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Introduction

The ageing of society and the prolonged survival of patients affected by chronic diseases are the main factors behind an imminent epidemic of heart failure (HF) in the Western countries¹. The overall prevalence of HF is ~ 2% and rises distinctly above 10% in those aged > 70 yrs, the mean age of HF patients being ~ 75 yrs²⁻⁵. At age 40 yrs, the lifetime risk of developing overt HF is ~20% regardless of gender⁶. Previous population-based studies have explored etiology and common risk factors for incident HF^{3,7,8}. However, the identification of individuals at risk for developing HF still remains a challenge as the traditional risk factors are not always present in HF patients.

Orthostatic hypotension (OH) is a frequent concomitant disorder found in HF^{9,10}, mainly due to direct and indirect effects of an impaired left ventricular function. In parallel, although epidemiological data indicate that orthostatic hypotension predicts mortality, incident coronary event and stroke¹¹⁻¹⁵, relatively little is known about the risk of developing HF among individuals demonstrating impairment of the postural blood pressure response. A prospective study of a Dutch cohort, comprising mainly elderly individuals (n=5064, mean age ~70 yrs), showed that orthostatic hypotension may increase the risk of HF, but this association was markedly attenuated after adjustment for conventional risk factors, such as body-mass index, systolic and diastolic blood pressure (SBP and DBP), and diabetes¹⁶.

Consequently, the aim of this study was to explore whether or not orthostatic hypotension (OH) is associated with incident HF in a large Swedish urban-based cohort of middle-aged individuals within the “Malmö Preventive Project (MPP)”.

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Methods

Study population

The MPP is an ongoing prospective study, which from 1974 until 1992 enrolled 33,346 inhabitants (67.3% men; mean age, 45.6±7.4 yrs; range, 26-61 yrs) of the city of Malmö in southern Sweden. At baseline participants were screened for hypertension, diabetes, obesity, hyperlipidaemia, smoking, family history of cardiovascular disease (CVD) and cancer, and lifestyle habits. Briefly, the invited men and women were fasting overnight prior to investigation, and specially trained nurses performed all examinations in the morning. Height was measured with a fixed stadiometer, and weight was measured in light indoor clothing, without shoes, using a balance-beam scale. The body-mass index (BMI) was calculated as weight in kg divided by height squared in meters. Blood samples were collected and analyzed by routine methods at the Department of Clinical Chemistry, Malmö University Hospital. The baseline examination was complemented by a questionnaire focused on personal and family history of CVD (myocardial infarction and stroke), hypertension, diabetes, cancer, smoking habits, and lifestyle patterns. The following question was relevant to the history of myocardial infarction, if the answer was yes: “*Have you ever been hospitalized for myocardial infarction?*” Antihypertensive treatment was defined as a positive answer to the following question: “*Do you take medication for high blood pressure?*”, but data on particular types of antihypertensive agents were not available. Those who confirmed regular or occasional current smoking were counted as smokers. A detailed description of recruitment and screening procedures

1 may be found elsewhere ¹⁷⁻¹⁹. The health service authority of Malmö approved and
2 funded the screening program. All participants gave informed consent.

3

4 **Blood pressure measurements**

5 Specially trained nurses measured BP (in mmHg) by auscultation using a mercury
6 sphygmomanometer and an appropriate cuff placed around the right arm at the level of
7 the heart. The first BP reading was taken twice after 10 min rest in the supine position.
8 Then, the participants were asked to stand up and the second BP measurement was taken
9 twice in the standing position after one minute. The mean values of two readings were
10 recorded for each position.

11

12 **Clinical characteristic definitions**

13 OH was defined according to the international consensus criteria as a decrease in SBP \geq
14 20 mm Hg and/or decrease in DBP \geq 10 mm Hg within three minutes of standing ²⁰.

15 For supplementary analyses, we also applied more restrictive criteria of orthostatic
16 hypotension (decrease of SBP \geq 25 mmHg and/or decrease of DBP \geq 15 mmHg) to
17 eliminate false positive borderline cases.

18 Hypertension was defined according to the current guidelines as supine SBP \geq 140
19 mmHg and/or supine DBP \geq 90mmHg, or use of antihypertensive treatment ²¹. Diabetes
20 was defined as fasting plasma glucose \geq 7.0 mmol/L, or current pharmacological
21 treatment of diabetes, or self-reported history of diabetes ²².

