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Excessive Orthostatic Changes in Blood Pressure are Associated with Incident Heart Failure in Older Men: a prospective analysis from The British Regional Heart Study

Running title – Orthostatic change in BP and heart failure

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Figure 1

Abstract

We have assessed the association between excessive orthostatic changes in blood pressure and risk of incident heart failure (HF) in older, community-dwelling men. This was a prospective cohort study of 3505 men (mean age 68.5 years); who did not have prevalent heart failure, myocardial infarction or stroke. Excessive orthostatic change in blood pressure was defined continuously and categorically as orthostatic hypotension (sitting-to-standing decrease in systolic blood pressure ≥20 mmHg and/or diastolic blood pressure ≥10 mmHg), systolic orthostatic hypertension (increase in systolic blood pressure ≥20 mmHg, diastolic orthostatic hypertension as diastolic blood pressure ≥10 mmHg) and orthostatic normotension (neither orthostatic hypotension, nor orthostatic hypertension). There was a U-shaped association between orthostatic changes in systolic blood pressure and the risk of incident heart failure; for diastolic blood pressure, only its fall predicted heart failure. After adjustment for possible confounders, the hazard ratio (95% CI) for incident heart failure was 1.65 (1.24–2.18) in men with orthostatic hypotension, 0.90 (0.65,1.24) and 1.88 (1,30,2.73) in men with diastolic and systolic orthostatic hypertension, respectively. Both components of orthostatic hypotension were associated with increased risk, although the systolic component was more predictive than the diastolic component.

Both orthostatic hypotension and orthostatic hypertension are associated with risk of incident heart failure in older men. Our findings suggest that orthostatic hypertension is defined by a rise beyond threshold in systolic blood pressure only. Further prospective studies in diverse cohorts are needed to confirm our findings.

Key Words

Heart failure; Cardiovascular epidemiology; Orthostatic hypotension; Orthostatic hypertension;

Introduction

Heart failure (HF) is a growing, but already major, worldwide public health problem (1). It has a lifetime risk of almost 40% at 90 years of age (2). Major clinical risk factors include age, hypertension, myocardial infarction, valvular heart disease, left ventricular hypertrophy, obesity and diabetes (2). The prognosis of HF is poor and comparable to some types of cancer, with 5-year survival rates approximately 57% (3, 4). Identifying novel risk factors may facilitate earlier diagnosis and inform preventative strategies (5).

Observational studies have described an association between exaggerated orthostatic blood pressure changes and incident cardiovascular disease (6-8). Such positional variability in blood pressure may mark a derangement of autonomic nervous system adaptation to postural changes, and these derangements may be related to cardiovascular disease (9). Increases or decreases in blood pressure on standing each increase risk of cerebral infarction (10), lacunar stroke (11) and death due to cerebrovascular disease (12). In younger adults, there is a strong association between orthostatic hypotension – a decrease in blood pressure on standing – and risk of incident heart failure (7). However, the predictive role of orthostatic hypotension in older adults – in whom the burden of both orthostatic hypotension and heart failure is greatest (13-15) – is unclear. Furthermore, although orthostatic hypertension – an increase in blood pressure on standing – has been associated with biochemical and clinical predictors of HF, including high-sensitivity troponin T (16), NT-proBNP (16) and left ventricular hypertrophy (17), paradoxically, two prospective studies in middle-aged adults have shown increases in blood pressure on standing to be associated with reduced risk of HF (8,16). The aim of this study was to examine

the prospective association between orthostatic blood pressure change and risk of incident HF in older, community-dwelling men.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request (contact Lucy Lennon at l.lennon@ucl.ac.uk).

Study Population – The British Regional Heart Study (BRHS) is an on-going prospective cohort study. It initially recruited 7735 men aged 40-59 years between 1978 and 1980 (18). The majority of participants (>99%) were of white European ethnicity. Seated and standing blood pressure measurements were first taken during the 20th year re-examination of the cohort, between 1998 and 2000. The baseline data for the present analysis is from this re-examination. During the re-examination, men completed a questionnaire about lifestyle and medical background, underwent physical examination and provided a fasting venous blood sample. 4252 men (77% response rate) of those invited for re-examination attended. Ethical approval was obtained from the National Research Ethics Service Committee London.

