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# **Hypotension in heart failure is less harmful if associated with high or increasing doses of heart failure medication:**

## **Insights from the Swedish Heart Failure Registry**

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## Abstract

**Background:** Heart failure (HF) medication may reduce blood pressure (BP). Low BP is associated with worse outcomes but how this association is modified by HF medication has not been studied. We evaluated the association between BP and outcomes according to HF medication dose in HF with reduced ejection fraction (HFrEF).

**Methods:** We studied HFrEF patients from the Swedish HF registry (2000-2018). Associations between systolic BP (SBP) and cardiovascular death and/or HF hospitalization (CVD/HFH) were analyzed according to doses of renin-angiotensin system (RAS) inhibitors, beta-blockers and mineralocorticoid receptor antagonists (MRA).

**Results:** Among 42040 patients (median age 74.0), lower baseline SBP was associated with higher risk of CVD/HFH (adjusted HR per 10 mmHg higher SBP: 0.92 [0.92-0.93]), which was less high risk under optimized RAS inhibitors and beta-blockers doses (10% decrease in event rates per 10 mmHg SBP increase in untreated patients versus 7% decrease in patients at maximum dose, both adjusted  $p < 0.02$ ). Among the 13761 patients with repeated measurements, 9.9% reported a SBP decrease  $> 10$  mmHg when HF medications' doses were increased, whereas 24.6% reported a SBP decrease  $> 10$  mmHg with stable/decreasing doses. Decreasing SBP was associated with higher risk of CVD/HFH in patients with stable (HR=1.10 [1.04-1.17]) or decreasing (HR=1.29 [1.18-1.42]) HF medication dose but not in patients with an increase in doses (HR=0.94 [0.86-1.02]).

**Conclusions:** The association of lower SBP with higher risk of CVD/HFH is attenuated in patients with optimized HF medication. These results suggest that low or declining SBP should not limit HF medication optimization.

**Keywords:** Heart failure; Heart failure with reduced ejection fraction; Medication; Dose; Blood pressure; Cardiovascular disease.

## Introduction

In heart failure with reduced ejection fraction (HFrEF), novel interventions continue to be developed and to show efficacy in randomized controlled trials, but less attention is focused on implementing already established-evidence based therapy<sup>1,2</sup>. One major limiting factor to the implementation of HFrEF treatments in clinical practice is low blood pressure (BP), as all these drug classes can cause hypotension, thus causing symptoms, or concerns for potential symptoms and complications among both patients and health care providers. As recently highlighted in large European Registries<sup>1,3-5</sup>, the proportion of HF patients receiving target dose of HF medication (or receiving at least 50% of the target dose) is overall low, partly because of actual hypotension or fear of hypotension<sup>3,5</sup>.

In chronic HFrEF, very low baseline SBP (<90 mmHg) and large reductions in SBP (>10 mmHg) were associated with higher risk of death and heart transplant<sup>6</sup>. Similar results were previously reported in the Swedish Heart Failure Registry (SwedeHF)<sup>7</sup> and in a retrospective analysis of Valsartan Heart Failure Trial (Val-HeFT)<sup>8</sup>. However, the association between moderate BP lowering and prognosis remains controversial<sup>9</sup>, and current evidence is mostly derived from trials in hypertensive populations<sup>9</sup>. While the treatment goal in hypertensive patients is to lower BP to improve prognosis<sup>10</sup>, the focus of HF management is to initiate and titrate drugs which have been shown to improve survival irrespectively of and often despite their effect on lowering BP. Low BP may be a risk factor per se, i.e. driving poor outcomes, or a risk marker for e.g. severity of HF. It may also be a risk marker for poor use of and sub-optimal dosing of HF medications. Indeed, although low BP is associated with worse outcome and higher doses of HF medications are associated with better outcome, there is little data regarding the interaction between these two variables. Furthermore, specific analyses assessing the impact of BP changes, rather than baseline BP, are scarce<sup>11</sup>. We hypothesized that low or declining BP because of high-dose medication is less associated with detrimental outcomes than low BP and less optimized HF medication.