22

23

1 **Follow-up and end-points**

2 Out of 33,346 participants we excluded 546 (1.6%) because of missing information on
3 BP measurements. Furthermore, we excluded nine individuals who before baseline
4 examination had been hospitalized due to HF according to SNHDR (code 428 for the 9th
5 *Revision of ICD*), and 122 individuals with prevalent MI, leaving 32,669 persons eligible
6 for statistical analyses.

7 All study participants were followed from the baseline examination until the first
8 hospitalization attributable to HF, death, emigration from Sweden, or December 31,
9 2006, whichever came first. We applied linkage of the unique 10-digit personal
10 identification number with the Swedish National Hospital Discharge Register (SNHDR),
11 and the Swedish National Cause of Death Register. The occurrence of the first
12 hospitalization due to congestive HF episode was ascertained from SNHDR using
13 diagnosis codes 428 for the 9th *Revision (ICD-9)*, and I50 or I11.0 for the 10th *Revision*
14 *(ICD-10)* if HF was listed as a primary diagnosis. Myocardial infarction (MI) was defined
15 on the basis of *the International Classification of Diseases 9th and 10th Revisions (ICD-9*
16 *and ICD-10) codes 410 and I21 in the SNHDR, respectively. High case validity in these*
17 *registers has previously been described for both HF and MI*^{23,24}. Participants who
18 reported a history of MI before baseline were classified as prevalent MI (n=122, 0.4%) if
19 this was confirmed by the corresponding diagnosis codes in SNHDR.

20 Those who emigrated from Sweden before December 31, 2006, and had been event-free
21 at the time of emigration (n=634, 1.9%), were assigned the date of emigration as the last
22 follow-up date. The mean follow-up time was 24.1±6.5 years.

23

1 **Statistical analysis**

2 Groupwise differences in continuous variables between OH negative and positive
3 individuals were compared using the t-test, and dichotomous variables were compared
4 using the chi-square test.

5 The relation of OH to HF events during follow-up was assessed by the Kaplan-Meier and
6 life table method and quantified by means of the log-rank test. Then the Cox-proportional
7 hazard model was applied to assess the independent association of OH with the risk of
8 incident HF events. The proportional hazard assumption was assessed graphically and
9 based on the multivariate model. A basic model (Model 1) was adjusted for age and
10 gender. Next, besides the main factor of OH and the variables of age and gender, BMI,
11 SBP, DBP, antihypertensive treatment, diabetes, total cholesterol, current smoking were
12 included in the multivariate analyses as potential confounders (Model 2), according to the
13 previous epidemiological studies^{3, 8, 25}. Possible interactions between the presence of OH
14 and age, gender, and antihypertensive treatment, respectively, were evaluated by
15 including interaction terms in the final multivariate model.

16 In order to study the association of OH with the development of non-ischemic HF, we
17 excluded all HF events which occurred concomitantly with or after the first incident MI.
18 The participants were then followed up until the first MI and censored thereafter, or until
19 the first HF episode, death, emigration, or December 31, 2006, whichever occurred first.
20 All analyses were performed using SPSS statistical software version 17.0 for Windows
21 (SPSS Inc., Chicago, IL). All tests were two-sided whereby $p < 0.05$ was considered
22 statistically significant for non-interaction terms and $p < 0.10$ for interaction terms.

23

1 **Results**

2 At baseline, out of 32,669 participants 1,991 (6.1%) were found to have OH. As can be
3 seen in Table 1, OH positive individuals were older, more likely to be women and current
4 smokers. Hypertension, antihypertensive treatment, and diabetes were significantly more
5 common among those with than those without OH.

6 During the follow-up period 1293 participants (4.0%; 1.7 events/1,000 person-yrs, mean
7 age at presentation: 67.9 ± 7.9 yrs) were hospitalized for new-onset HF, 912 of whom
8 (2.8%; 1.2 events/1,000 person-yrs) without prior or concurrent MI. The corresponding
9 figures among OH positive individuals were 6.5% (n=129), and 4.6% (n=92),
10 respectively.