BP measurement – Blood pressure was measured on the right arm using an automatic Dinamap 1846SX. The bladder centre of the cuff was aligned over the brachial artery. If arm circumference was <32 cm, an adult cuff was used; ≥32 cm and a large adult cuff was used. For sitting measurements, participants were asked to rest their arm on the examination table so that the upper arm was at chest level. The Dinamap blood pressure monitor overestimated systolic blood pressure by ~8 mmHg compared with the standard mercury sphygmomanometer which was the standard reference instrument for blood pressure measurement at the time (19). 8 mmHg

was therefore subtracted from the raw systolic blood pressure readings.

The Dinamap was set to take repeated measurements at one minute intervals. Four consecutive blood pressure measurements – two sitting, followed by two standing – were taken. Participants had not been seated nor supine for a prescribed duration prior to the first measurement. After the second sitting measurement had completed, the participant was asked to stand. The first standing blood pressure measurement was made within one minute of the participant standing. The second standing blood pressure measurement began after one minute, but before two minutes, of standing.

Definition of orthostatic changes in blood pressure – Orthostatic changes in blood pressure were categorised into orthostatic hypotension, orthostatic hypertension and orthostatic normotension. "Orthostatic hypotension" was defined fulfilling the consensus definition (20) as a decrease in systolic blood pressure ≥20 mmHg and/or diastolic blood pressure ≥10 mmHg that occurred between either the first or second standing blood pressure measurements and the mean of the two sitting blood pressure measurements. If the decrease only affected systolic blood pressure, this was classified as "isolated systolic orthostatic hypotension". If the drop only affected diastolic blood pressure, this was classified as "isolated diastolic orthostatic hypotension". If the drop affected both systolic and diastolic blood pressure, this was classified as "combined systolic and diastolic orthostatic hypotension". Since a uniform definition of orthostatic hypertension is still not established and it is argued that defining orthostatic hypertension by elevated diastolic blood pressure is less reliable (21) we considered systolic and diastolic orthostatic hypertension separately. There is no consensus definition of orthostatic hypertension, but a recent review (8)

has suggested the definition should mirror the thresholds used to define orthostatic hypotension. "Orthostatic systolic hypertension" was therefore defined as an increase in systolic blood pressure ≥20 mmHg irrespective of rise in diastolic blood pressure; orthostatic diastolic hypertension was defined as an increase in diastolic BP ≥10 mmHg only that occurred between either, the first or second standing blood pressure measurements and the mean of the two sitting blood pressure measurements. Orthostatic hypertension was also further sub-divided into "isolated systolic orthostatic hypertension", "isolated diastolic orthostatic hypertension" and "combined systolic and diastolic orthostatic hypertension". Men in the "orthostatic normotension" group had neither orthostatic hypotension, nor orthostatic hypertension.

Follow-up – Follow-up took place between the 20th year re-screening examination of The BRHS (between 1998 and 2000) and June 2016. All-cause mortality and morbidity events were based on data collected during this period. Survival times were censored at date of HF, death from any cause or end of the follow-up period, whichever occurred first. Evidence of non-fatal myocardial infarction and HF was obtained by ad-hoc reports from general practitioners and supplemented by biennial review of primary care records, which included correspondence from secondary care. Incident HF was based on doctor diagnosis and confirmed by a review of available clinical information including symptoms, signs, investigations and response to treatment. The incidence and determinants of HF cases identified through this process have been reported previously and are consistent with results from other studies (22,23). Incident HF included incident non-fatal HF as well as death from HF (ICD 9th revision code 428 or ICD 10th revision I28). Case definitions – based on primary care record reviews – have been reported previously (23). Atrial fibrillation (AF) was defined according to Minnesota codes 8.3.1 and 8.3.3. Hypertension was defined as mean sitting blood pressure ≥140/90 mmHg. Antihypertensive medications were defined as use

of any antihypertensive medication as per British National Formulary (version 38) code 3.1. Chronic obstructive pulmonary disease (COPD) was defined as a forced expiratory volume in one second to forced vital capacity ratio of <0.7.

Methods used for data collection, measurement and classification for measures of lipids, lung function, smoking status, physical activity, alcohol intake, social class and cardiac markers NT-proBNP concentration and high sensitivity Troponin T (cTnT) have been reported previously (18,22,24-26). Predicted glomerular filtration rate (eGFR) was estimated from serum creatinine with the MDRD formula: $eGFR = 186 \times (Creatinine / 88.4)^{-1.154} \times (Age)^{-0.203}$. A resting 12-lead electrocardiogram (ECG) was recorded.