Therefore, we evaluated the interaction between SBP and HF medication dose with regards to CV death and hospitalization for HF in a large HF registry. We also aimed to determine whether spontaneous SBP decrease during follow-up is differently associated with outcome compared to SBP decrease related to HF medications' titration.

## Methods:

### *Study population*

The Swedish Heart Failure Registry (SwedeHF; [www.SwedeHF.se](http://www.SwedeHF.se)) has been previously described<sup>12</sup>. Briefly, patients with clinician-judged HF have been included in this ongoing registry since 11 May 2000. Approximately 80 variables are recorded at discharge from the hospital or after an outpatient clinic visit and entered into a web-based case report form and database managed by Uppsala Clinical Research Center ([www.UCR.UU.se](http://www.UCR.UU.se)). The protocol, case report form and annual reports are available at [www.SwedeHF.se](http://www.SwedeHF.se). Echocardiographic parameters other than left ventricular ejection fraction (LVEF) are not collected. Key laboratory measurements collected in the registry include N-terminal pro-brain natriuretic peptide (NT-proBNP), estimated glomerular filtration rate (eGFR), potassium and hemoglobin. Blood pressure is measured as per clinical routine. We included for this analysis patients with HFrEF defined as LVEF<40%.

The Swedish Board of Health and Welfare ([www.socialstyrelsen.se](http://www.socialstyrelsen.se)) administers the National Patient Registry, which provided additional data on baseline comorbidities and the outcome HF hospitalization, and the Cause of Death registry which provided the underlying cause (rather than the immediate mode of death), defined by ICD-10 codes. ICD-10 coding in Sweden has been validated, with a positive predictive value ranging between 85% and 95% for most diagnoses. From Statistics Sweden ([www.scb.se](http://www.scb.se)) we obtained socioeconomic characteristics. All Swedish citizens have unique personal identification numbers that allow linking of disease-specific health registries and governmental health and statistical registries. The SwedeHF registry and the present analysis with linking of the above registries were approved by the Swedish Ethical Review Authority. Individual patient consent was not required, but patients were informed of entry into national quality registries and allowed to opt out.

### *Percentage of HF medication dose*

For each HF medication class (namely, angiotensin-converting enzyme inhibitor [ACE-I], angiotensin receptor blocker [ARB], beta-blockers, and mineralocorticoid receptor antagonist [MRA]), the proportion of target dose used was calculated according to European HF guidelines<sup>13,14</sup>.

As the proportion of patients with Sacubitril/Valsartan was not sufficient to perform a dedicated analysis during the considered period, only patients under ACE-I/ARB were considered.

## Outcomes

The primary outcome was time to the composite of cardiovascular death (CVD) or first heart failure hospitalization (HFH). Secondary outcomes were CVD, and hospitalization for syncope.

## Statistical methods

Categorical variables are presented as numbers and percentages and compared with chi-square test; continuous variables are presented as median and interquartile range (IQR) and compared with Kruskal-Wallis Rank Sum test. For multivariable models, missing data was imputed by Multivariate Imputation by Chained Equations (mice) with 10 dataset generated and 10 iterations performed<sup>15</sup>. HF medications' dose variable was created as follows: 0 points for non-prescription, 0.5 points for use of <50% of target dose (<100% of target dose for MRA – as MRA are actually used at either 50 or 100% of the recommended dose), 1 point for use of  $\geq 50\%$  of target dose ( $\geq 100\%$  target dose for MRA). Accordingly, one variable is derived for ACE-I/ARB, 1 for beta-blockers, and 1 for MRA. The supremum medication dose variable is the mean of the 3 (ACE-i/ARB, beta-blockers, MRA) variables. Since MRA dose was not collected in SwedeHF prior to 2014, MRA use was given 1 point and no MRA 0 points. Additionally, a consistency analysis was performed for the primary endpoint with only observations from 2014 with MRA dose included in the supremum treatment variable as reported above.

We first used survival models to explore the association of SBP with outcomes. A spline-transformed SBP variable was included in one of the models to investigate the shape of the association between SBP and outcome. We then used crude and adjusted cox proportional hazards regression models to evaluate the association of dose variables, SBP and their interaction with outcomes. Adjustments were performed for the covariates indicated in Table 1. In order to test a potential interaction between treatment (ACE-I/ARB, beta-blockers, and MRA) and SBP for the incidence of clinical outcomes, in the models for each HF medication category an interaction term between SBP variable (in units of 10) and treatment dose strata was introduced.

