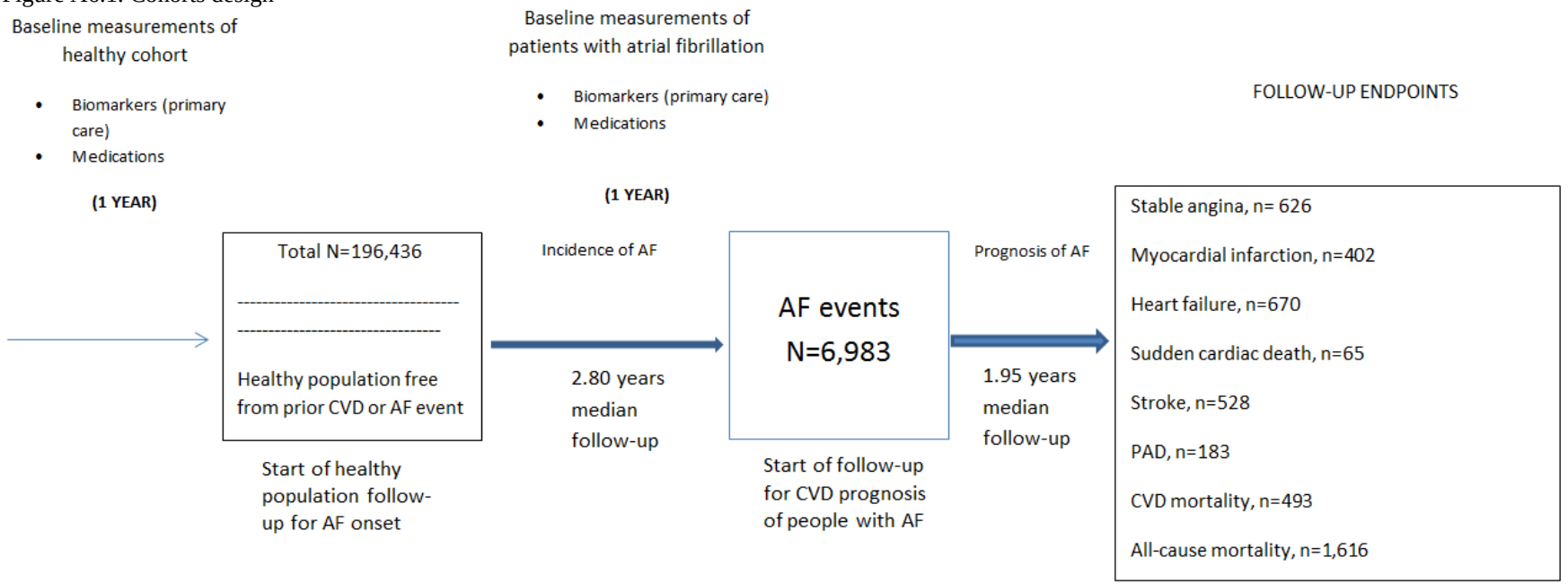






13. Appendix 6

Figure A6.1. Cohorts design



A6.2. Study Flow diagram

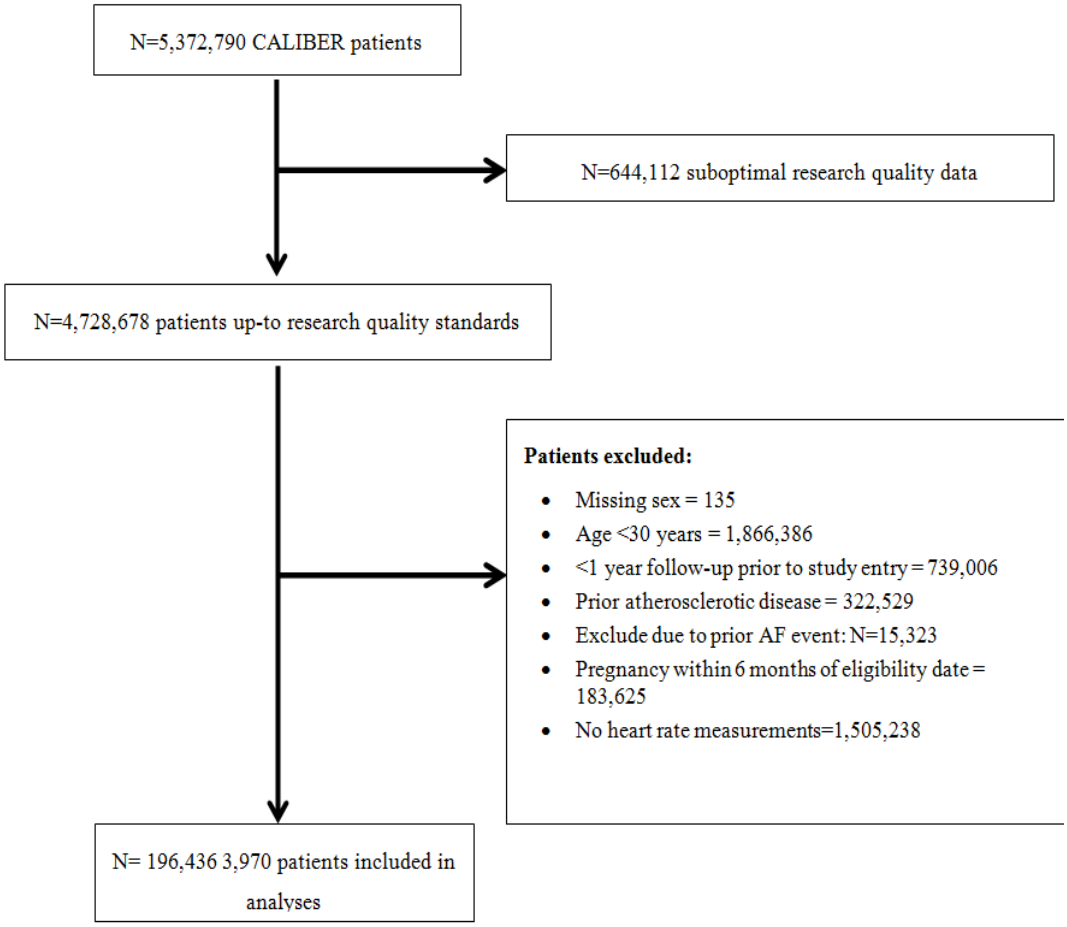
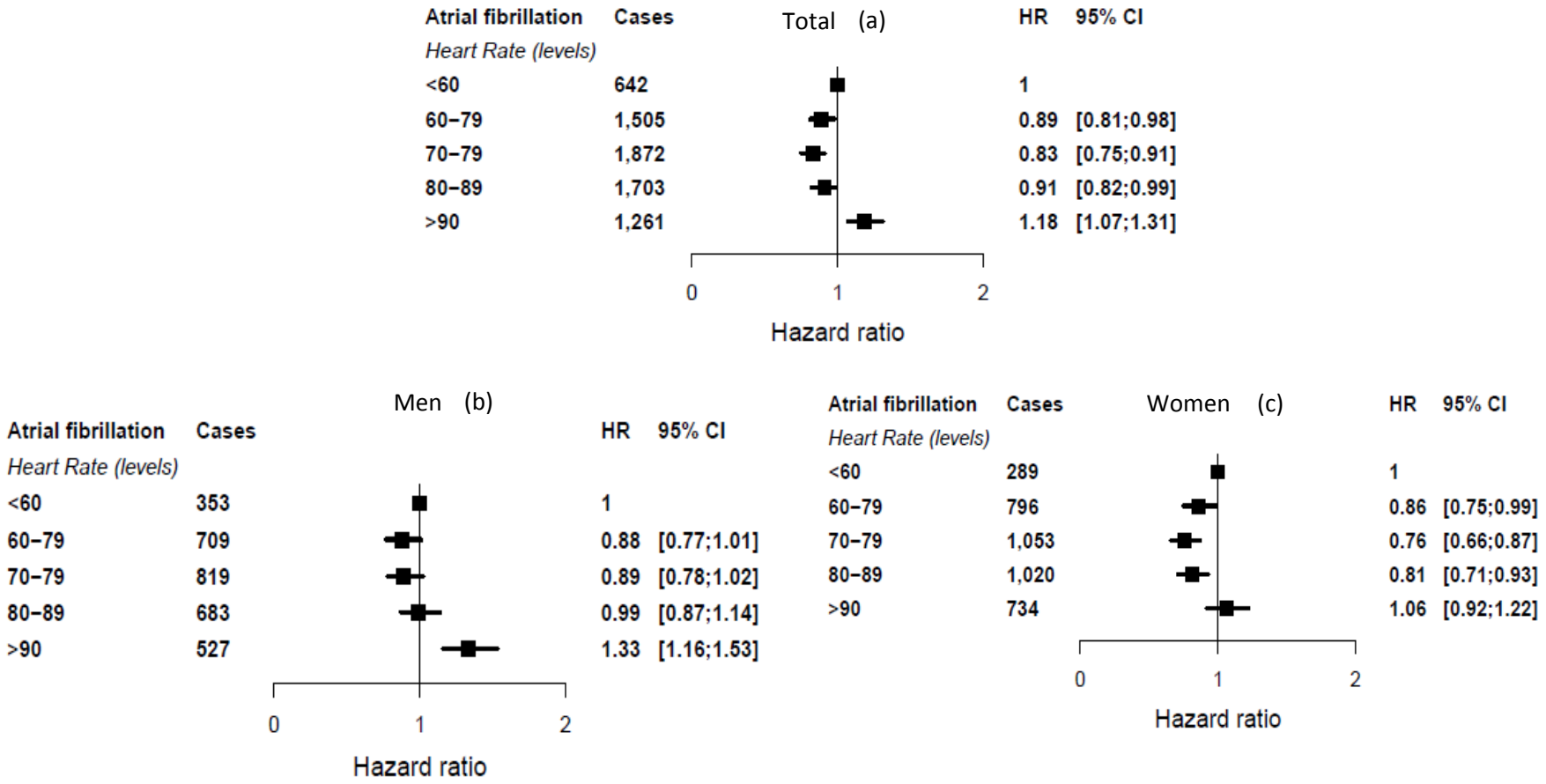