11 Figure 1 shows the Kaplan-Meier curve for incident non-ischemic HF according to
12 presence or absence of OH at baseline (results for all-cause and non-ischemic HF were
13 similar). As presented in Table 2, in age- and gender-adjusted Cox proportional hazard
14 models OH positive individuals had a significantly increased risk of first incident HF
15 (hazard ratio; 95% confidence interval: 1.55; 1.29-1.86). This risk increase was
16 attenuated, but remained significant for both all-cause and non-ischemic HF events (1.22;
17 1.01-1.46, and 1.31; 1.05-1.63, respectively), after adjustment for other traditional risk
18 factors associated with both OH and HF. As subclinical myocardial ischemia may have
19 been present before and during the first hospitalization for “non-ischemic” HF, in a
20 complementary analysis we reclassified as “ischemic” all cases of non-ischemic HF
21 where MI was diagnosed after the first episode of HF (n=192), obtaining essentially the
22 same result for association of OH with non-ischemic HF (HR, adjusted: 1.31, 1.01-1.69).

1 After reclassification, 44.3 % (n=573) of new-onset HF cases were potentially
2 attributable to ischemic heart disease.

3 As shown in Table 2, the association between OH and all-cause HF was more
4 pronounced in younger (<45 yrs) than in older (\geq 45 yrs) individuals (2.05; 1.31-3.22, vs.
5 1.12; 0.92-1.38, respectively; $p<0.001$ for interaction between age and OH on incident
6 HF). This age-relationship was also seen in the association between OH and non-
7 ischemic HF (2.43; 1.48-3.97, vs. 1.16; 0.90-1.48, respectively). The number-needed-to-
8 diagnose for OH in the younger stratum of cohort was 27 (3.7% with OH, n=496). No
9 significant interaction was observed between gender ($p=0.67$) or antihypertensive
10 treatment ($p=0.55$) and OH on incident HF.

11 In a supplementary analysis, we also examined the association between OH and non-
12 ischemic HF episodes preceded by incident atrial fibrillation (codes 427.3 for *ICD-9*, and
13 I48 for *ICD-10*). One hundred and forty-two (15.6%) of 912 study participants diagnosed
14 with non-ischemic HF developed atrial fibrillation prior to hospitalization for HF. In
15 these, OH was predictive of non-ischemic HF in Model 1 (HR, adjusted for age and
16 gender: 1.82, 1.09-3.05; $p=0.022$), but not in Model 2 after adjustment for other
17 confounders (HR: 1.44, 0.85-2.44; $p=0.17$).

18 As can be seen in Table 3, when we applied higher cut-off limits for selection of OH
19 positive individuals (n=567), the results obtained in fully adjusted Model 2 were more
20 consistent. Again among those aged < 45 yrs the presence of OH conferred a higher risk
21 of HF (3.15; 1.48-6.70, $p=0.003$) compared with those aged 45 yrs and over (1.31, 0.96-
22 1.80, $p=0.09$). In parallel, after adjustment for traditional risk factors the association
23 between prevalent OH and incident HF was slightly stronger for non-ischemic etiology

1 (1.63; 1.15-2.29), as compared with that for all-cause incident HF (1.43; 1.07-1.91,
2 $p < 0.05$ for all).
3 Figures 2 and 3 show how OH and traditional risk factors are associated with all-cause
4 and non-ischemic new onset HF. All presented hazard ratio values were obtained in a
5 multivariate adjusted Cox proportional hazard model applied to the study sample and
6 analyzed with OH entered as covariate, where SBP, DBP, and antihypertensive treatment
7 were replaced by dichotomous covariate “hypertension”.

8

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Discussion

10 There is growing evidence that disorders of postural blood pressure control predict all-
11 cause mortality and incidence of cardiovascular disease. According to available
12 longitudinal data, OH is independently associated with the increased risk of incident
13 coronary events and stroke^{12, 13, 15}. To the best of our knowledge, this is the first
14 prospective cohort study to demonstrate that the presence of OH can also predict long-
15 term incidence of HF in unselected middle-aged individuals.