We then analyzed the subset of patients in whom SBP changes and HF drug's dose changes over time could be assessed. For the sake of simplicity and clinical interpretability, to investigate the association of SBP changes over time according to HF treatment dose optimization with outcomes, patients were stratified into 4 groups: i) no noteworthy decrease in BP (<10 mmHg decrease in SBP between the first visit and the follow-up visit), ii) decrease in SBP probably due to medication dose increase (>10 mmHg decrease in SBP AND

increase in the supremum treatment variable between the first visit and the follow-up visit), and decrease in SBP while medication dose remained stable (iii) or decreased (iv). For this specific analysis, the baseline variables presented in the table and used for adjustment, and the start of follow-up in the Cox models, were considered as the visit at which BP change has been assessed (i.e. not the initial visit but a visit occurring during follow-up).

The level of significance was set to 5%, two-sided. Statistical analyses were performed using R version 4.0.2 (2020-06-22) (R Core Team 2019, Vienna, Austria).

## Results

### *Patient characteristics*

Between 2000 and 2018 there were 42,040 unique patients with HFrEF (Median age 74.0 [65.0-82.0], 29.3% females) in SwedeHF. Approximately 22% were at target dose of all 3 HF medications (n=9124) and less than 20% of patients had 0 or less than 50% of the target dose of all 3 HF medication (n=7500) (*Supplementary Table 1*). Overall, patients with no use or lower doses of HF medication (*Table 1*) were older, had lower education level, were more likely to have been registered in an outpatient setting, and had worse NYHA class and kidney function as well as higher NT-proBNP levels. Differences in SBP across categories of HF medication dose were <5 mmHg (all mean SBP ranging from 120 to 123 mmHg across categories of dose of HF treatments, *Table 1*). ACE-I was used in 89.2%, mostly ramipril (n=13,424, 51.0%) and enalapril (n=12,451, 47.3%). Beta-blockers were used in 91.7%, mostly metoprolol (n=20,193) and bisoprolol (n=16,616) (*Supplementary Table 1*). MRA was used in 45.3%.

### *Association between SBP and outcomes*

Patients were followed-up for a median duration of 27.8 months (range: 0.0-203.0 months), resulting in a total of 142,543 patient-years of follow-up.

We observed a gradual increase in the risk of CV death/ HF hospitalization with lower SBP, starting at SBP levels lower than 130 mmHg. The crude HR observed at 80 mmHg was approximately 2.5 whereas it was less than 1.5 at 100 mmHg (with SBP 120 mmHg as reference) (*Figure 1*).

### *Association between baseline SBP and outcome according to treatment dose category*

Overall, rates of the primary outcome (CV death / HF hospitalization) increased with lower HF medications' doses and with lower SBP as expected (*Figure 2*). The highest SBP category ( $\geq 140$  mmHg) with maximum HF medication dose (i.e. maximal dose of all 3 medications) was set as the reference (HR 1.0). A marked higher risk of CV death / HF hospitalization was observed in patients with  $< 50\%$  of the maximum HF medication dose. In crude analysis (*Figure 2*), the risk was lower for patients with SBP 100-119 and maximum HF treatment (HR=1.4, 1.3-1.5) than with SBP 120-139 and low HF medication dose (i.e.  $< 50\%$ ; HR=1.9, 1.8-2.1). The highest risk was observed in patients with SBP  $< 90$  mmHg and low HF medication dose (HR=4.3, 3.6 to 5.1) and this increase was greater than in patients with similarly low SBP but under maximum HF medications' doses (HR=2.8, 2.3 to 3.5) (*Figure 2*).

In addition, when further adjusting for NT-proBNP, associations were numerically lower, but the overall pattern of association of SBP with outcome according to treatment dose category remained unchanged (*Figure S1*).