Statistical Analysis – Statistical analyses were conducted in SAS 9.4. F-tests and chi-squared tests were used to examine the association between baseline characteristics and categories of orthostatic change in blood pressure. Continuous variables that were skewed (triglycerides, glucose, CRP, IL-6, NT-proBNP and cTnT) were log-transformed to approximate normality for parametric tests. Restricted cubic splines were used to visually depict the association between orthostatic changes in blood pressure and risk of incident HF. Cox proportional hazards model was used to assess the multivariate-adjusted hazards ratio (HR) in a comparison of the orthostatic blood pressure changes groups using the orthostatic normotension group as the reference. BMI, heart rate, average sitting systolic blood pressure, total cholesterol, IL-6, NT-proBNP and cTnT were fitted as continuous variables. Physical activity (inactive or not inactive), smoking status (never smoked, ex-smoker for 0–15 years, ex-smoker for >15 years and current smoker), alcohol consumption (0–15 units per week and >16 units per week), social class (manual or non-manual)

and the presence or absence of AF (0/1), diabetes (0/1), chronic kidney disease (CKD) (0/1), COPD (0/1) and anti-hypertensive medication use (0/1) were fitted as categorical variables. We further adjusted for incident myocardial infarction as a time-dependent variable.

Study Population – Of the 4252 men, 4045 had measurements of biochemistry. Men with prevalent heart failure (n=117), MI (n=261), stroke (n=101) and incomplete sitting and standing blood pressure measurements (n=61) were excluded, leaving 3505 participants for the present analysis.

Results

The mean age of the 3505 men was 68.5 years. Over a mean follow-up of 13.3 years, there were 336 cases of incident HF. At baseline, 20.3% of men had orthostatic hypotension; 17% had diastolic orthostatic hypertension and 6.9% had systolic orthostatic hypertension (Table 1). Compared to those with orthostatic normotension, men with orthostatic hypotension were older, had lower BMI, more likely to be prescribed anti-hypertensive medications, have hypertension, AF, CKD and COPD. The majority of men prescribed antihypertensive treatment (75%) were on beta blockers, diuretics or ace inhibitors. Men with orthostatic systolic or diastolic orthostatic hypertension tended to have characteristics more akin to the orthostatic normotension group. Orthostatic hypotension was associated with a range of circulating cardiovascular risk markers, including HDL, IL-6, VWF, NT-proBNP and high-sensitivity troponin T; orthostatic systolic hypertension and diastolic orthostatic hypertension were not associated with these markers.

When orthostatic change in blood pressure was assessed continuously, risk of incident HF was U-shaped for systolic blood pressure: increases and decreases in orthostatic systolic blood pressure were associated with increased risk of HF, regardless of whether the change occurred within or after one minute of standing (Figure 1 panel A and B). For diastolic blood pressure only a decrease in blood pressure was associated with increased risk (Figure 1 panel C and D). Further analyses by categories of systolic blood changes using -10-+10 mmHg change as the reference showed that risk of HF started to increase at decreases of 15-20 mmHg (HR=1.45 (0.97,2.16) but was only significantly raised at changes $\geq$20 mmHg. For diastolic blood pressure compared to the -5 to +5 mmHg orthostatic change, risk of heart failure was already increased when orthostatic diastolic blood pressure fell by 7-10 mmHg [HR (95%CI) =2.13 (1.41,3.21)] .

When orthostatic change in blood pressure was categorised by threshold changes in blood pressure, compared to men with orthostatic normotension, men with orthostatic hypotension and those with systolic orthostatic hypertension had significantly increased risk of incident HF, while men with diastolic orthostatic hypertension did not (Table 2). These associations persisted even after adjustment for lifestyle factors, comorbidity, inflammation, markers of cardiac dysfunction (NT-proBNP and cTnT) and incident MI. Diastolic orthostatic hypertension is more common; thus if orthostatic hypertension was defined on the basis of including either diastolic or systolic orthostatic hypertension, no association would have been seen with orthostatic hypertension [HR (95%CI) 1.17 (0.89,1.52)] compared to the orthostatic normotensive men).

The systolic component of orthostatic hypotension was associated with stronger risk of incident HF than the diastolic component (Table 3). The age-adjusted hazard ratio for risk of incident HF in men with isolated systolic orthostatic hypotension was 1.71 (95% CI 1.28 – 2.30), compared to 1.35 (95% CI 0.78 – 2.34) in men with isolated diastolic orthostatic hypotension and 2.57 (95% CI 1.49 – 4.46) in men with combined systolic and diastolic orthostatic hypotension. The association between isolated systolic orthostatic hypotension and HF remained even after adjustment for factors in model 5 and incident MI; the association with combined systolic and diastolic orthostatic hypotension, was however significantly attenuated (Table 3).