Potential pathomechanisms

17 During approximately 24 yrs of follow-up, four percent of study participants were
18 hospitalized due to symptomatic HF at a mean age of 67 yrs. At this stage, it is
19 impossible to decide whether or not autonomic dysfunction was causally related to HF,
20 and whether or not OH was only a marker of a generally increased risk of HF
21 development. Although chronic cardiac failure is a disease common among the elderly,
22 processes which lead to it may start much earlier. The predominant etiology of incident
23 HF in the western world remains coronary artery disease, responsible for up to 50% of all

1 cases in those aged < 75 yrs²⁶. The relationship between OH and the development of
2 symptomatic coronary artery disease has already been demonstrated^{13, 15}. Interestingly, in
3 our study exclusion of cases potentially related to incident MI resulted in slightly
4 increased hazards of HF, suggesting that other than coronary pathomechanisms also play
5 an important role in the association between OH and HF. According to previous reports,
6 higher diurnal BP variability and nocturnal hypertension, both present in OH, correlate
7 with target-organ damage, specifically with left ventricular hypertrophy^{27, 28}. In one
8 recent cross-sectional study of Chinese hypertensive patients, an independent association
9 of OH with left ventricular hypertrophy (and prevalent coronary artery disease) was
10 demonstrated²⁹. Consequently, autonomic dysfunction underlying OH may lead to
11 changes in both myocardium and vasculature similar to those observed in essential
12 hypertension. As hypertension and OH are correlated³⁰, we believe that the increased risk
13 of incident HF is partly mediated through elevated BP. Indeed, adjustment for both
14 systolic and diastolic BP values distinctly attenuated HF hazards, but not in persons
15 younger than 45 yrs or selected by more restrictive cutoff limits. Accordingly, subtle
16 pronounced autonomic dysfunction found already in early decades of life may be an
17 independent risk factor for HF, whereas that developed later may be partly attributed to
18 aging and other chronic states, such as hypertension or diabetes. Our findings are in
19 accord with previous studies^{14, 15}, which have demonstrated that younger individuals
20 with OH have relatively higher all-cause mortality risk.

21 *Clinical implications*

22 These results prompt several questions, such as the consequences of BP lowering in
23 patients with asymptomatic autonomic dysfunction and OH. In elderly patients, the use of

1 antihypertensive agents is generally associated with higher prevalence of OH³¹, whereas
2 this relationship in younger and hypertensive individuals is still debatable^{30,32}. Many
3 patients with HF, hypertension, angina or diabetes are routinely treated with different
4 classes of antihypertensive drugs, but in the light of our findings it is unclear what effect
5 BP lowering therapy may exert on the prognosis in patients with asymptomatic OH.
6 Recent studies have shown that lower SBP increases mortality risk in patients with
7 already manifest HF³³. This phenomenon is better known as “reverse causation”³⁴ and
8 may indicate a need to develop new drugs for HF treatment without the predominant
9 hypotensive effect. We surmise that patients with autonomic dysfunction leading to
10 impairment of orthostatic BP response may constitute a specific and important risk group
11 in this regard. However, to be confirmed, our assumption would require further
12 prospective studies and the identification of patients with OH in randomized trials
13 evaluating antihypertensive treatment. In a recent work exploring the effects of different
14 losartan doses on prognosis in HF, between two and three percent of participants reported
15 symptoms due to hypotension as an adverse event, and some discontinued treatment³⁵.
16 Consequently, we postulate that evaluation for OH should be considered in the study
17 recruitment procedures.

18 *Study limitations*

19 Our study has some limitations that should be addressed. The first incident HF episode
20 was tracked in the hospital discharge register only. It is obvious that this definition
21 generally includes patients whose condition is most serious, and we may have
22 underestimated the overall incidence of new-onset HF, since less complicated, milder,
23 and asymptomatic cases may have been diagnosed and treated outside the hospital. On

1 the other hand, because the patients had a primary diagnosis of HF, which was confirmed
2 during the hospital stay, we can assume that the diagnosis in most cases was valid.
3 Moreover, the orthostatic BP response was determined only once during baseline
4 examination, and we infer that some individuals who met the diagnostic criteria of OH
5 may have demonstrated a temporary and not a persistent disorder³⁶. We partly
6 compensated by applying higher cutoff limits, which resulted in relatively higher hazards
7 of HF, and hopefully a more accurate picture of the studied association. In addition,
8 standing BP was recorded between the 1st and 2nd minute after assuming an upright
9 position and we may have missed those with initial (<1 min) OH. Furthermore, the heart
10 rate on standing was not recorded so we were unable to analyze the chronotropic
11 response during the orthostatic challenge. However, supine heart rate was not
12 independently predictive of incident HF ($p=0.4$) and the chronotropic response is not a
13 part of OH definition, so it is unlikely that these data would change our results, although
14 they might contribute to a better understanding of the underlying mechanisms. Finally,
15 coronary artery disease can be subclinical³⁷ and it is still possible that silent episodes of
16 myocardial ischemia and MI could contribute to the increased incidence of heart failure,
17 even if corresponding HF events were classified as “non-ischemic”. It is estimated that up
18 to 50% of incident HF is associated with coronary artery disease, but the definitive
19 diagnosis would require myocardial perfusion scanning or coronary angiography²⁶.
20 However, in a separate analysis, the exclusion of all participants who suffered MI after
21 their first hospitalization did not essentially change our results.
22 In conclusion, among middle-aged individuals, the presence of OH is related to an
23 increased risk for incident HF, independently of conventional risk factors. The