When considering men and women separately, the pattern of association remains largely consistent. However, we did observe numerically lower HR values in women compared with men (e.g., HR for SBP 90-99 mmHg was 1.3 for 100% treatment dose and 2.0 for  $< 50\%$  treatment dose in women, compared to 2.2 and 3.0 in men, respectively) (*Figure S2*).

### *Interaction between baseline SBP and treatment dose with regards to outcome*

In adjusted analyses, lower baseline SBP remained less associated with CVD/HFH with both increasing RAS inhibitor and increasing beta-blockers doses (10% decrease in rates of CVD/HFH per 10 mmHg higher SBP in untreated patients versus a 7% decrease in patients at maximum dose) (*Supplementary Table 2 and Figure 3*). A similar pattern of association was observed when considering CVD (*Supplementary Table 2*). This pattern was not observed when considering MRAs.

When considering the occurrence of syncope as outcome (*Supplementary Table 2*), higher SBP was associated with a higher risk of syncope in patients not treated with RASi (15% increase in syncope rates per 10 mmHg SBP increase) but otherwise not significantly associated with syncope (all  $p > 0.20$ ). Specifically, the association of SBP with syncope was HR=1.00 (0.96-1.04) in patients treated with a beta-blockers dose  $\geq 50\%$  and HR=0.99 (0.95-1.02) in patients treated with a RASi dose  $\geq 50\%$ . When assessing the risk of syncope



based on SBP and HF drug dose, it was observed that only patients with SBP > 140 mmHg and < 50% HF drug dose exhibited a significantly higher risk (Figure S3).

#### *Association of SBP changes over time according to treatment dose changes over time*

In the 13,761 patients in whom changes in SBP and treatment dose could be quantified during follow-up, 9.9% of patients had SBP decrease >10 mmHg while their HF medications' doses were increased whereas 18.6% had decreasing SBP while on stable dose and 6.1% had decreasing SBP while on decreasing doses between the first visit and the follow-up visit (*Supplementary Table 3*). Patients with decreasing SBP while under stable or decreasing HF medications' doses were older, more likely to be seen in an outpatient setting and had worse kidney function than patients with decreasing SBP while doses were increased. The respective SBP values at the follow-up measurement of patients with decreasing SBP while under stable or increased doses were similar (110 mmHg in both groups) whereas the SBP at follow-up of patients with decreasing SBP and decreasing treatment was lower (105 mmHg). Patients with decreasing SBP while under stable or decreasing treatment had overall a lower number of HF medications and higher NT-proBNP than patients with decreasing SBP while treatment was increased (*Supplementary Table 2*).

After adjustment, decreasing SBP >10 mmHg was associated with increased risk for events in patients with stable (HR=1.08 [1.01-1.17]) or decreasing (HR=1.31 [1.17-1.46]) HF medication dose whereas it was not in patients who had an increase in the dose of HF medication (HR=0.96 [0.86-1.06]) (*Figure 4*). A similar pattern of association was observed when considering CVD rates (*Figure 4*).

## **Discussion**

It is known that in HFrEF, both lower BP and lower use of and doses of HF medications are associated with greater risk. We confirm these findings. However, we provide important novel findings related to the interaction between BP and medication use and doses. Specifically, the main results are that (1) lower baseline SBP was exponentially associated with higher risk of CV death or HF hospitalization, but this association was attenuated in patients with increasing dosage of HF medication and (2) a decline in SBP over time in the setting of increasing RAS inhibitor and beta-blocker doses was not associated with higher risk. Overall, these results suggest that, even though low SBP is associated with worse outcomes in HFrEF, the increase in risk is mostly observed in patients with low doses or those that are unable to increase doses, whereas it is attenuated in

patients with higher doses or those that are able to increase doses. Therefore, based on our findings, it is important to acknowledge that a low SBP or a reduction in SBP should not be hastily perceived as a contraindication to optimizing HF medication. This is because the magnitude of the increase in risk associated with lowering blood pressure while optimizing HF medication appears to be sizably smaller than the decrease in risk observed with higher doses of HF drugs. To ascertain the potential benefits of a more flexible approach to HF medication optimization, including considerations for low blood pressure, it would be worth undertaking clinical trials that specifically investigate the impact of such approaches on clinical outcomes.