Discussion

In this study of older, community-dwelling men without HF, myocardial infarction or stroke at baseline, there was a U-shaped relationship between orthostatic change in systolic blood pressure and risk of incident HF: risk increased as orthostatic change in systolic blood pressure increased, regardless of whether it was a rise, or fall. For diastolic blood pressure only a fall was associated with increased risk. Exaggerated falls in blood pressure on standing (orthostatic hypotension) are well-recognised among clinicians, while exaggerated increases in blood pressure on standing (orthostatic hypertension) are under-appreciated. Our study extends the current literature by showing that both conditions, depending on the components used to define them, are associated with increased risk of developing HF in older men, and the systolic component of change in orthostatic blood pressure appears more strongly associated with risk than the diastolic component.

Diastolic blood pressure has generally been omitted in definitions of orthostatic hypertension (8).

Our findings support this and suggest that orthostatic hypertension should be defined on the basis of orthostatic increase in systolic blood pressure only. The prevalence of orthostatic hypertension will thus depend on how it is defined ranging from 6.9% on the basis of a rise in systolic only to 23.9% if diastolic blood pressure is included.

Orthostatic Hypotension and Risk of Heart Failure – There is a strong association between orthostatic hypotension and risk of HF in middle-aged adults (6). Whether this is the case in older adults, in whom HF and orthostatic hypotension are more common is less clear (15-17). Among eight prospective studies included in a meta-analysis, four had a mean age >65 years and there was a statistically significant association between orthostatic hypotension and risk of incident HF in only one of these (7,27). In general, follow-up in middle-aged cohorts has been over 10 years, but shorter in older cohorts (7). Differences in follow-up duration may account for the inconsistencies between studies.

The study confirms an association between orthostatic hypotension fulfilling the consensus definition and risk of HF in older adults which was seen to be independent of important predictors of HF, including IL-6 (a proinflammatory cytokine implicated in the aetiology of HF (28)), high-sensitivity troponin T (a marker of myocardial injury) and NT-proBNP (a marker of cardiac stress). There was suggestion that risk of HF was increased even if the decrease in diastolic blood pressure on standing is below clinical thresholds used to define orthostatic hypotension (>10 mmHg) as risk was already seen to be elevated at levels of 7-10 mmHg drop .

Orthostatic Hypertension and Risk of Heart Failure –We observed that only orthostatic systolic

hypertension is associated with increased risk of HF irrespective of the rise in diastolic blood pressure. However, two prospective studies in middle-aged adults have shown increases in blood pressure on standing to be associated with reduced risk of HF (8,16). The ages at baseline in these cohorts were 54.2 years and 45.6 years, compared to 68.5 years in the present study. If the underlying mechanisms, and affected bodily systems, causing exaggerated orthostatic increases in blood pressure are different in younger and older people, the prognostic role of this clinical sign, with respect to risk of developing HF, may be different across age groups.

Mechanisms - The mechanisms underlying the association between exaggerated orthostatic changes in blood pressure and increased risk of HF are unknown but are likely to be multifactorial. Orthostatic hypotension has been associated with inflammatory mediators (29) and left ventricular hypertrophy (30) (both are implicated in the aetiology of HF), while orthostatic increases and decreases in blood pressure have each been associated with markers of myocardial injury (high-sensitivity troponin T) and cardiac stress (NT-proBNP) (16); biochemical predictors of risk of developing HF. Although in this study neither diastolic nor systolic orthostatic hypertension related to NT-proBNP or cTnT, accepted markers of cardiac dysfunction/myocardial injury. However we did not have echocardiographic measurements or results from other imaging modalities that may have detected subclinical cardiac dysfunction. We speculate that exaggerated orthostatic fall in blood pressure in older adults may be an early sign of cardiovascular autonomic dysfunction. Short-term blood pressure variability in general (not that specifically related to orthostatic changes, nor that related to the night-time vs daytime dipping) is associated with adverse cardiovascular outcomes, and - consistent with the findings of the present analysis - risk is particularly related to the variability in systolic blood pressure

(31). The systolic component of orthostatic hypertension may be more predictive of HF as it may reflect both stroke volume and cardiac output [21]. The baroreceptors are arterial stretch receptors and functions less well with less compliant arteries which can also lead to systolic hypertension and increased pulse pressure. Further analyses revealed that those with both systolic hypertension and orthostatic hypotension had the highest mean pulse pressure. Thus blood vessel disease may have caused both orthostatic dysfunction and subsequent HF.