1 association between OH and HF appears to be most pronounced in younger adults (aged
2 <45 years) and for the incident HF of non-ischemic etiology. Our findings confirm that
3 OH should be considered as an independent marker of increased cardiovascular risk, and
4 may also suggest a need for development of new pharmacological agents for HF
5 treatment without the vasodepressor effect during orthostasis.

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Disclosures

16 None

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1 **Figure legends**

2 **Figure 1.** Kaplan-Meier estimates of the first hospitalization for non-ischemic heart
3 failure event during follow-up among 32,669 individuals according to presence or
4 absence of orthostatic hypotension (OH) at baseline. Participants with incident non-fatal
5 MI were followed until the day of infarction and censored thereafter, if MI occurred not
6 later than during the first admission for heart failure (n=3,207); $p < 0.001$ between groups.

7 **Figure 2.** Orthostatic Hypotension and Conventional Risk Factors in Prediction of
8 Incident Heart Failure in a Multivariate Adjusted* Cox Proportional Hazard Model
9 among 32,669 Participants of the Malmö Preventive Project. Age stratified analyses were
10 performed on the corresponding study subsets (age at baseline < 45 yrs, or ≥ 45 yrs).

11 * *Covariates used in the model: age, gender, BMI, current smoking, hypertension,*
12 *diabetes, total cholesterol, and orthostatic hypotension;*

13 **Figure 3.** Orthostatic Hypotension (OH) and Conventional Risk Factors in Prediction of
14 Non-ischemic† Incident Heart Failure in a Multivariate Adjusted* Cox Proportional
15 Hazard Model among 32,669 Participants of the Malmö Preventive Project. Age stratified
16 analyses were performed on the corresponding study subsets (age at baseline < 45 yrs, or
17 ≥ 45 yrs).

18 * *Covariates used in the model: age, gender, BMI, current smoking, hypertension,*
19 *diabetes, total cholesterol, and orthostatic hypotension;*

20 † *All individuals with incident non-fatal MI were followed until the day of infarction and*
21 *censored thereafter, if MI occurred not later than during the first admission for HF*
22 *(n=3,207).*