Table A6.1. Categories and codes of atrial

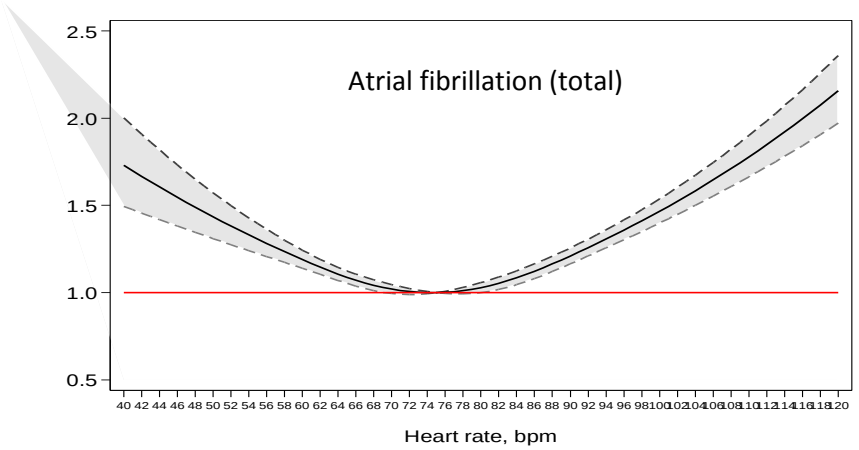
GPRD	**Read codes**
1. History of atrial fibrillation or flutter	14AN.00:H/O: atrial fibrillation
	14AR.00: History of atrial flutter
	212R.00: Atrial fibrillation resolved
2. Atrial fibrillation monitoring	662S.00:Atrial fibrillation monitoring
	6A9..00:Atrial fibrillation annual review
	9Os..00:Atrial fibrillation monitoring administration
	9Os0.00:Atrial fibrillation monitoring first letter
	9Os1.00:Atrial fibrillation monitoring second letter
	9Os2.00:Atrial fibrillation monitoring third letter
	9Os3.00:Atrial fibrillation monitoring verbal invite
	9Os4.00:Atrial fibrillation monitoring telephone invite
	9hF..00:Exception reporting: atrial fibrillation quality indicators
	9hF1.00:Excepted from atrial fibrillation qual indic: Inform dissent
3. Paroxysmal atrial fibrillation	G573200:Paroxysmal atrial fibrillation
4. Persistent or permanent atrial fibrillation	G573400:Permanent atrial fibrillation
	G573500:Persistent atrial fibrillation
5. Atrial fibrillation, not otherwise specified	3272:ECG: atrial fibrillation
	G573000:Atrial fibrillation
	G573300:Non-rheumatic atrial fibrillation
6. Atrial fibrillation or flutter	G573.00:Atrial fibrillation and flutter
	G573z00:Atrial fibrillation and flutter NOS
7. Atrial flutter	3273:ECG: atrial flutter
	G573100:Atrial flutter
HES	**Icd codes**
All the above	I48: Atrial fibrillation and flutter

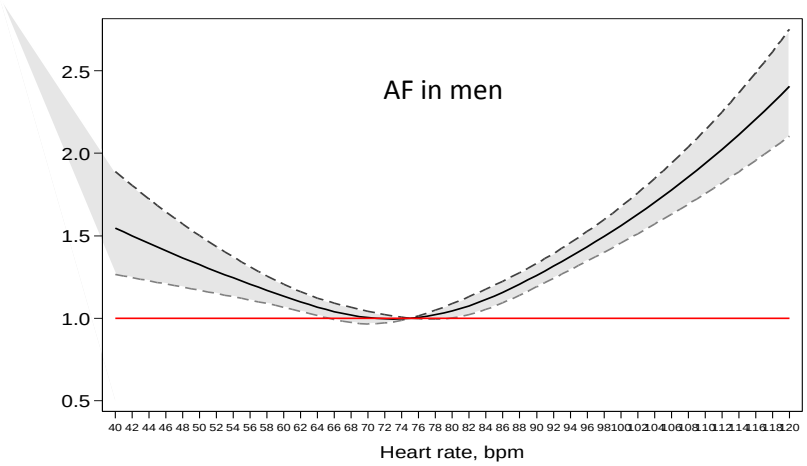
Figure A6.4 Multivariably adjusted hazard ratios for the association between heart rate (5L vs 1L) and the risk of atrial fibrillation



Note: CI, confidence interval; HR, hazard ratios adjusted for age, sex, social deprivation, smoking, systolic blood pressure, BP medication, total cholesterol, HDL, LDL, diabetes II and BMI

Figure A6.5. Restricted cubic splines of heart rate and atrial fibrillation incidence in general population and by gender





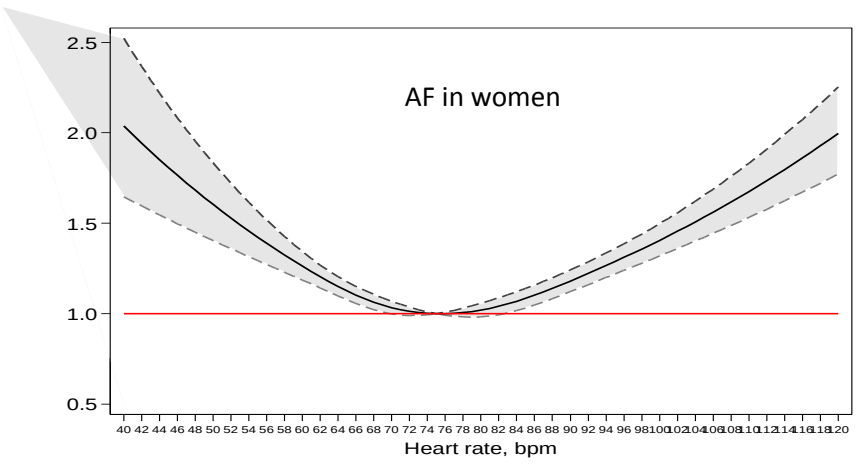
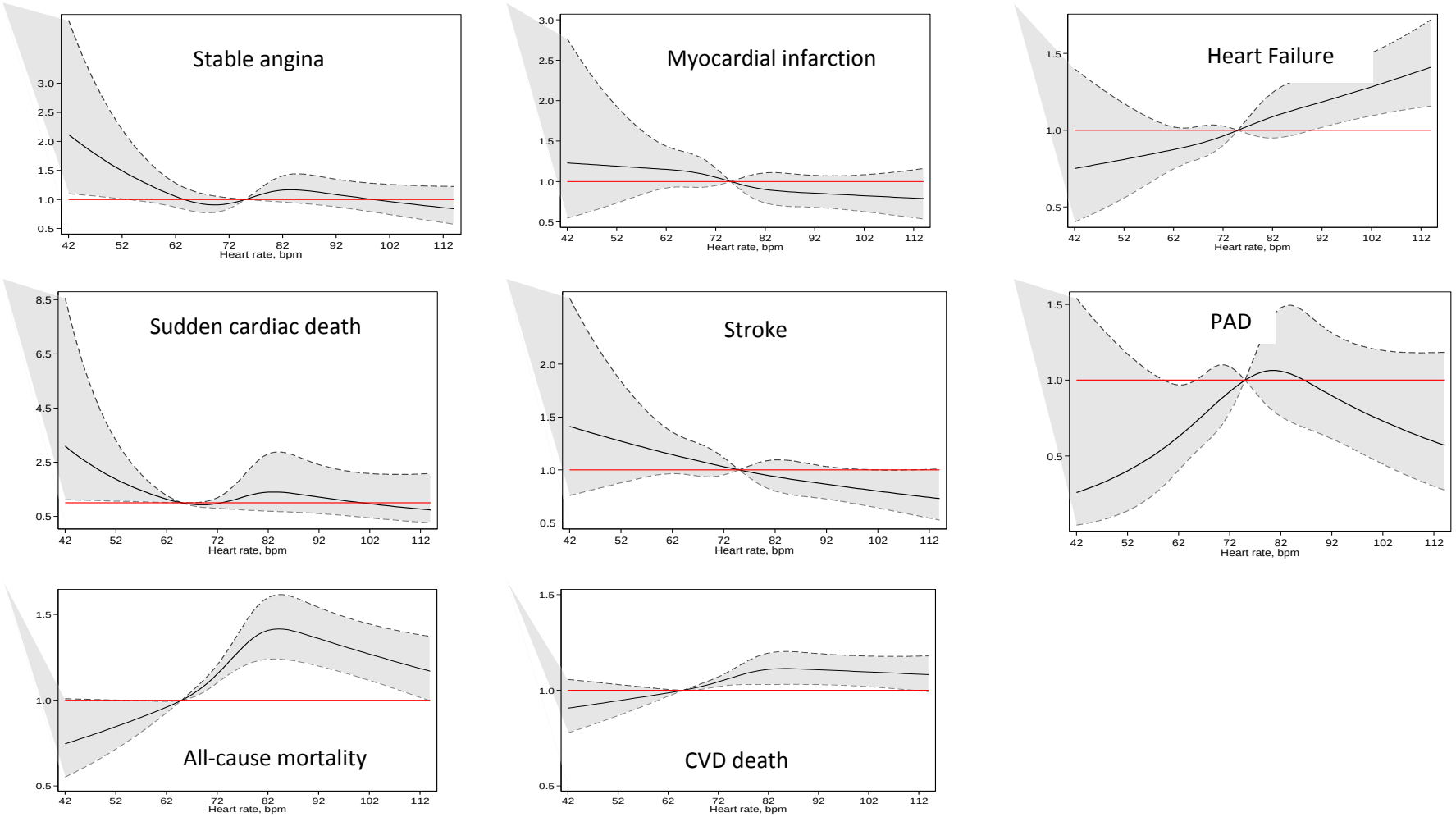
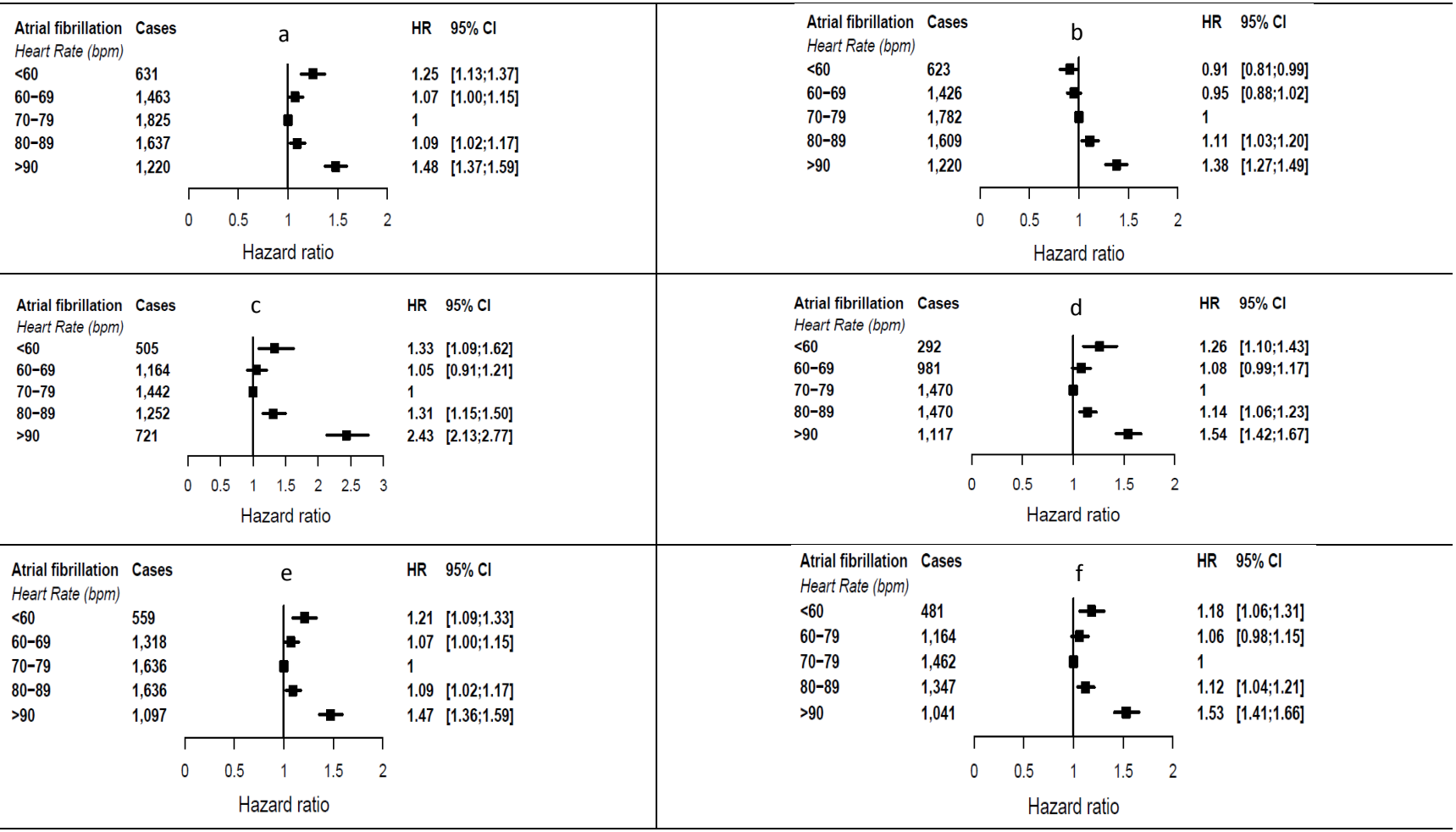