An alternative explanation for the observed association between orthostatic hypotension and risk of HF is reverse causality. An early sign of HF may be the impairment of quick adaptations of cardiac output in response to baroreceptor signalling of decreased blood pressure in the carotid bulb, due to venous pooling upon standing. In this case, HF that is otherwise asymptomatic would manifest as orthostatic hypotension; orthostatic hypotension itself, directly or indirectly, would not be causing HF.

Clinical Implications – Our findings may have practical implications in the diagnostic and therapeutic approaches to patients. From a diagnostic standpoint, diagnosis of orthostatic BP instability would need a 24h ambulatory blood pressure monitoring with accurate compilation of patients' diaries in order to correlate short-term blood pressure changes with postural changes, with specific instructions provided to patients. From a therapeutic standpoint, better tailored pharmacological approaches would be advisable in such cases, including night time administration of antihypertensive drugs as recently proposed by Hermida et al. (32), more attention to fluid intake and balance, as well as the avoidance of drugs more likely to affect

autonomic blood pressure control, such as beta-blockers, alpha-blockers, and centrally acting drugs (33,34).

Strengths and limitations- Strengths of our study include the long duration of follow-up, that we examined an older cohort and adjusted for a wide range of biomarkers associated with HF. We also examined the individual systolic and diastolic components of orthostatic change in blood pressure; a distinction made infrequently in the past. Limitations of our study include that our sample consisted only of men and that the vast majority (>99%) were of white European ethnicity. Hence, the generalisability of our findings is limited. We did not have measurements of orthostatic change in blood pressure beyond three minutes and would have misclassified men with orthostatic changes in blood pressure that were delayed beyond this point in time. We did not have information on alpha-1 blocking drugs which are known to cause orthostatic hypotension and HF (35) but the vast majority of the men (75%) were on beta blockers, diuretics or ace inhibitors at time of examination. Although we found no association between prevalent diabetes (nor diabetes duration of at least 10 years vs less) and orthostatic hypotension in this cohort it is possible that there is a subset of people with diabetes who have autonomic neuropathy and marked orthostatic hypotension who are at increased risk of cardiovascular disease and may contribute to the high risk seen in those with orthostatic hypotension.

Perspective- Exaggerated orthostatic changes particularly in systolic blood pressure – be they orthostatic increases or decreases in blood pressure – are associated with increased risk of incident HF in older, community-dwelling men. The exaggerated changes in blood pressure may be an early sign of cardiovascular compromise and/or autonomic dysfunction. Assessment of autonomic co-morbidities, such as Parkinson's disease, and measures of autonomic function

would be important in further prospective studies in this area to better understand the contribution of autonomic dysfunctions to this association. Older adults in whom exaggerated orthostatic changes in systolic blood pressure are found may benefit from further cardiac investigation. Our findings confirm that orthostatic hypotension fulfilling the consensus definition is associated with increased HF risk in older adults but suggest that orthostatic hypertension is defined on the basis of a rise in systolic blood pressure only rather than either systolic or diastolic blood pressure. Further prospective studies in diverse populations are needed to confirm our findings.

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Conflicts of Interest

None

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Novelty and Significance

What is New?

- Previous studies have frequently examined orthostatic hypotension (a decrease in blood pressure on standing) but neglected orthostatic hypertension (an increase in blood pressure on standing).
- We show that both excessive orthostatic increases and decreases in systolic blood pressure are associated with increased risk of developing heart failure in older men independent of known cardiovascular risk factors; in contrast only orthostatic decreases in diastolic blood pressure are associated with increased HF risk.

What is Relevant?

- The findings suggest that orthostatic hypertension in older adults should be defined on the basis of a systolic blood pressure rise only of at least 20mmHg.
- The prevalence of orthostatic hypertension in the community is over estimated if diastolic hypertension is included.
- There is currently no recommended treatment for orthostatic hypertension. Large randomised trials are required to determine therapeutic approach.

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Summary

Orthostatic hypotension fulfilling the consensus definition' is associated with increased risk of HF in older men independent of known cardiovascular risk factors. Excessive orthostatic increase in systolic blood pressure is associated with increased risk of heart failure. Further studies in diverse cohorts are required to confirm our findings.

LEGEND

Figure 1: Continuous association of orthostatic change in diastolic (panels A and B) and systolic (panels C and D) blood pressure with risk of incident heart failure. Dotted lines represent 95% confidence intervals.