23

Figure 1

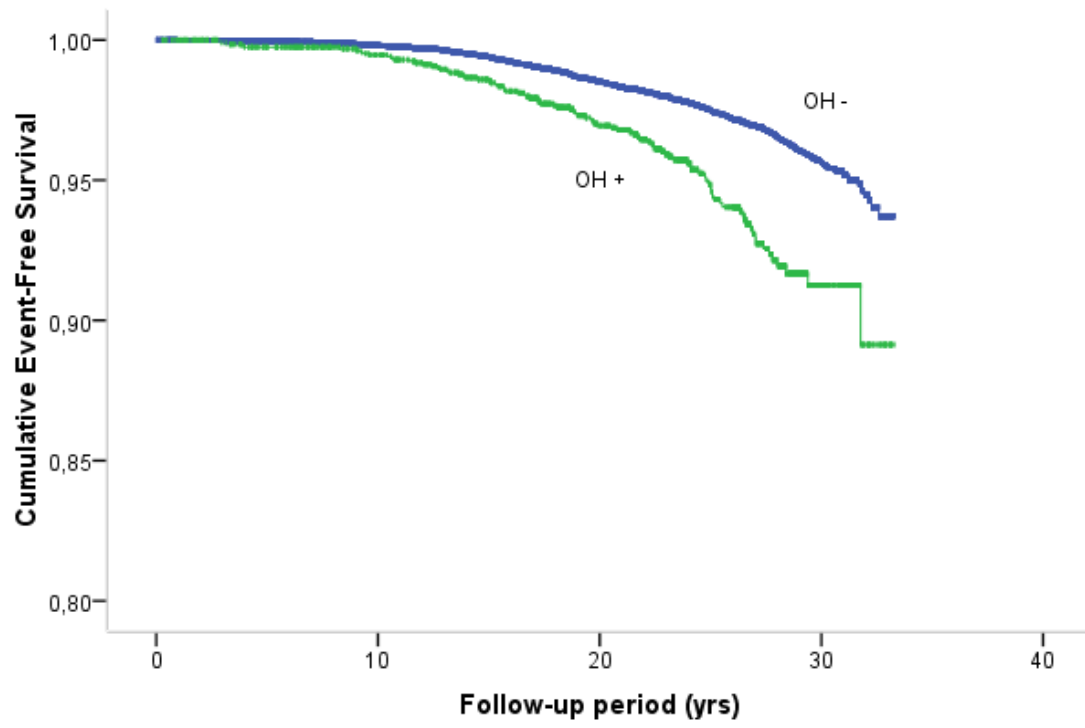


Figure 2

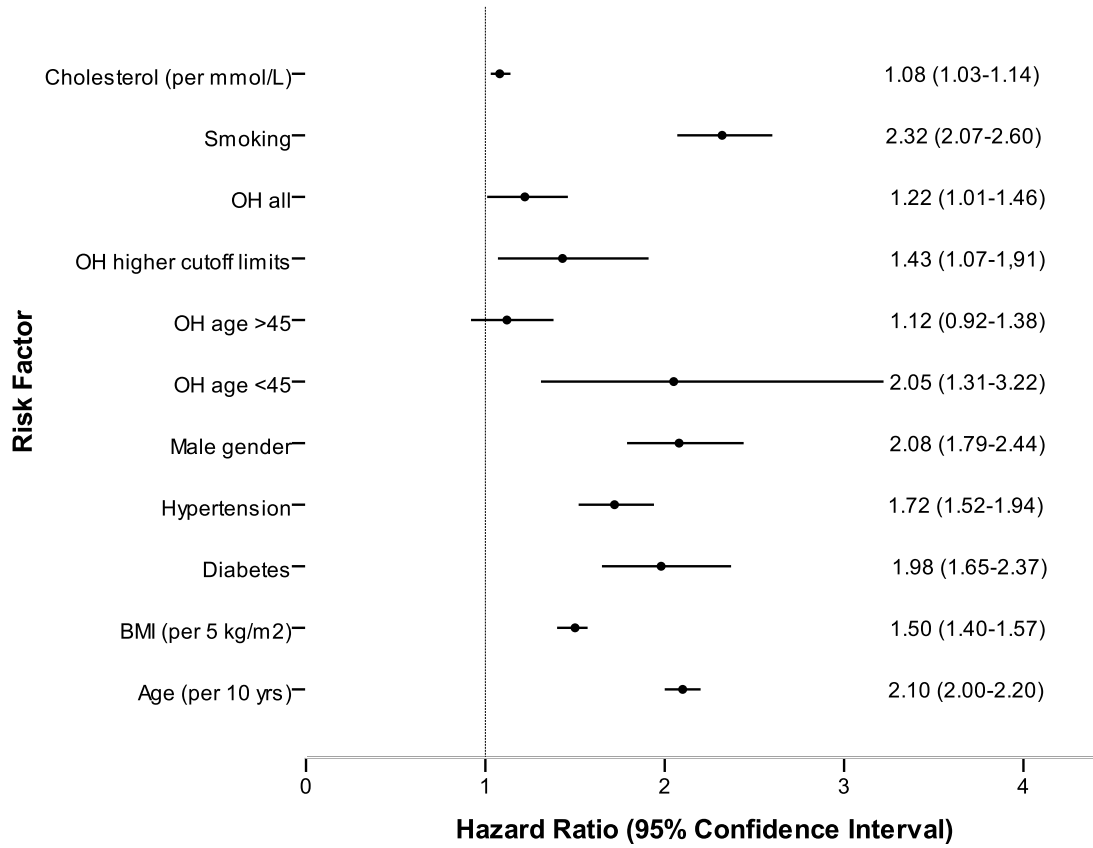
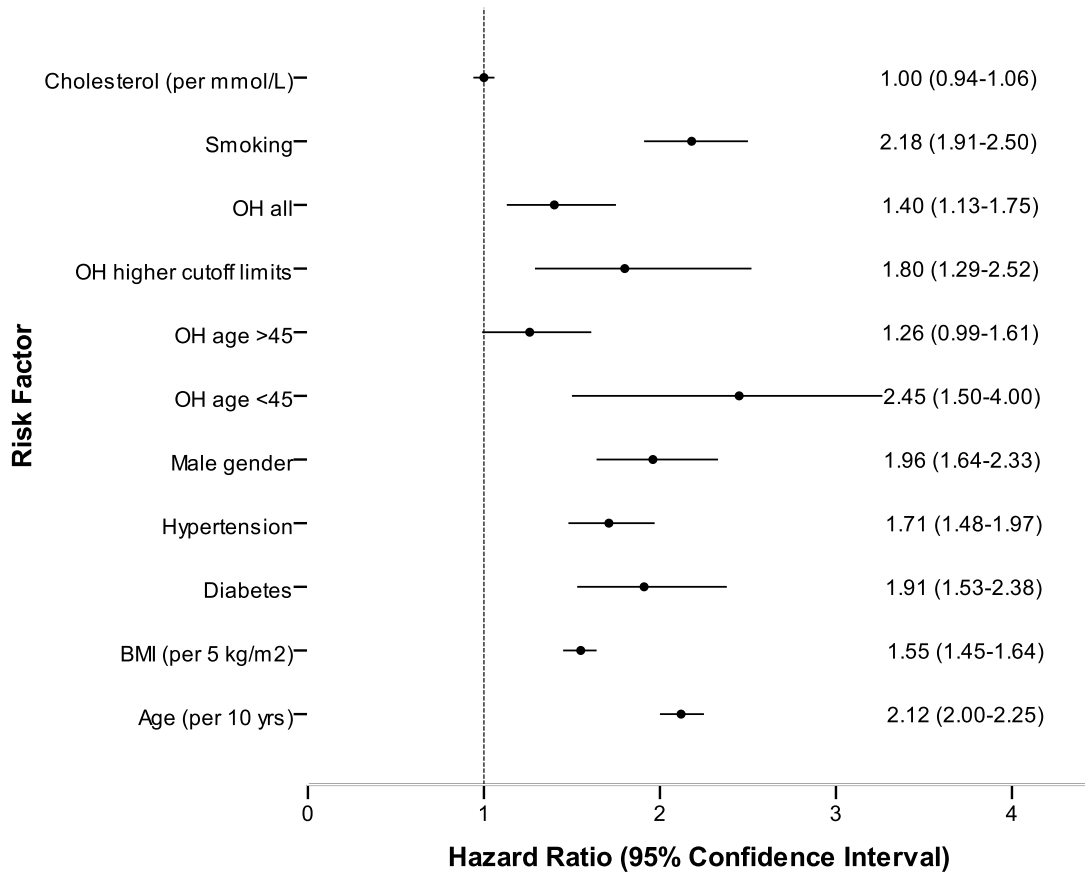