#### *Association of blood pressure and blood pressure changes with outcome*

The association of BP with outcome has been mostly studied in acute HF cohorts<sup>16</sup>. In the chronic phase of HFrEF, a 10 mmHg decrease in systolic BP has been reported to be associated with a 13% higher risk of all-cause death<sup>17</sup>. More recently, low SBP (<90 mmHg) was shown to be significantly associated with the risk for death in a tertiary care center<sup>6</sup> and in the Val-HeFT study<sup>8</sup>, the lowest quartile of systolic BP (i.e. <110 mmHg) had a significantly increased adjusted risk of death, first morbid event, and HF hospitalization (HR=1.21, 1.25, and 1.45, respectively) if compared with patients in the upper 3 quartiles. Our results further strengthen these previous findings by showing a significant association between baseline SBP and outcome. However, the magnitude of the association of SBP with outcome seems less in the results we report herein than in some previous reports with very low SBP (80 mmHg) being associated with a HR of approximately 2.5 versus a SBP of 120 mmHg.

The association of BP changes over time with outcome among stable HFrEF patients has been poorly studied. A study by Schmid et al. showed that, in their tertiary care cohort with a sizeable proportion of patients with advanced HF (8% underwent heart transplantation during follow-up), a BP increase or decrease greater than  $\pm 10$  mmHg over 1 year conferred a significantly higher risk for the combined endpoint of death or heart transplantation (HR=1.8 and 2.0, respectively)<sup>6</sup>. The association of BP changes with clinical outcomes has also previously been investigated in the Val-HeFT study<sup>8</sup>. In this study, average change in SBP assessed at 4 months (a timepoint comparable to those adopted in our study) was about 4 mmHg in patients with Valsartan. In multivariable models, a BP drop over time was associated with an increase in the subsequent risk of adverse outcome in the entire population, independently of baseline SBP. However, none of these studies evaluated whether the association differed according to changes in background HF treatment.

### *Association of blood pressure and blood pressure changes with outcome according to HF treatment dose*

To the best of our knowledge, we are the first to observe a significant interaction of ACE-I/ARB and beta-blocker use and dose with SBP with respect to outcomes. With higher doses of HF medications, the association between low BP and outcomes was weaker. This suggests that hypotension may be less harmful if it is associated with higher medication doses than if associated with “spontaneous” lower SBP, occurring e.g. as a marker of more severe HF. In addition, to the best of our knowledge, our study is the first to evaluate whether the association of falling blood pressure over time with increased risk differs according to changes in HF treatment during that time. Importantly, SBP reductions occurring concomitantly with increases in HF medication were not associated with increased risk. This suggests that hypotension occurring in association with dose increases is not harmful. In addition, low BP was not associated with increased rates of syncope. In fact, higher SBP appeared associated with increased rates of syncope in patients not treated with RASi. Taken together, these findings strongly suggest that hypotension should not limit use of and dosing of HF medications.

When analyzing men and women separately, we observed a generally similar pattern of association between SBP, HF treatments’ doses, and outcome. However, assessing the association in patients with the lowest SBP (<90 mmHg) was challenging due to the limited number of women. This finding holds significant importance as previous studies have reported that women with HFrEF experience maximum benefits on all-cause death or HF hospitalization when beta-blocker doses reach 50-60% of recommended target and 40-60% of ARBs/ACE inhibitors target dose<sup>18</sup>. In our cohort, we found that women receiving less than 50% of the recommended HF treatment dose consistently exhibited a worse prognosis compared to those treated with higher doses except in the subgroup of patients with SBP<90 mmHg in which the limited number of cases preclude any firm inference. However, overall, the increased risk with lower BP was attenuated with higher doses of medication but this attenuation appeared to occur at lower doses in women than for men, which would be consistent with the above studies demonstrating benefits at lower doses in women.