Orthostatic change in blood pressure was modelled using restricted cubic regression splines with knots at the 5^{th}, 25^{th}, 75^{th} and 95^{th} percentiles. The models adjusted for age, mean sitting systolic blood pressure, BMI, heart rate, social class, physical activity, smoking status, alcohol consumption, total cholesterol, prevalent AF, diabetes, CKD, COPD, anti-hypertensive drug use, circulating IL-6, high-sensitivity troponin T and NT-proBNP. SBP1 refers to change in systolic blood pressure between the first standing and mean sitting blood pressure measurements; SBP2 between the second standing systolic measurement and mean sitting blood pressure measurements; DBP1 refers to change in diastolic blood pressure between the first standing and mean sitting blood pressure measurements; DBP2 between the second standing diastolic measurement and mean sitting blood pressure measurements.

Table 1: Baseline characteristics of the study population by category of orthostatic change in blood pressure.

Characteristics	***Orthostatic Hypotension (n=710)***	***Orthostatic normotension (n=1956)***	***Orthostatic diastolic hypertension only (n=596)***	***Orthostatic Systolic hypertension (n=243)***	***p for overall difference***
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	
Age, years	69.4 (5.5)	68.3 (5.4)	68.1 (5.4)	68.6 (5.6)	<.0001
BMI, kg/m^2	26.5 (3.6)	27.0 (3.7)	26.4 (3.5)	27.3 (3.5)	0.0003
Sitting systolic BP, mmHg	161.2 (23.8)	147.8 (23.1)	147.0 (24.1)	142.9 (23.0)	<.0001
Sitting diastolic BP, mmHg	89.5 (12)	85.3 (10.5)	82.2 (10.7)	85.1 (11.1)	<.0001
Heart rate, beats per minute	67.4 (14.6)	65.5 (11.7)	64.9 (12.3)	65.6 (13.6)	0.002
Current smokers (%)	13.80	13.16	12.92	10.70	0.67
Moderate to heavy alcohol consumption (%)	19.23	20.32	18.96	18.52	0.86
Inactive (%)	33.80	31.13	30.87	30.86	0.57
Manual Social Class (%)	52.12	50.15	50.00	52.67	0.73
Resting tachycardia (HR >90) (%)	7.06	3.39	3.52	5.35	0.0003
Co-morbid conditions (%)					
Prevalent AF	4.38	2.56	2.18	6.58	0.007
Prevalent Diabetes	5.49	5.67	6.04	3.70	0.59
Prevalent CKD	16.12	12.76	14.43	12.76	0.15
BP medications	31.48	26.76	26.89	26.34	0.12
Diuretics	7.6	6.8	5.8	7.5	0.64
Beta blockers	13.4	10.5	10.1	11.3	0.16
Ace inhibitors	8.1	6.4	8.4	9.2	0.16
Hypertension+	78.45	63.09	59.56	58.85	<.0001
COPD	31.12	26.24	25.50	18.93	0.002
Circulating cardiovascular risk markers	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	
Cholesterol, mmol/L	6.04 (1.07)	6.04 (1.07)	6.01 (1.02)	6.06 (1.12)	0.91
HDL, mmol/L	1.36(0.35)	1.32 (0.30)	1.35 (0.34)	1.30 (0.33)	0.005
Triglycerides, mmol/L*	1.63 (1.1-2.2)	1.55 (1.1-2.2)	1.72 (1.1-2.2)	1.56 (1.2-2.3)	0.02
Glucose, mmol/L*	5.87 (5.3-6.2)	5.81 (5.2-6.1)	5.81 (5.3-6.1)	5.93 (5.2-6.2)	0.54
Phosphate, mmol/L	1.17 (0.15)	1.15 (0.16)	1.15 (0.16)	1.14 (0.15)	0.006
eGFR, ml/min/1.73m^2	72.1 (12.7)	73.3 (12.1)	72.4 (12.1)	73.2 (15.3)	0.12

CRP, mg/L*	1.76 (0.8-3.3)	1.68 (0.8-3.4)	1.63 (0.7-3.2)	1.57 (0.7-3.9)	0.21
IL-6, pg/ml*	2.56 (1.6-3.9)	2.36 (1.5-3.3)	2.29 (1.5-3.2)	2.34 (1.4-3.3)	0.008
VWF, IU/dl	145.9 (48.4)	135.7 (44.3)	135.7 (44.4)	138.9 (45.1)	<.0001
NT-proBNP, pg/ml*	108.9 (51-213)	83.9 (42 - 160)	85.6 (41-154).	88.2 (41-166)	<.0001
Troponin T, pg/ml*	12.4 (9.2-16.1)	11.4 (8.5-5.5)	11.7 (8.7-15.5)	11.4 (8.4-15.2)	0.0007

* = Geometric mean (interquartile range); all other values are the mean (standard deviation) or proportions.