Figure 3



Tables

Table 1. Baseline characteristics of study population according to presence or absence of orthostatic hypotension (OH).

Characteristic	Total (N=32,669)	OH negative (N=30,678)	OH positive (N=1,991)	P-value
Age (yrs)	45.6±7.4	45.4±7.4	48.7±7.1	<0.001
Gender (male, %)	68.2	68.8	58.6	<0.001
BMI (kg/m ²)	24.6±3.6	24.6±3.6	24.7±4.0	0.23
Current smoker (%)	44.7	44.5	47.7	0.007
Hypertension (%)	40.2	38.8	62.1	<0.001
Antihypertensive treatment (%)	5.3	4.9	11.9	<0.001
Systolic blood pressure (mmHg)	126.3±15.5	125.7±15.0	136.8±19.6	<0.001
Diastolic blood pressure (mm Hg)	84.3±9.6	84.0±9.5	88.3±11.0	<0.001
Heart rate (beats/min)	67.5±9.7	67.4±9.7	68.9±10.7	<0.001
Diabetes (%)	4.7	4.5	7.2	<0.001
Total cholesterol (mmol/L)	5.7±1.1	5.7±1.1	5.8±1.1	<0.001

Data are presented as proportions or mean ± standard deviation. MI, myocardial infarction; BMI, body mass index.