Figure A.6.6. Restricted cubic splines of heart rate and cardiovascular diseases and mortality



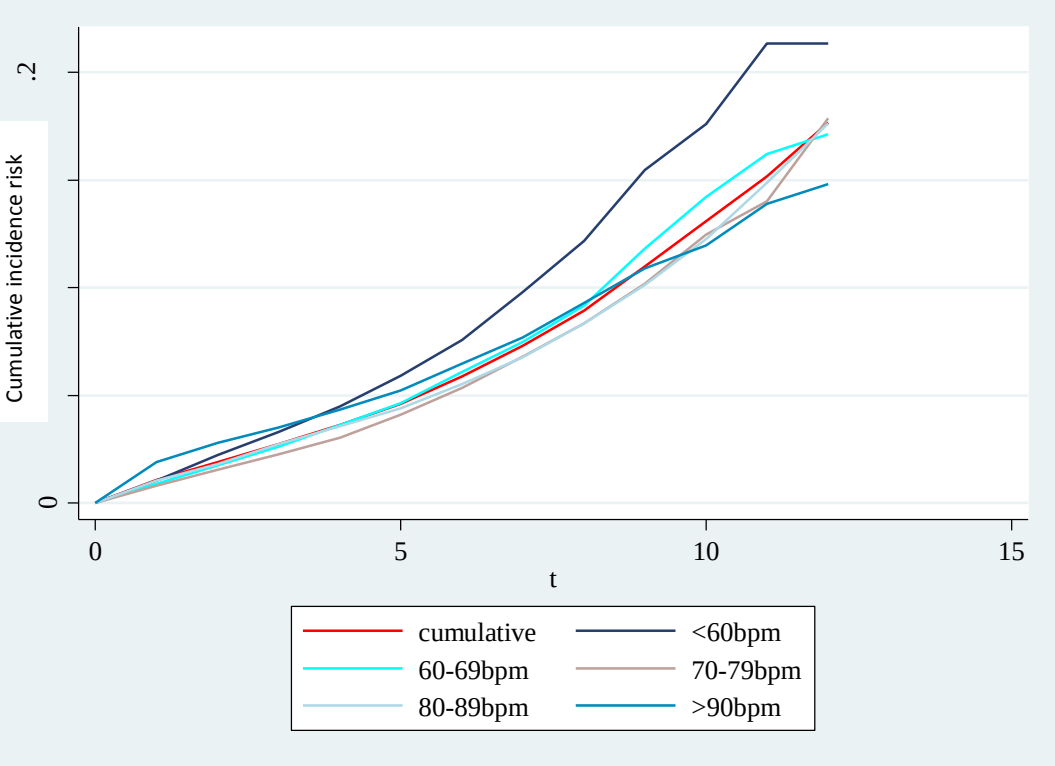
Note: Adjustments include sex, age, quadratic age, and stratification by primary care practice

Figure A6.7 Heart rate and atrial fibrillation incidence in healthy population



Note: a. Restricted to those without warfarin/digoxin intake, b. Exclusion of AF events for 6 months after an MI event, c. Exclusion of AF events during the first year after the heart rate measurement., d. No beta-blockers medication intake, e. No thyroid disease diagnosis at baseline, f. No prior CVD event (before the AF incident)

Figure A6.8 Kaplan-Meier curves of AF cumulative hazard (by heart rate level and overall)



14. Appendix 7.1

Participant consent form used in the Clinical Cohorts in Coronary disease Collaboration (4C) study

My Healthy Heart

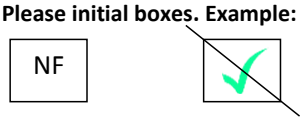
Participant consent form

Chief investigator: *Professor Harry Hemingway*

Thank you for reading the information sheet about the 'My Healthy Heart' study examination. Please read this consent form carefully and put your initials in the boxes by the items to which you agree or give your consent. Please put a line through the box if you do not wish to give your consent to a particular item.

<Affix patient unique study identifier label here>

Please initial boxes. Example:



1. I have read and understand the information sheet dated 10th July 2012 *(version* 1.2A), and and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason. ☐
3. I understand that I may be contacted again by the study team (e.g. to answer some more questions and/or attend another assessment visit), but this is optional. ☐
4. I give permission for long-term storage and use of my blood samples for health-related research purposes (even after my incapacity or death), and relinquish all rights to these samples which I am donating to the My Healthy Heart study. ☐
5. I give permission for full access to my past, present and future medical and other health-related records, and for long-term storage and use of this and other information about me, for health-related research purposes (even after my incapacity or death). I understand that information held and managed by The Health and Social Care Information Centre and other central UK NHS bodies may be used in order to help contact me or provide information about my health status. ☐
6. I understand that all research data will be anonymised in a form that will preclude me from being identified personally, and all data will be stored securely at the study co-ordinating centre. ☐
7. I understand that none of my results will be given to me including my blood results. ☐

8. I agree to take part in this study. ☐

_____	_____	_____
Name of participant (CAPITALS)	**SIGNATURE**	**Date (dd/mm/yyyy)**
_____	_____	_____
Name of person taking consent (CAPITALS)	**SIGNATURE**	**Date (dd/mm/yyyy)**

15. Appendix 7.2

Clinical Cohorts in Coronary disease Collaboration (4C) participant baseline health questionnaire

UCL

My Healthy Heart

Participant study information sheet

YOUR INVITATION TO PARTICIPATE IN A STUDY ON CHEST PAIN OR DISCOMFORT

We would like to invite you to take part in a research study looking at ways to improve the care of people suffering with chest pain or discomfort. Before you decide, it is important for you to understand why the study is being done and what it will involve. We would very much like you to be involved in this study. Please take time to read this information sheet carefully and discuss it with your family or friends if you wish.

WHAT IS THE STUDY ABOUT?

Chest pain is a worrying symptom and in some people it *may* be caused by heart disease. By collecting detailed information from patients who are undergoing investigation or treatment of their chest pain we hope to develop new ways of diagnosing symptoms of chest pain. We want to study how blood and other tests might help to improve chest pain care in the future, and would like our findings to enhance early detection and better care of people with chest pain.

WHAT WILL HAPPEN IF I AGREE TO PARTICIPATE IN THIS STUDY?

With your permission, a member of the research team will speak with you about what the study involves. If you agree to participate you will be asked to sign a consent form to indicate that you understand what the study involves. A consent form is attached for you to look at. Your care will not be affected by your decision to take part or not in the study.

If you agree to take part, the research nurse or assistant will ask you to complete a short health questionnaire and will take a blood sample (approximately 4 tablespoons of blood will be taken). In some circumstances where we are unable to obtain a sample of your blood, we will ask you to provide a buccal swab sample in its place. The research nurse or assistant will use a buccal swab (a cotton-tipped applicator similar to a cotton bud used in personal care but with a longer stem) to collect buccal cells from your cheek. Buccal cells are the cells that are found in the inside of your cheek and underneath your lower and upper lips. These cells are routinely replaced with new ones so the dead cells can easily be collected by buccal swabs. From the buccal swab sample provided by you we can obtain your genetic material (DNA). Collecting a buccal swab sample is easy, painless and quick - it will only take a few seconds.

WHAT WILL THE QUESTIONNAIRE INVOLVE?

We will ask you a series of questions about your chest pain and your health. If you have any difficulty with the questions, the research nurse or assistant will be available to help you. The questionnaire should take approximately 5-10 minutes to complete.

WHY WILL A BLOOD SAMPLE BE TAKEN?

For many medical conditions, tests are carried out in order assess future risk and severity of a condition, by measuring substances in the blood. For people experiencing chest pain, we need to know more about these substances and in particular which ones could help clinical care. Therefore we would like to measure the levels of a number of these substances in the blood samples we collect in this study. We would also like to look at genetic material, using DNA from your blood sample. Different people have different combinations of genes. Studying this information may help to identify if some people are more at risk of angina than others, so that new treatments can be developed. This is a long-term study, so it is possible that your sample may be tested after some years have passed. All samples will be securely stored in a 'biobank'. The results of these tests will remain confidential and be used for research purposes only. Your GP will not be informed of these results and they will not be put on your medical record, or passed on to any third parties including insurance companies. If you decide to withdraw from the study you will be able to request that your samples are no longer stored or analysed. You will not be notified of the results of any of the blood tests performed as part of the research.

WILL I HEAR FROM THE RESEARCH TEAM AGAIN?

With your permission, we will invite you to complete a short questionnaire in around two years' time. Again with your permission we *may* invite you to complete a further questionnaire in the future. This study is a long term study and my data and blood samples may be kept for up to 30 years.

WILL ANY INFORMATION FROM THE STUDY BE GIVEN TO CLINIC STAFF OR MY GP?

Information that you provide to the research team will not be passed on to the clinic staff or your GP.

WILL THE RESEARCH TEAM HAVE ACCESS TO MY MEDICAL RECORDS?

We would like to review your health over a period of years before and after your hospital attendance. With your permission, we would like to collect information from your GP and hospital medical record. This is the first time a link like this will have been undertaken for chest pain patients and will provide valuable information that we hope will improve patient care. With your permission we will also collect information relating to your past and previous hospital admissions and will be notified in the event of your death by the NHS Information Centre for Health and Social Care who is responsible for collecting such information for all people in England. All information will be anonymised and stored securely at the study coordinating centre.

WILL MY PERSONAL INFORMATION BE KEPT SAFE?

Yes. We will keep all study data in a secure facility. Information will only be accessible to staff who are part of the research team. Your personal information (such as your name) will be kept securely and separately from the rest of the information we collect. We will ensure that outside of the immediate study team you cannot be identified from the information you provide and only anonymised data will be analysed by researchers.

CAN I WITHDRAW FROM THE STUDY?

You may withdraw from the study at any time and you do not have to give a reason. If you choose to withdraw, you should inform the research nurse or assistant or study coordinator verbally or in writing. Your normal care will not be affected and we will not contact you again.

WHAT WILL HAPPEN IF I LOSE THE CAPACITY TO CONSENT DURING THE COURSE OF THE STUDY?