+ hypertension =SBP $\geq$ 140 or DBP $\geq$ 90 or on antihypertensive treatment .

Table 2: Hazard ratio (95% confidence interval) for incident heart failure by category of orthostatic change in blood pressure.

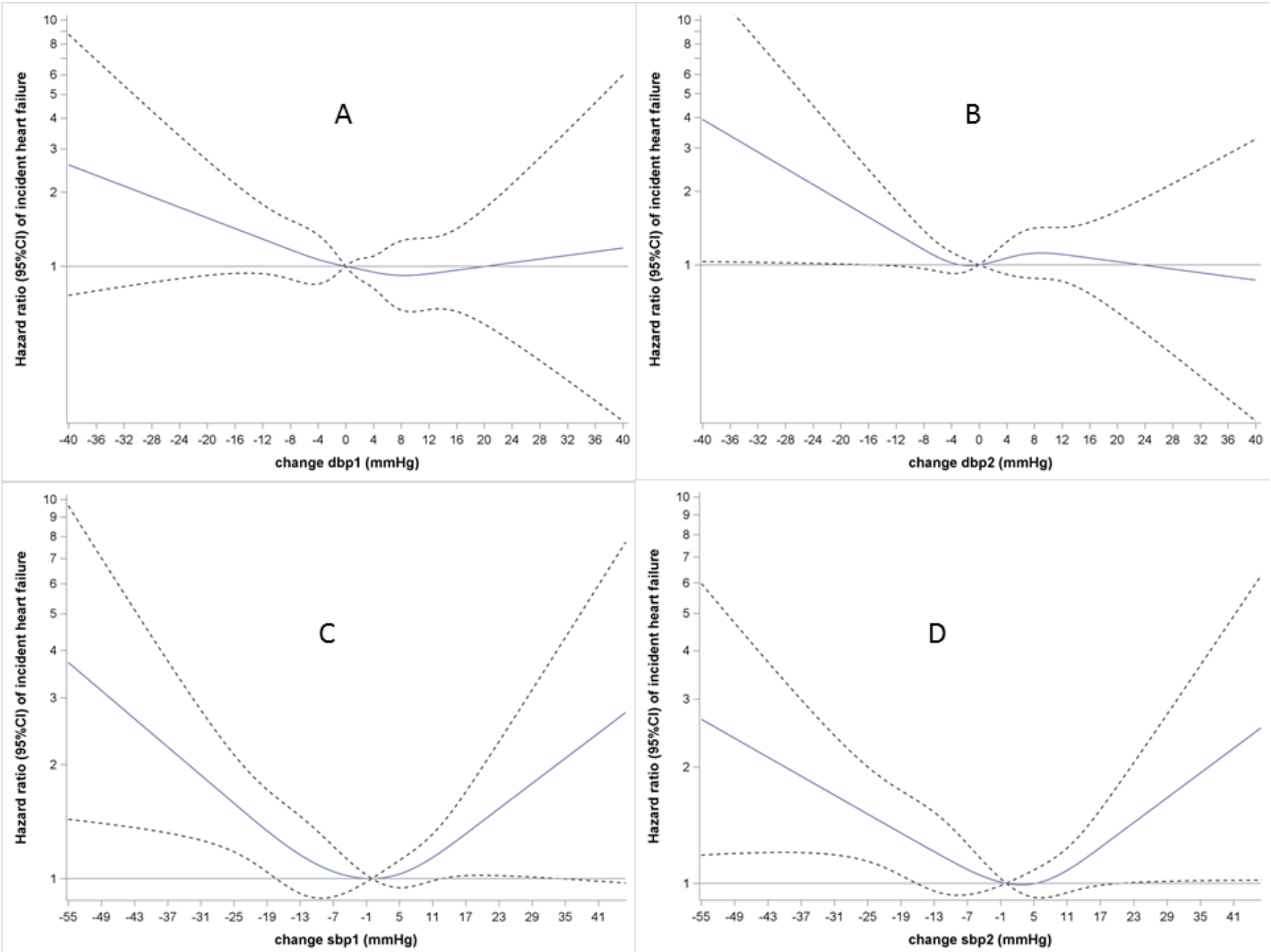
Model	Orthostatic Hypotension	Orthostatic Normotension	Orthostatic diastolic Hypertension only	Orthostatic Systolic Hypertension
Number (%)	710 (20.3)	1956 (55.8)	596(17.0)	243 (6.9)
Incidence (per 1000 person years)	10.0	6.1	6.2	10.8
Age-adjusted model	1.73 (1.34-2.25)	1.00	0.96 (0.70-1.32)	1.57 (1.09-2.24)
Model 1	1.63(1.25-2.14)	1.00	1.02 (0.74-1.40)	1.68 (1.17-2.42)
Model 2	1.59 (1.21-2.09)	1.00	1.01 (0.74-1.39)	1.71 (1.18-2.46)
Model 3	1.52 (1.16-1.99)	1.00	1.00 (0.73-1.37)	1.68 (1.16-2.42)
Model 4	1.64 (1.24-2.16)	1.00	0.98 (0.71-1.36)	1.83 (1.27-2.66)
Model 5	1.61 (1.21-2.02)	1.00	0.96 (0.69-1.32)	1.86 (1.28-2.69)
Model 5+ Incident MI	1.64 (1.24-2.18)	1.00	0.90 (0.65-1.24)	1.88 (1.30-2.73)