Table 2. Association of orthostatic hypotension at baseline with first hospitalization due to incident heart failure during follow-up among 32,669 middle-aged individuals.

End-point and Age Stratification <i>(incidence rate)</i>	Model 1 Hazard Ratio[95%CI]	Model 2 Hazard Ratio[95%CI]
All new-onset heart failure events <i>(n=1293, 1.7 events/1,000 person-yrs)</i>	1.55 [1.29-1.86] <i>P<0.001</i>	1.22 [1.01-1.46] <i>P=0.04</i>
Age at baseline < 45 yrs <i>(n=248, 0.7 events/1,000 person-yrs)</i>	2.50 [1.60-3.92] <i>P<0.001</i>	2.05 [1.31-3.22] <i>P=0.002</i>
Age at baseline ≥ 45 yrs <i>(n=1045, 2.4 events/1,000 person-yrs)</i>	1.45 [1.18-1.77] <i>P<0.001</i>	1.12 [0.92-1.38] <i>P=0.27</i>
Only non-ischemic heart failure events† <i>(n=912, 1.2 events/1,000 person-yrs)</i>	1.62 [1.30-2.01] <i>P<0.001</i>	1.31 [1.05-1.63] <i>P=0.02</i>
Age at baseline < 45 yrs <i>(n=189, 0.6 events/1,000 person-yrs)</i>	2.83 [1.74-4.60] <i>P<0.001</i>	2.43 [1.48-3.97] <i>P<0.001</i>
Age at baseline ≥ 45 yrs <i>(n=723, 1.7 events/1,000 person-yrs)</i>	1.46 [1.14-1.86] <i>P=0.002</i>	1.16 [0.90-1.48] <i>P=0.25</i>

Model 1: adjusted for age and gender; Model 2: adjusted for age, gender, body mass index, systolic and diastolic blood pressure, antihypertensive treatment, diabetes, total cholesterol, and current smoking; † all individuals with incident non-fatal MI were followed until the day of infarction and censored thereafter, if MI occurred not later than during the first admission for heart failure (n=3,207); MI, myocardial infarction.

Table 3. Association of orthostatic hypotension at baseline according to modified definition* with first hospitalization due to incident heart failure during follow-up among 32,669 middle-aged individuals.

End-point and Age Stratification <i>(incidence rate)</i>	Model 1 Hazard Ratio[95%CI]	Model 2 Hazard Ratio[95%CI]
All new-onset heart failure events <i>(n=1293, 1.7 events/1,000 person-yrs)</i>	2.04 [1.53-2.72] <i>P<0.001</i>	1.43 [1.07-1.91] <i>P=0.02</i>
Age at baseline < 45 yrs <i>(n=248, 0.7 events/1,000 person-yrs)</i>	4.03 [1.90-8.56] <i>P<0.001</i>	3.15 [1.48-6.70] <i>P=0.003</i>
Age at baseline ≥ 45 yrs <i>(n=1045, 2.4 events/1,000 person-yrs)</i>	1.90 [1.39-2.60] <i>P<0.001</i>	1.31 [0.96-1.80] <i>P=0.09</i>
Only non-ischemic heart failure events† <i>(n=912, 1.2 events/1,000 person-yrs)</i>	2.25 [1.61-3.14] <i>P<0.001</i>	1.63 [1.15-2.29] <i>P=0.005</i>
Age at baseline < 45 yrs <i>(n=189, 0.6 events/1,000 person-yrs)</i>	4.53 [2.01-10.23] <i>P<0.001</i>	3.47 [1.52-7.94] <i>P=0.003</i>
Age at baseline ≥ 45 yrs <i>(n=723, 1.7 events/1,000 person-yrs)</i>	2.04 [1.41-2.95] <i>P<0.001</i>	1.45 [1.00-2.11] <i>P=0.05</i>

Model 1: adjusted for age and gender; Model 2: adjusted for age, gender, body mass index, systolic and diastolic blood pressure, antihypertensive treatment, diabetes, total cholesterol, and current smoking; † all individuals with incident non-fatal MI were followed until the day of infarction and censored thereafter, if MI occurred not later than during the first admission for heart failure (n=3,207); * decrease of SBP ≥ 25 mmHg and/or decrease of DBP ≥ 15 mm Hg; MI, myocardial infarction.