In the event that you have given informed consent and subsequently lose the capacity to consent during the study, we will continue to collect follow up information from your medical records and analyse your blood samples, and you will remain in the study. If the research team is made aware of your loss of capacity to consent, we would seek to ask a close family member or friend to complete a follow up questionnaire about your health on your behalf, where possible. If we are unable to identify a next of kin we will not collect further questionnaire data from you at follow up.

WHO IS RUNNING THE STUDY?

This study has been designed and is being run by a group of researchers from University College London, Barts Health NHS Trust and the University of Bristol. The research is funded by the National Institute for Health Research (NIHR) which is part of the NHS. All research in the NHS is approved by an independent group of people, called a Research Ethics Committee, to protect your safety, rights, wellbeing and dignity. This research has also been reviewed and designed with the help of a Public and User Involvement Group which includes patients who have suffered chest pain and had experience of chest pain clinics.

WHAT IF I HAVE MORE QUESTIONS?

You will have the chance to talk with the research nurse or assistant when you attend hospital. For more information and advice, you may contact Natalie Fitzpatrick, the study coordinator by phone (020 3108 3065), e-mail (n.fitzpatrick@ucl.ac.uk) or by writing to: Natalie Fitzpatrick or Professor Harry Hemingway (Chief Investigator) at the Department of Epidemiology & Public Health, University College London, 1-19 Torrington Place, London WC1E 6BT. For independent advice about the study you can contact your local Research and Development department or Patient Advice and Liaison Service (PALS) at: Ground Floor Atrium, University College Hospital, 235 Euston Road, London NW1 2BU ***Thank you for taking the time to read this leaflet***

Funded by: NHS National Institute for Health Research

Institutions: UCL Barts Health NHS Trust University of BRISTOL

My Healthy Heart

Research nurse to affix patient unique study identifier label here

PARTICIPANT HEALTH QUESTIONNAIRE

Study entry

Thank you for agreeing to take part in the ***"My Healthy Heart" study***, which is seeking to improve early detection of possible heart disease and care of people with chest pain or chest discomfort.

It is important that you answer **all** the questions in this questionnaire, which should take approximately 5-10 minutes to complete. Please take your time and answer questions as honestly as possible. All information you provide will be kept strictly confidential. If you have any difficulty with any of the questions, the research nurse will be able to help you at the clinic.

Please hand your completed questionnaire to the research nurse at the clinic. *For more information about the study*, please contact Natalie Fitzpatrick (e-mail: n.fitzpatrick@ucl.ac.uk)

SECTION 1: Background information about you

First, we would like you to tell us a little about yourself. Please answer **all** the questions below and **tick only one response** from each question

1 a. What is your sex? Male[1] ☐ Female[2] ☐

1 b. At what age did you complete your continuous full time education? _____ years ☐ Do not know

SECTION 2: Your general health

The next questions are about your general health. Please indicate which of the statements best describe your **own health today**. Please answer **all** questions. Please **tick only one option** from each question

2. Mobility

I have no problems in walking about[1] ☐ | I have some problems in walking about[2] ☐ | I am confined to bed[3] ☐

3. Self-care

I have no problems with self care[1] ☐ | I have some problems washing or dressing Myself[2] ☐ | I am unable to wash or dress myself[3] ☐

4. Usual activities (e.g. work, study, housework, family or leisure activities)

I have no problems performing my usual Activities[1] ☐ | I have some problem performing my usual Activities[2] ☐ | I am unable to perform my usual activities[3] ☐

5. Pain/discomfort		
I have no pain or discomfort[1] ☐	I have moderate pain/ discomfort[2] ☐	I have extreme pain/ discomfort[3] ☐
6. Anxiety/depression		
I am not anxious or Depressed[1] ☐	I am moderately anxious or depressed[2] ☐	I am extremely anxious or depressed[3] ☐

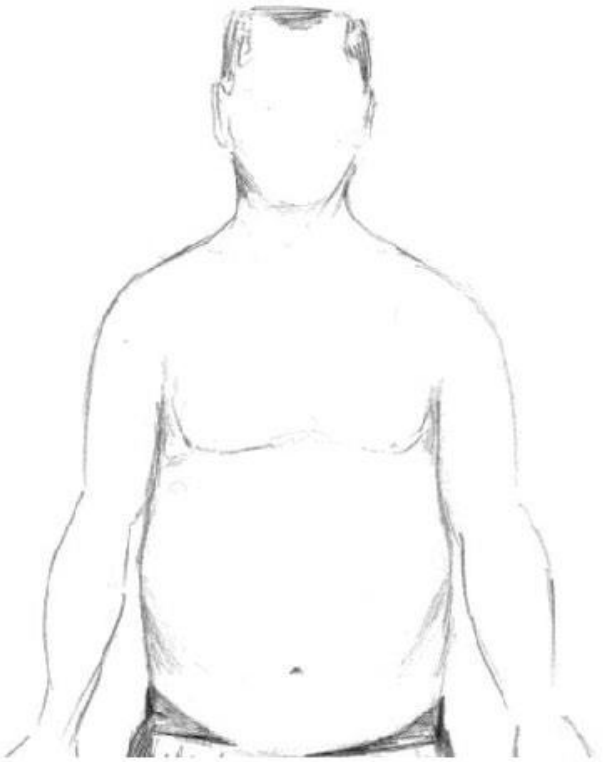
SECTION 3: Your chest pain

The following questions relate to chest pain, chest tightness or angina you may have experienced. Please answer **all** the questions in this section

7. Have you ever had any pain or discomfort in your chest?	Yes[1] ☐	No[2] *If no, go to Section 4*	☐
8. Do you get this pain or discomfort if you walk uphill or hurry?	Yes[1] ☐	No[2]	☐
9. Do you get this pain when you walk at an ordinary pace on the level?	Yes[1] ☐	No[2]	☐
10. When you get this pain or discomfort, what do you do?			
Stop[1] ☐	Slow down[2] ☐	Continue at the same pace[3]	☐
11. Does the pain go away when you stand still?	Yes[1] ☐	No[2]	☐
12. How soon does the pain go away?	Within 10 minutes or less[1] ☐	More than 10 minutes[2]	☐

*13. Please mark with an '**X**' on the diagram below **each area** you experience pain or discomfort*

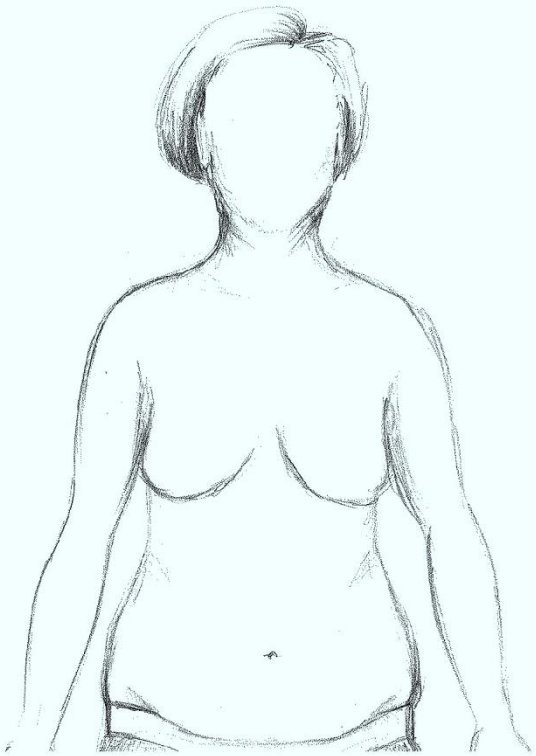
For male participants:



Right **Left**

Baseline questionnaire_Version 1.1 (10.7.12)

For female participants:



Right **Left**

*14. Please tick **one** box that best describes your chest pain or tightness*	I get chest pain or tightness on strenuous exercise[1]	☐
	I get chest pain or chest tightness on walking more than 200 yards on the flat, or climbing stairs rapidly or in the cold or under emotional stress[2]	☐
	I get chest pain or chest tightness on walking 100-200 yards on the flat[3]	☐
	I get chest pain or chest tightness on any physical activity, including at rest[4]	☐

SECTION 4: More about you

Over the last 2 weeks, how often have you been bothered by any of the following problems? Please select **one answer** from each of the following questions:

15. Little interest or pleasure in doing things

Not at all[1]	☐	Several days[2]	☐
More than half the days[3]	☐	Nearly every day[4]	☐

16. Feeling down, depressed or hopeless

Not at all[1]	☐	Several days[2]	☐
More than half the days[3]	☐	Nearly every day[4]	☐

17. Trouble falling or staying asleep, or sleeping too much

Not at all[1]	☐	Several days[2]	☐
More than half the days[3]	☐	Nearly every day[4]	☐

18. Feeling tired or having little energy

Not at all[1]	☐	Several days[2]	☐
More than half the days[3]	☐	Nearly every day[4]	☐

19. Poor appetite or overeating

Not at all[1]	☐	Several days[2]	☐
More than half the days[3]	☐	Nearly every day[4]	☐

20. *Feeling bad about yourself - or that you are a failure or have let yourself or your family down*

Not at all[1] ☐ Several days[2] ☐

More than half the days[3] ☐ Nearly every day[4] ☐

21. *Trouble concentrating on things, such as reading the newspaper or watching television*

Not at all[1] ☐ Several days[2] ☐

More than half the days[3] ☐ Nearly every day[4] ☐

22. *Moving or speaking so slowly that other people could have noticed. Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual*

Not at all[1] ☐ Several days[2] ☐

More than half the days[3] ☐ Nearly every day[4] ☐

23. *Thoughts that you would be better off dead, or of hurting yourself in some way*

Not at all[1] ☐ Several days[2] ☐

More than half the days[3] ☐ Nearly every day[4] ☐

24. *Feeling nervous, anxious or on edge?*

Not at all[1] ☐ Several days[2] ☐

More than half the days[3] ☐ Nearly every day[4] ☐

25. *Not being able to stop or control worrying?*

Not at all[1] ☐ Several days[2] ☐

More than half the days[3] ☐ Nearly every day[4] ☐

26. *Worrying too much about different things?*

Not at all[1] ☐ Several days[2] ☐

More than half the days[3] ☐ Nearly every day[4] ☐

27. *Having trouble relaxing?*

Not at all[1] ☐ Several days[2] ☐

More than half the days[3] ☐ Nearly every day[4] ☐

28. *Being so restless that it is hard to sit still?*

Not at all[1]	☐	Several days[2]	☐
More than half the days[3]	☐	Nearly every day[4]	☐

29. *Becoming easily annoyed or irritable?*

Not at all[1]	☐	Several days[2]	☐
More than half the days[3]	☐	Nearly every day[4]	☐

30. *Feeling afraid, as if something awful might happen?*

Not at all[1]	☐	Several days[2]	☐
More than half the days[3]	☐	Nearly every day[4]	☐

SECTION 5: Ethnicity

31. *Please state in which country you were born:* _____

32. *What is your ethnic group?*

White:	White British[1]	☐	White Irish[2]	☐
	Any other white background[3]	☐		
Mixed race:	White and black Caribbean[4]	☐	White and black African[5]	☐
	White and Asian[6]	☐	Any other mixed background[7]	☐
Asian or Asian British:	Indian[8]	☐	Pakistani[9]	☐
	Bangladeshi[10]	☐	Any other Asian background[11]	☐
Black or black British:	Caribbean[12]	☐	African[13]	☐
	Any other black background[14]	☐		
Chinese[15]		☐		
Other ethnic group:	Please state which[16] _____	☐		
Do not know		☐		