Model 1: Adjusted for age, BMI, heart rate, average sitting systolic blood pressure, physical activity, smoking status, alcohol consumption, social class, total cholesterol. Model 2: Model 1 plus prevalent AF, diabetes, CKD, COPD and anti-hypertensive medication use. Model 3: Model 2 plus IL-6. Model 4: Model 3 plus NT-proBNP. Model 5:Model 4+cTnT

Table 3: Hazard ratios (95% confidence intervals) for incident heart failure by the specific systolic and diastolic components of orthostatic hypotension and orthostatic hypertension

Model	*Isolated systolic OHypo*	*Isolated diastolic OHypo*	*Combined systolic and diastolic OHypo*	*Orthostatic Normotension*	*Isolated systolic OHyper*	*Isolated Diastolic OHyper*	*Combined systolic and diastolic OHyper*
Number (%)	450 (12.8)	155 (4.4)	105 (3.0)	1956 (55.8)	118 (3.4)	596 (17.0)	125 (3.6)
Incidence (per 1000 person years)	10.6	7.2	11.9	6.1	13.0	6.2	8.7
Age-adjusted model	1.71 (1.28-2.30)	1.35 (0.78-2.34)	2.57 (1.49-4.46)	1.00	1.7 (1.08-2.68)	0.96 (0.7-1.32)	1.41 (0.83-2.40)
Model 1	1.74 (1.28-2.35)	1.27 (0.73-2.20)	2.05 (1.17-3.59)	1.00	1.78 (1.12-2.82)	1.00 (0.72-1.37)	1.53 (0.90-2.60)
Model 2	1.70 (1.26-2.31)	1.18 (0.67-2.06)	1.90 (1.08-3.33)	1.00	1.79 (1.13-2.84)	0.96 (0.70-1.32)	1.57 (0.92-2.68)
Model 3	1.65 (1.21-2.23)	1.16 (0.66-2.03)	1.73 (0.97-3.10)	1.00	1.74 (1.10-2.75)	0.96 (0.70-1.31)	1.55 (0.91-2.65)
Model 4	1.82 (1.31-2.45)	1.41 (0.80-2.49)	1.37 (0.74- 2.54)	1.00	1.96 (1.22-3.08)	0.93 (0.67-1.29)	1.67 (0.98-2.87)
Model 5	1.76 (1.28-2.41)	1.44 (0.82-2.53)	1.42 (0.79-2.63)	1.00	1.96 (1.23-3.13)	0.91 (0.66-1.27)	1.74 (1.01-2.98)
Model 5 + Incident MI	1.75 (1.28-2.51)	1.42 (0.80-2.50)	1.43 (0.78- 2.64)	1.00	1.90 (1.19- 3.04)	0.90 (0.65-1.24)	1.85 (1.08-3.18)

Model 1: Adjusted for age, BMI, heart rate, average sitting systolic blood pressure, physical activity, smoking status, alcohol consumption, social class, total cholesterol. Model 2: Model 1 plus prevalent AF, diabetes, CKD, COPD and anti-hypertensive medication use. Model 3: Model 2 plus IL-6. Model 4: Model 3 plus NT-proBNP. Model 5: Model 4 plus cTnT OHypo = orthostatic hypotension; OHyper = orthostatic hypertension.


A
Hazard ratio (95%CI) of incident heart failure
change dbp1 (mmHg)
B
Hazard ratio (95%CI) of incident heart failure
change dbp2 (mmHg)
C
Hazard ratio (95%CI) of incident heart failure
change sbp1 (mmHg)
D
Hazard ratio (95%CI) of incident heart failure
change sbp2 (mmHg)