End of questionnaire

Thank you for helping us with this important study investigating chest pain and chest discomfort

Sponsor: UCL University of Bristol Barts Health NHS NHS Trust

16. Appendix 7.3

Clinical Cohorts in Coronary disease Collaboration (4C)

CLINICAL CASE RECORD FORM VERSION 1.1 (14.08.13)

Affix unique patient identifier label here

Case notes reviewed by (recruiter ID): _ _ _ **Date of case note review:** _ _ / _ _ / _ _

(full name, for external reviewers):

Site: 001 ☐ 002 ☐ 003 ☐ 004 ☐

Method of admission/setting

		Elective planned[1]	☐	Inpatient transfer[2]	☐	Emergency[3]	☐

Final diagnosis

		Stable angina[1]	☐	Unstable angina[2]	☐	STEMI[3]	☐
		NSTEMI[4]	☐	Non-CAD chest pain[5]	☐	Other[6]	☐

	Specify other:

Outcome

		No treatment[1]	☐	Medical management[2]	☐	PCI[3]	☐
		Surgery[4]	☐	Further investigation[5]	☐	Other[6]	☐

	Specify further investigation:	Specify other:

Date of recruitment ☐☐☐☐☐☐☐☐ D D M M Y Y Y Y

Patient deceased? Yes[1] ☐ Enter date of death ☐☐☐☐☐☐☐☐ D D M M Y Y Y Y

SECTION A: HISTORY/PHYSICAL EXAMINATION

A1. HISTORY OF CHEST PAIN

1.1 Chest pain/discomfort as a presenting symptom

Yes[1] ☐ No[2] *(go to qn A2)* ☐

1.2 Other symptoms or reasons referred for investigation (tick all that apply)

Shortness of breath[1]	☐	Non-specific symptoms[8]	☐	Palpitations[3]	☐	Other pain[9]	☐
Dizziness[10]	☐	Syncope[11]	☐	Pre-operative[12]	☐	Not recorded[7]	☐
Other[5]	☐	Specify:					

1.3 Chest pain characterization in the history

Typical[1] ☐ Atypical[2] ☐ Non-cardiac[4] ☐

1.4 Physician diagnosis

Stable exertional angina (go to qn A1.5)1	☐	ACS: Unstable angina[8] (go to qn A1.7)	☐	ACS: STEMI[9] (go to qn A1.7)	☐	Non-cardiac chest pain[4] (go to qn A2)	☐
				ACS: NSTEMI[10] (go to qn 1.7)	☐		

1.5 If stable angina, based on the history provided about the patient's activity level select CCS class *(select only one option)*

Angina only during strenuous or prolonged exertion at work or recreation[1]	☐
Slight limitation, with angina only during vigorous physical activity[2]	☐
Symptoms with everyday living activities, i.e. moderate limitation[3]	☐
Inability to perform any activity without angina or angina at rest, i.e. severe limitation[4]	☐

1.6 If stable angina, pre-test probability of coronary artery disease

Low[1] ☐ Medium[2] ☐ High[3] ☐

Duke % probability of CAD ____ %

1.7 If ACS

Peak troponin level ____ Units ____ Troponin T or Troponin I value recorded? T[1] ☐ I[2] ☐

ECG changes: ST elevation[7] ☐ ST depression[1] ☐ Yes, not further specified[8] ☐ Other[3] (e.g. T wave inversion) ☐ None[0] ☐

A2. RISK FACTORS (at time of index investigation)

2.1 Smoking ☐ Current smoker[1] ☐ Ex-smoker[2] ☐ Never smoked[4]

2.2 Hypertension ☐ Yes[1] Year of diagnosis ____

2.3 Hyperlipidaemia ☐ Yes[1] Year of diagnosis: ____

2.4 Diabetes mellitus ☐ Yes[1] Year of diagnosis: ____ ☐ [1]Type 1 ☐ [2]Type 2

2.5 Body weight ☐ Normal weight[1] ☐ Overweight[2] ☐ Obese[3] ☐ Morbidly obese[4] ☐ Elevated[5]

2.6 Family history (1st degree relative) of coronary heart disease

Positive[1] ☐

Relation	Age at diagnosis	Diagnosis
Mother[1] ☐	☐☐	MI[1] ☐ CAD[2] ☐
Father[2] ☐	☐☐	MI[1] ☐ CAD[2] ☐

2.7 Body measurements – record measurements closest to index

Date of measurements ☐☐☐☐☐☐☐☐ D D M M Y Y Y Y

Body weight	☐ _____stones _____ pounds	OR	☐ _____ kg	AND	☐ _____ BMI
Height	☐ _____feet _____ inches	OR	☐ _____ cm		

2.8 Blood pressure reading

	1) Enter value **at index** or **before**, but closest to index investigation (D D M M Y Y Y Y)	2) *Enter value **after**, but closest to index investigation* (D D M M Y Y Y Y)
Systolic BP	mmHg	mmHg
Diastolic BP	mmHg	mmHg
Method of BP measurement	Invasive[1] (ascending aorta) ☐ Non-invasive[2] ☐	Invasive[1] (ascending aorta) ☐ Non-invasive[2] ☐
2.9 Heart rate	bpm	bpm

A3. PHYSICIAN DIAGNOSED PREVIOUS CARDIAC HISTORY *Include all events leading to but not including the current admission*

☐ Yes[1]
☐ No[2] *(go to qn A4)*

Ischaemic heart disease (IHD) or coronary heart disease (CHD)	☐ Yes[1]		Date of first diagnosis (D D M M Y Y Y Y)	
		Treatment (first admission for IHD/CHD): PCI[1] ☐ Medical[2] ☐ Surgery[3] ☐		
Myocardial infarction (MI)	☐ Yes[1]	Number of total MIs	Date of first MI (D D M M Y Y Y Y)	
		Type (first MI if known): STEMI[1] ☐ NSTEMI[2] ☐		
Unstable angina	☐ Yes[1]	Number of total admissions	Date of first admission for unstable angina (D D M M Y Y Y Y)	
Angiogram	☐ Yes[1]	Number of total angiograms	Date of first Angiogram (D D M M Y Y Y Y)	
Percutaneous coronary intervention (PCI)	☐ Yes[1]	Number of total PCIs	Date of first PCI (D D M M Y Y Y Y)	
		Number of total vessels revascularised ever (prior to index)	Number of total stents ever (prior to index)	
Coronary artery bypass graft (CABG)	☐ Yes[1]	Number of total surgeries	Date of first CABG (D D M M Y Y Y Y)	
		Number of total vessels bypassed ever (prior to index)		
Heart failure	☐ Yes[1]	Type: Ischaemic[1] ☐ Non-ischaemic cardiomyopathy[2] ☐ Hypertensive[3] ☐ Other[4] ☐		
		NYHA class at enrolment: I[1] ☐ II[2] ☐ III[3] ☐ IV[4] ☐		
		Latest LVEF value Good[1] ☐ Mild[2] ☐ Moderate[3] ☐ Severe[4] ☐ %	Enter month and year of LVEF result (M M Y Y Y Y)	

Arrhythmia	☐ Yes[1]	Date of first diagnosis	D D M M Y Y Y Y
		Type of arrhythmia (at first diagnosis): Atrial fibrillation[1] ☐ Ventricular tachycardia[2] ☐ Supraventricular tachycardia[3] ☐ Bradyarrhythmia[4] ☐ Atrial flutter[5] ☐ Other[6] (state below) ☐	
		1st device: Pacemaker[1] ☐ Implantable cardioverter defibrillator[2] (ICD) ☐ Biventricular pacemaker[3] ☐	
		Date first device inserted	D D M M Y Y Y Y

A4. NON-CARDIAC HISTORY

☐ Yes[1]
☐ No[0] *(go to Section B)*

Peripheral arterial disease	☐ Yes[1]	Location: Abdominal aortic aneurism[1] ☐ Lower limb ischaemia[2] ☐	Date of first diagnosis	D D M M Y Y Y Y
Stroke	☐ Yes[1]	Type of stroke: Ischaemic[1] ☐ Haemorrhagic[2] ☐	Date of first diagnosis	D D M M Y Y Y Y
TIA	☐ Yes[1]		Date of first diagnosis	D D M M Y Y Y Y
Chronic obstructive pulmonary disease/asthma	☐ Yes[1]	On treatment? Yes[1] ☐ No[0] ☐	Date of first diagnosis	D D M M Y Y Y Y
Chronic renal disease	☐ Yes[1]	Aetiology: Hypertension[1] ☐ Diabetes mellitus[2] ☐ Other[3] ☐	Date of first diagnosis	D D M M Y Y Y Y
		Treatment: None[0] ☐ Haemodialysis[1] ☐ Chronic peritoneal dialysis[2] ☐	(e)GFR at enrolment	Value ☐ GFR[1] ☐ eGFR[2] ☐ Units ☐
Obstructive sleep apnoea	☐ Yes[1]	Treated? Yes[1] ☐ No[0] ☐	Date of first diagnosis	D D M M Y Y Y Y
Depression	☐ Yes[1]	Treated? Yes[1] ☐ No[0] ☐	Date of first diagnosis	D D M M Y Y Y Y
Cancer	☐ Yes[1]	Type of cancer ☐	Date of first diagnosis	D D M M Y Y Y Y

Other diagnoses	**Year of diagnosis**		**Year of diagnosis**
Diagnosis 1 ☐	☐☐☐☐	**Diagnosis 4** ☐	☐☐☐☐
Diagnosis 2 ☐	☐☐☐☐	**Diagnosis 5** ☐	☐☐☐☐
Diagnosis 3 ☐	☐☐☐☐	**Diagnosis 6** ☐	☐☐☐☐

SECTION B: CORONARY CATHETERISATION

B. Results of index (preferred) or non-index angiogram soonest after date of index investigation

1.1 Invasive coronary angiogram +/- PCI = NATIVE VESSELS

D D M M Y Y Y Y	*Enter date of procedure*	*Normal study* ☐ *Yes*[1]

	Had previous stent? *(tick if yes*[1]*)*	Occlusion now *(state % or mod/sev/ blocked))*	Treated now? *(enter BMS or DCS for type)*		Had previous stent? *(tick if yes*[1]*)*	Occlusion now *(state % or mod/sev/ blocked))*	Treated now? *(enter BMS or DCS for type)*		Had previous stent? *(tick if yes*[1]*)*	Occlusion now *(state % or mod/sev/ blocked))*	Treated now? *(enter BMS or DCS for type)*
LM				**P LAD before 1st branch**				**P LAD after 1st branch**			
D1				**Septal**				**D2**			
Mid LAD				**Distal LAD**				**Ramus**			
P LCX				**OM1**				**OM2**			
OM3				**M LCX**				**D LCX**			
P RCA				**MRCA**				**D RCA**			
PDA				**PLV branch**							
Dominance	Right[1] ☐ Left[2] ☐ Co-dominance[3] ☐			**LVEF** %	Good[1] ☐ Moderate[3] ☐	Mild[2] ☐ Severe[4] ☐		**Outcome (state)**			

1.2 Coronary CT angiogram

D D M M Y Y Y Y	*Enter date of procedure*	*Normal study* ☐ *Yes*[1]

	Had previous stent? *(tick if yes*[1]*)*	Occlusion now *(state % or mod/severe/ blocked)*		Had previous stent? *(tick if yes*[1]*)*	Occlusion now *(state % or mod/severe/ blocked)*		Had previous stent? *(tick if yes*[1]*)*	Oocclusion now *(state % or mod/severe/ blocked)*
LM			**P LAD before 1st branch**			**P LAD after 1st branch**		
D1			**Septal**			**D2**		
Mid LAD			**Distal LAD**			**Ramus**		
P LCX			**OM1**			**OM2**		
OM3			**M LCX**			**D LCX**		
P RCA			**MRCA**			**D RCA**		
PDA			**PLV branch**					
Dominance	Right[1] ☐ Left[2] ☐ Co-dominance[3] ☐		**LVEF** %	Good[1] ☐ Moderate[3] ☐	Mild[2] ☐ Severe[4] ☐	**Outcome (state)**		

1.3 Invasive coronary angiogram +/- PCI = GRAFTS

D D M M Y Y Y Y	*Enter date of procedure*	*Normal study* ☐ *Yes*[1]

	Type of graft *(state IMA[1] or vein graft (VG)[2])*	Occlusion now *(state % or mod/sev/ blocked))*	Treated now? *(enter BMS or DCS for type)*		Type of graft *(state IMA[1] or vein graft (VG)[2])*	Occlusion now *(state % or mod/sev/ blocked))*	Treated now? *(enter BMS or DCS for type)*		Type of graft *(state IMA[1] or vein graft (VG)[2])*	Occlusion now *(state % or mod/sev/ blocked))*	Treated now? *(enter BMS or DCS for type)*
LM				**P LAD before 1st branch**				**P LAD after 1st branch**			
D1				**Septal**				**D2**			
Mid LAD				**Distal LAD**				**Ramus**			
P LCX				**OM1**				**OM2**			
OM3				**M LCX**				**D LCX**			
P RCA				**MRCA**				**D RCA**			
PDA				**PLV branch**							
Dominance	Right[1] ☐ Left[2] ☐ Co-dominance[3] ☐			**LVEF** %	Good[1] ☐ Mild[2] ☐ Moderate[3] ☐ Severe[4] ☐			**Outcome (state)**			

1.4 Overall assessment (from 1.1, 1.2 or 1.3)

Normal angiogram[1] ☐	1 diseased vessel[2] ☐	2 diseased vessel[3] ☐	3 diseased vessel[4] ☐

SECTION C: OTHER INVESTIGATIONS

TESTS CARRIED OUT AT INDEX (PREFERRED) OR SOONEST BEFORE/AFTER INDEX, IF RELATED TO INDEX INVESTIGATION *Collected from test reports or discharge summary*

C1. Resting ECG findings

Test performed: ☐ Yes[1] ☐ No[2] *(If no, go to QC2)*	Date of resting ECG closest to index investigation D D M M Y Y Y Y	
Normal study *(if the conclusion states normal)* ☐ Yes[1]	LBBB ☐ Yes[1]	RBBB ☐ Yes[1]
Paced ☐ Yes[1] Type ☐ Single-chamber[1] ☐ Dual-chamber[2] ☐ Rate-responsive[3] ☐ Other (state below)[4]	Abnormal findings (from text)	

C2. Exercise electrocardiogram finding

Test performed:	☐ Yes[1] ☐ No[2] *(If no, go to QC3)*	Date of exercise ECG closest to index investigation	D D M M Y Y Y Y
		Normal study *(if the conclusion states normal)* Yes[1] ☐	Minutes exercised ____ mins
		BP response Normal[1] ☐ Abnormal[2] ☐	Excessive high/fall? Excessive High[1] ☐ Excessive Fall[2] ☐
Pre-test HR: ____ bpm		Age predicted max HR reached Yes[1] ☐	Maximal HR reached: ____ bpm
		>1 mm ST segment flattening/down sloping Yes[1] ☐	Leads I[1] ☐ II[2] ☐ III[3] ☐ aVF[4] ☐ aVL[5] ☐ aVR[6] ☐ V1[7] ☐ V2[8] ☐ V3[9] ☐ V4[10] ☐ V5[11] ☐ V6[12] ☐
		ST elevation Yes[1] ☐	Leads I[1] ☐ II[2] ☐ III[3] ☐ aVF[4] ☐ aVL[5] ☐ aVR[6] ☐ V1[7] ☐ V2[8] ☐ V3[9] ☐ V4[10] ☐ V5[11] ☐ V6[12] ☐
		Territory of ECG changes: Anterior[1] ☐ Lateral[2] ☐ Inferior[3] ☐	
		Ventricular ectopy during test Yes[1] ☐	Chest pain during test Yes[1] ☐

C3. Resting trans-thoracic echocardiogram findings

Test performed:	☐ Yes[1] ☐ No[2] *(If no, go to QC4)*	Date of resting trans-thoracic echo closest to index investigation	D D M M Y Y Y Y
		Normal study *(if the conclusion states normal)* Yes[1] ☐	LVEF ____ %
		LVEF *(from text)* Good[1] ☐ Mild[2] ☐ Moderate[3] ☐ Severe[4] ☐	Regional wall motion abnormality Yes[1] ☐ (Go to C8 to enter results)
		Left atrial size: Area (cm²) ____ AP diameter (cm) ____	LVED dimension ____ cm
		Any **significant** valve disease? Yes[1] ☐	

Tick the appropriate combination:

		Aortic[1]	Mitral[2]	Tricuspid[3]	Pulmonary[4]
Stenosis[1]	Moderate[1]				
	Severe[2]				
Regurgitation[2]	Moderate[1]				
	Severe[2]				

C4. Stress echocardiogram test findings

Test performed:	☐ Yes[1] ☐ No[2] *(If no, go to QC5)*	Date of stress echo test closest to index investigation	D D M M Y Y Y Y
		Normal study *(if the conclusion states normal)* Yes[1] ☐	Regional wall motion abnormality Yes[1] ☐ (Go to C8 to enter results)
		LVEF ____ % Good[1] ☐ Mild[2] ☐ Moderate[3] ☐ Severe[4] ☐	Was ischaemia induced? Yes[1] ☐ Stressor: Adenosine[1] ☐ Dobutamine[2] ☐ Dipyridamole[3] ☐

C5. Nuclear myocardial perfusion test findings

Test performed: ☐ Yes[1] ☐ No[2] *(If no, go to QC6)*

Date of nuclear myocardial perfusion test closest to index investigation: D D M M Y Y Y Y

Normal study *(if the conclusion states normal)* Yes[1] ☐

LVEF % Good[1] ☐ Mild[2] ☐ Moderate[3] ☐ Severe[4] ☐

Was ischaemia induced? Yes[1] ☐

Stressor : Adenosine[1] ☐ Dobutamine[2] ☐ Dipyridamole[3] ☐

Tick the appropriate combination

Type of perfusion defect	Severity	Basal anterior[1]	Basal anteroseptal[2]	Basal inferoseptal[3]	Basal inferior[4]	Basal inferolateral[5]	Basal anterolateral[6]	Mid-anterior[7]	Mid-anteroseptal[8]	Mid-inferoseptal[9]	Mid-inferior[10]	Mid-inferolateral[11]	Mid-anterolateral[12]	Apical anterior[13]	Apical septal[14]	Apical inferior[15]	Lateral[16]	Apex[17]
Reversible[1]	Mild[1]																	
	Moderate[2]																	
	Severe[3]																	
Fixed[2]																		

If fixed, give details

C6. CMR test findings

Test performed: ☐ Yes[1] ☐ No[2] *(If no, go to QC7)*

Date of CMR test closest to index investigation: D D M M Y Y Y Y

Normal study *(if the conclusion states normal)* Yes[1] ☐

LVEF % Good[1] ☐ Mild[2] ☐ Moderate[3] ☐ Severe[4] ☐

Was ischaemia induced? Yes[1] ☐

Stressor : Adenosine[1] ☐ Dobutamine[2] ☐ Dipyridamole[3] ☐

Tick the appropriate combination

Type of perfusion defect	Severity	Basal anterior[1]	Basal anteroseptal[2]	Basal inferoseptal[3]	Basal inferior[4]	Basal inferolateral[5]	Basal anterolateral[6]	Mid-anterior[7]	Mid-anteroseptal[8]	Mid-inferoseptal[9]	Mid-inferior[10]	Mid-inferolateral[11]	Mid-anterolateral[12]	Apical anterior[13]	Apical septal[14]	Apical inferior[15]	Lateral[16]	Apex[17]
Reversible[1]	Mild[1]																	
	Moderate[2]																	
	Severe[3]																	
Fixed[2]																		

If fixed, give details

C7. CT calcium scoring test findings

Test performed:	☐ Yes[1] ☐ No[2] *(If no, go to QC8)*	Date of CT calcium scoring test closest to index investigation	☐☐☐☐☐☐☐☐ D D M M Y Y Y Y
		Territory of calcium LAD[1] ☐ RCA[2] ☐ LCX[3] ☐	Agatston score: ☐☐☐

C8. Regional wall motion abnormality

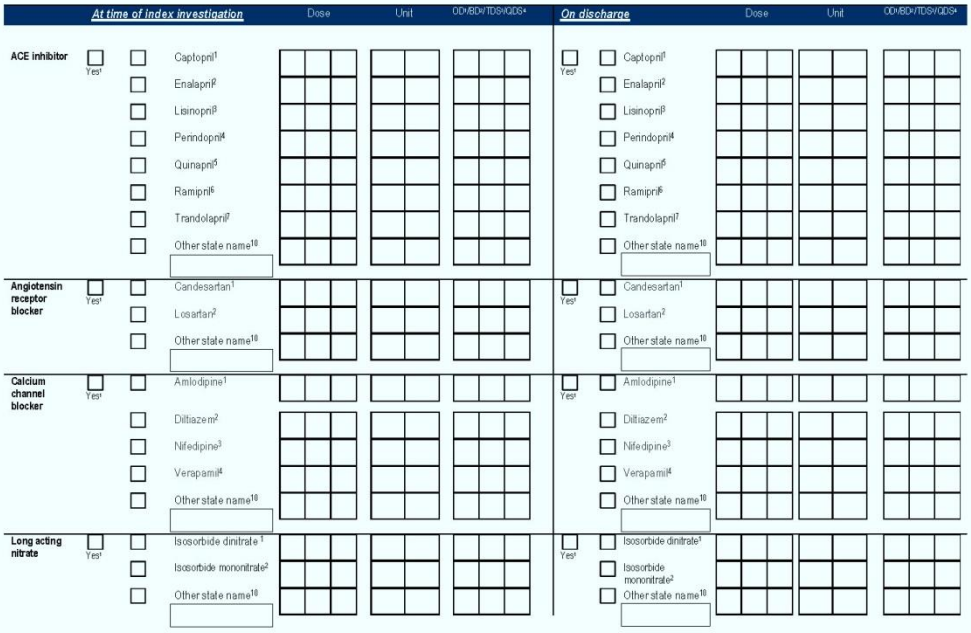
Present:	☐ Yes[1] ☐ No[2] *(If no, go to Section D)*			
Source of information:	Resting echocardiogram[1] ☐	Stress echocardiogram[2] ☐	Nuclear myocardial perfusion scan[3] ☐	MRI stress perfusion scan[4] ☐

Tick the appropriate combination

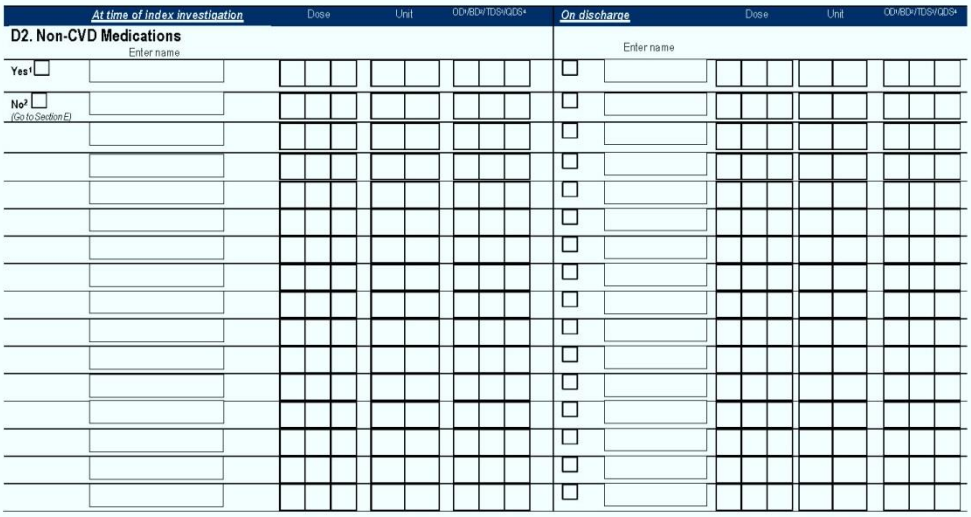
	Basal anterior[1]	Basal anteroseptal[2]	Basal inferoseptal[3]	Basal inferior[4]	Basal inferolateral[5]	Basal anterolateral[6]	Mid-anterior[7]	Mid-anteroseptal[8]	Mid-inferoseptal[9]	Mid-inferior[10]	Mid-inferolateral[11]	Mid-anterolateral[12]	Apical anterior[13]	Apical septal[14]	Apical inferior[15]	Lateral[16]	Apex[17]
Hypokinetic[1]																	
Dyskinetic[2]																	
Akinetic[3]																	

SECTION D: MEDICATION

	At time of index investigation		Dose	Unit	OD/BD/TDS/QDS	On discharge		Dose	Unit	OD/BD/TDS/QDS
D1. CVD Medications										
Beta-blocker	☐ Yes[1]	☐ Atenolol[1]				☐ Yes[1]	☐ Atenolol[1]			
		☐ Bisoprolol[2]					☐ Bisoprolol[2]			
		☐ Carvedilol[3]					☐ Carvedilol[3]			
		☐ Metoprolol[4]					☐ Metoprolol[4]			
		☐ Other state name[10]					☐ Other state name[10]			
Antiplatelet	☐ Yes[1]	☐ Aspirin[1]				☐ Yes[1]	☐ Aspirin[1]			
		☐ Clopidogrel[2]					☐ Clopidogrel[2]			
		☐ Other state name[10]					☐ Other state name[10]			
Anticoagulant	☐ Yes[1]	☐ Heparin[1]				☐ Yes[1]	☐ Heparin[1]			
		☐ Warfarin[2]					☐ Warfarin[2]			
		☐ Other state name[10]					☐ Other state name[10]			
Statin	☐ Yes[1]	☐ Atorvastatin[1]				☐ Yes[1]	☐ Atorvastatin[1]			
		☐ Fluvastatin[2]					☐ Fluvastatin[2]			
		☐ Lovastatin[3]					☐ Lovastatin[3]			
		☐ Pravastatin[4]					☐ Pravastatin[4]			
		☐ Simvastatin[5]					☐ Simvastatin[5]			
		☐ Other state name[10]					☐ Other state name[10]			


At time of index investigation
Dose
Unit
OD/BD/TDS/QDS4
On discharge
Dose
Unit
OD/BD/TDS/QDS4
ACE inhibitor
Yes1
Captopril1
Enalapril2
Lisinopril3
Perindopril4
Quinapril5
Ramipril6
Trandolapril7
Other state name10
Angiotensin receptor blocker
Yes1
Candesartan1
Losartan2
Other state name10
Calcium channel blocker
Yes1
Amlodipine1
Diltiazem2
Nifedipine3
Verapamil4
Other state name10
Long acting nitrats
Yes1
Isosorbide dinitrate1
Isosorbide mononitrate2
Other state name10

	At time of index investigation			Dose	Unit	OD=1/BD=2/TDS=3/QDS=4	On discharge			Dose	Unit	OD=1/BD=2/TDS=3/QDS=4
GTN	☐ Yes[1]	☐	n/k[9]				☐ Yes[1]	☐	n/k[9]			
Diuretic	☐ Yes[1]	☐	Chlorothiazide[1]				☐ Yes[1]	☐	Chlorothiazide[1]			
		☐	Metolazone[2]					☐	Metolazone[2]			
		☐	Bumetanide[3]					☐	Bumetanide[3]			
		☐	Ethacrynic acid[4]					☐	Ethacrynic acid[4]			
		☐	Frusemide[5]					☐	Frusemide[5]			
		☐	Torsemide[6]					☐	Torsemide[6]			
		☐	Amiloride[7]					☐	Amiloride[7]			
		☐	Eplerenone[8]					☐	Eplerenone[8]			
		☐	Spironolactone[9]					☐	Spironolactone[9]			
		☐	Other state name[10]					☐	Other state name[10]			
Glucose lowering	☐ Yes[1]	☐	Insulin[1]				☐ Yes[1]	☐	Insulin[1]			
		☐	Metformin[2]					☐	Metformin[2]			
		☐	Gliclazide[3]					☐	Gliclazide[3]			
		☐	Other state name[10]					☐	Other state name[10]			
Cardiac glycosides	☐ Yes[1]	☐	Digoxin[1]				☐ Yes[1]	☐	Digoxin[1]			
		☐	Other state name[10]					☐	Other state name[10]			
Other	☐ Yes[1]	☐	Enter name				☐ Yes[1]	☐	Enter name			


At time of index investigation
Dose
Unit
OD/BD/TDS/QDS
On discharge
Dose
Unit
OD/BD/TDS/QDS
D2. Non-CVD Medications
Enter name
Enter name
Yes
No
(Go to Section E)

SECTION E: RESEARCH BLOOD SAMPLE COLLECTION

	Please tick:	
Was a fasting blood sample collected from the patient?	Yes[1] ☐	No[2] ☐
	If no, give reason below:	
Was the blood taken: Venous[1] ☐ Arterial sheath[2] ☐	Other[3] ☐	
Was patient given heparin before blood draw? Yes[1] ☐		

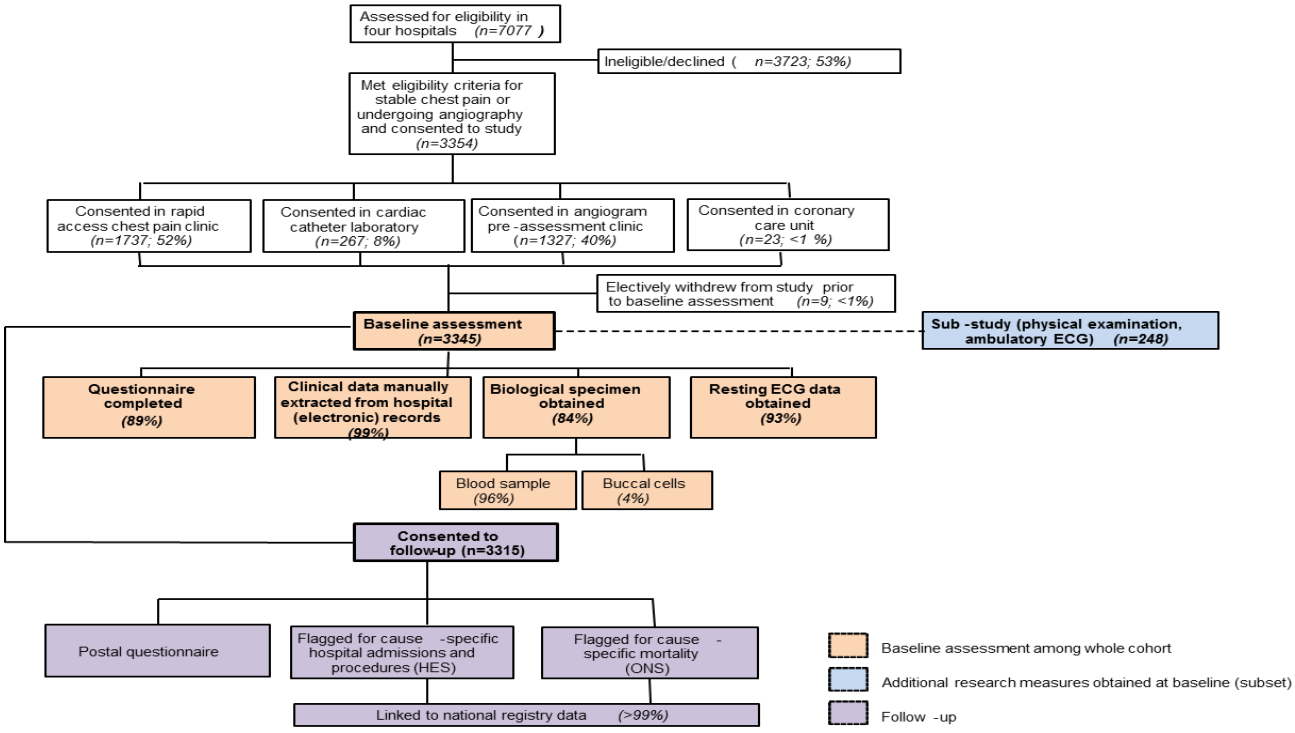
Please record which samples were collected and how the samples were processed below. **Tubes must be collected in the order specified below:**	**Sample collected?** Yes[1]	No[2]	**Sample processing**
			Date of blood draw: ☐☐☐☐☐☐☐☐ (D D M M Y Y Y Y)
			Time of blood draw: ☐☐:☐☐ (H H M M)
2 tubes EDTA (4.0mls each)	☐	☐	Time centrifuged: ☐☐:☐☐ Time aliquoted: ☐☐:☐☐ Deviation from protocol? Yes[1] ☐ No[2] ☐ If yes, give reason:
1 tube PST (4.5ml)	☐	☐	Time centrifuged: ☐☐:☐☐ Time aliquoted: ☐☐:☐☐ Deviation from protocol? Yes[1] ☐ No[2] ☐ If yes, give reason:
1 tube SST (5.0ml)	☐	☐	Time centrifuged: ☐☐:☐☐ Time aliquoted: ☐☐:☐☐ Deviation from protocol? Yes[1] ☐ No[2] ☐ If yes, give reason:
1 tube RNA (PAXgene) (2.5ml)	☐	☐	

Time spent on CRF extraction (hh:min): __ __ : __ __

END OF FORM

17. Appendix 7.4

Figure 7.1 Clinical Cohorts in Coronary disease Collaboration (4C) study flow diagram.



ECG: electrocardiogram; HES: Hospital Episode Statistics; ONS: Office for National Statistics

Figure 7.2. Summary of the standard operating procedure for processing and storage of research blood samples

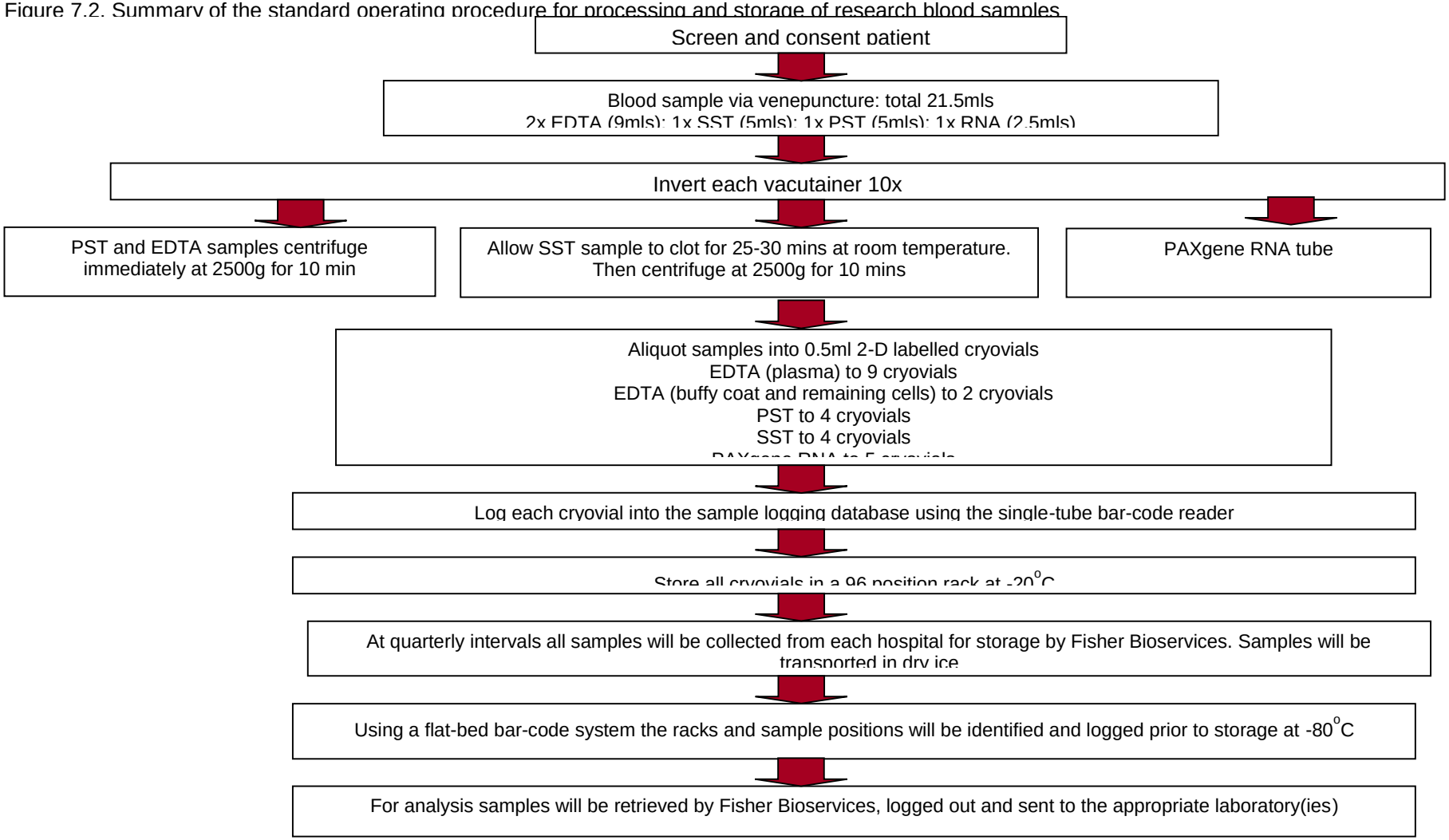


Table 7.2 Methods of extracting clinical data and extent to which data could be accessed

Heart Hospital of London		
	Data available for electronic download	Method of collection
Clinical biochemistry results	Yes	Not done
Resting electrocardiogram	No	Manual photocopying of paper ECG from notes or manual extraction of data from clinical database
Exercise treadmill test	No	Not done
Clinical risk factors	No	Manual extraction of information from the GP referral letter
Medical history	No	Manual extraction of information from the GP referral letter
Symptoms and clinical examination	No	Manual extraction of information from discharge letter and database
Diagnosis	No	Manual extraction of information from discharge letter and database
Coronary angiogram results	No	Manual extraction of information from clinical system
Cardiac investigations/ imaging	No	Manual extraction from clinical systems and imaging reports
Medical management	No	Manual extraction from discharge summary

Table 7.2. Baseline characteristics of patients by heart rate level

	<60 bpm		60-69bpm		70-79 bpm		80-89bpm		90-150bpm	
	Mea	SD	Mea	SD	Mea	SD	Mea	SD	Mea	SD
Demographic										
Age at entry (years)	62.1	12.	59.9	12.	57.0	12.	55.0	12.	56.8	12.
Women	72.7		62.7		62.5		58.0		56.6	
White Ethnicity	65.5		63.0		60.0		59.2		59.9	
Age of education	18.3	7.3	18.0	6.8	19.3	9.2	19.0	7.4	17.8	5.4
Clinical biomarkers										
Heart rate	54.0	4.4	64.6	2.7	74.1	2.8	83.7	2.7	97.9	9.4
Systolic blood	132.	22.	132.	20.	128.	18.	139.	19.	131.	20.
Diastolic blood	73.9	11.	78.1	11.	78.5	11.	80.1	10.	80.8	11.
Hypercholesterole	58.2		54.8		48.2		46.5		53.6	
BMI (kg/m^2)	28.8	4.9	29.1	5.5	29.4	5.2	30.7	5.6	30.2	6.0
Smoking										
Non-smokers	30.2		39.9		43.6		47.8		40.7	
Ex-smoker	47.1		35.1		30.8		25.6		29.0	
Current smoker	22.6		24.9		25.5		26.5		30.2	
Diabetes type II	20.6		28.3		22.1		14.1		14.7	
Medication										
Beta-blockers	24.9		15.4		10.0		6.65		8.36	
Calcium channel	11.0		8.80		9.48		9.03		12.9	
BP medication	32.9		27.8		23.2		20.4		24.7	
Statins	30.3		23.1		19.1		19.2		22.1	
Antiplatelets	26.4		8.78		20.8		16.2		14.2	

Note: Values are means ± standard deviation or % in categorical variables

Table 7.2 Clinical symptoms and assessment of CAD patients by heart rate level

	<60bpm	60-	70-79bpm	80-89bpm	>90bpm
Symptoms on					
Shortness of breath	30.5	33.1	34.9	27.6	37.3
Cardiac history					
Ischaemic/coronary	37.5	30.9	23.9	16.15	19.6
Acute myocardial	21.4	11.7	6.75	4.04	6.92
Unstable angina	1.75	0.74	0.72	0.24	0.29
Heart failure	3.33	2.11	1.72	1.19	2.02
Investigations performed (index					
Invasive coronary angiogram	77.4	55.27	45.4	33.5	40.0
Coronary computed tomography (CT)	3.33	6.07	7.90	9.74	6.92
Angiogram					
Normal angiogram	19.7	25.0	25.0	15.7	14.5
Non-obstructive	20.6	29.1	25.8	17.3	7.04
1 diseased vessel	23.5	19.5	14.2	0.00	16.6
2 diseased vessels	35.2	34.1	39.2	66.6	16.6
3 diseased vessels	41.1	46.3	46.4	33.3	66.6

Note: CAD: coronary artery disease; Values are %

Table 7.4 Baseline health questionnaire responses of the Clinical Cohorts in Coronary disease Collaboration (4C) study cohort.

Questionnaire	Heart rate				
	<60bpm	60-	70-	80-	>90bpm
Functional health status (EQ-					
Mobility					
No problem reported	61.27	60.64	60.98	63.69	53.77
Any problem reported	38.73	39.36	39.02	36.31	46.23
Self-care:					
No problem reported	87.09	86.15	87.07	85.83	82.53
Any problem reported	12.91	13.85	12.93	14.17	17.47
Usual activities:					
No problem reported	61.92	66.25	65.52	69.36	54.45
Any problem reported	38.08	33.75	34.48	30.64	45.55
Pain/discomfort					
No problem reported	25.92	23.78	20.50	21.88	17.99
Any problem reported	74.08	76.22	79.50	78.13	82.01
Anxiety/depression:					
No problem reported	59.30	53.38	51.75	56.29	48.04
Any problem reported	40.70	46.62	48.25	43.71	51.96
Rose angina[182]					
Chest pain	89.30	86.00	85.06	80.05	81.27
Non-cardiac chest pain	7.84	7.84	20.03	25.85	18.52
Canadian Cardiovascular Society					
I	15.63	32.29	27.08	11.46	13.54
II	26.47	32.35	14.71	16.18	10.29
III	11.89	25.26	27.90	19.82	15.12
IV	18.18	9.09	27.27	9.09	36.36
Mental health					
Depression (PHQ-9)[185]	2.98	5.20	4.74	4.28	6.92

Note: Values are (%); PHQ-9: Patient Health Questionnaire

Table 7.5 Follow-up for hospitalisations and mortality in the Clinical Cohorts in Coronary disease Collaboration (4C) cohort

	Office for National Statistics (ONS) (mortality)	**Hospital Episode Statistics (HES) (non-fatal diagnoses and procedures)***
Patients who consented to follow-up (of	3315 (99.1%)	3315 (99.1%)
N (%) patients sent for matching	3315 (100%)	867 (26.2%)*
N (%) patients matched to record	3311 (99.9%)	839 (96.7%)*
Follow-up (months): Median (inter-	20 (14-26)	326 (155-563)
Observed N (%) participants with		
All-cause deaths	110 (2.5%)	-
Cause of death registered	54 (64.3%)	-
CHD-related deaths (ICD-10 codes	25 (46.3%)	-
Non-CHD CVD-related deaths (ICD-10	9 (16.7%)	-
Non-CVD deaths	20 (37.3%)	-
Awaiting cause of death registration	30 (35.7%)	-
Observed N (%) participants with		
Non-fatal AMI + non-fatal stroke +	-	27 (3.2%)
Approximate annual risk (%)	1.3	3.6

AMI: acute myocardial infarction; CHD: coronary heart disease; CVD: cardiovascular disease
*Updated HES data are awaiting release by the NHS Information Centre
** International Classification of Diseases (ICD-10) codes I20 angina pectoris; I21 ST elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (NSTEMI); I22 Subsequent STEMI and NSTEMI; I23 Certain current complications following STEMI and NSTEMI (within 28 day period); I24 Other acute ischaemic heart diseases; and I25 Chronic ischaemic heart disease ***I010 to I99, excluding I200 Unstable Angina to I259 Chronic ischaemic heart disease, unspecified

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