Notably, considering the results depicted in Figure 2, a pertinent question arises as to whether patients with SBP<90 mmHg and 100% HF drug dose (HR=2.8) might actually fare better if their SBP is subsequently increased to the range of 90-99 mmHg (HR=2.7 for <50% dose and HR=2.3 for 50% dose). However, the comprehensive analysis conducted on BP trajectories, as presented in Figure 4, strongly suggests that lowering blood pressure through increasing HF drug dose is not associated with worse outcomes (with HR ranging from

0.90 to 0.96, depending on the considered outcome and model adjustment). Taken together, these findings indicate that having low blood pressure due to an optimized HF drug regimen is far less detrimental than having intrinsic or spontaneous low blood pressure.

### *Clinical implications*

In clinical practice, the use of HF life-saving drugs is suboptimal in community-based HF populations<sup>19</sup> and international registries<sup>3</sup>. Hypotension is listed as a common reason for non-use, sub-optimal dosing, and withdrawal of these drugs, along with worsening renal function and hyperkalemia. As the association of SBP changes with outcome was neutral when they occurred in the setting of HF treatment optimization, our results suggest that moderate drops in SBP should be accepted in HFrEF patients. Consequently, we show for the first time that HF drugs dosage should probably not be modified following these moderate SBP drops. It is of no surprise that patients with lower BP, having more advanced HF, have poorer outcome – Yet, adequately treating these patients with lower BP with HF drugs, which could decrease BP to some extent, should be encouraged.

In the frequent cases of non-severe and asymptomatic hypotension observed during HFrEF drug treatment, European and US guidelines recommend maintaining the same drug dosage<sup>13,14,20</sup>. In case of symptomatic or severe persistent hypotension (SBP < 90 mmHg), it is recommended to first decrease blood pressure reducing drugs not indicated in HFrEF as well as the loop diuretic dose in the absence of associated signs of congestion. If symptoms or severe hypotension persist, no recommendations exist. A practical algorithm to cope with low BP was recently published<sup>11</sup>. We suggest that the implementation of these approaches, intending to maintain HFrEF medication in patients with low SBP are further supported by our results. However, it is important to acknowledge that these results are derived from an observational study, and the specific process by which HF drugs were implemented was not captured, making our analysis susceptible to residual confounding. To better quantify the clinical benefits of a flexible approach to HF drug implementation, particularly in patients with lower blood pressure, it would be valuable to undertake trials specifically designed to evaluate the impact of voluntaristic approaches. These trials would provide more rigorous evidence regarding the potential clinical benefits arising from such a BP voluntaristic approach.

### *Limitations*

Our study is retrospective and observational, inherently subject to potential confounding. This limits our capacity to assert a causal link between low BP resulting from intensified HF treatment and favorable outcomes. The definitive evidence to support this connection could be established through a clinical trial. Such a study would examine a conservative strategy of reducing treatment when BP falls below a set threshold against a more liberal strategy that accepts low BP as a consequence of optimized HF treatment. It is essential to underscore that this interpretation should also consider the worsening renal function and increased potassium side effects associated with RASi, integral factors in the comprehensive understanding of the effects of these medications. In addition, in our analysis, changes in SBP according to changes in HF medication could be assessed only in a portion of the population, with differences in the timing of SBP reassessment, which could introduce selection bias. Visit-to-visit office BP variability has demonstrated to have prognostic implications independent of average BP across several populations in the cardiovascular field, including in HFrEF<sup>21-23</sup>, with some intrinsic and unavoidable limitations (strictly post-hoc assessment likely to be affected by baseline between-group differences, not entirely independent on mean BP values)<sup>24</sup>. This parameter was not investigated; however, this is beyond the scope of this study, whose main aim was to investigate prognostic implication (overall and according to treatment) of a simple parameter which could be interpreted in a given consultation without data from numerous follow-ups.

Other relevant adverse outcomes related to low blood pressure, such as orthostatic hypotension, fractures, and changes in renal function, were not considered in our analysis because of their unavailability. Therefore, it is important for future studies to specifically explore these outcomes to gain a more comprehensive understanding of their association with low BP.

### *Conclusions*

The association of lower SBP with greater risk of cardiovascular death and HF hospitalization was attenuated in patients with higher doses of HF medication. In addition, a drop in SBP while increasing HF medication doses was not associated with increased risk. These findings suggest that low BP and reductions in SBP over time should not be perceived as limitations for HF medication optimization.

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None.

## **Conflict of interest**

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## **Data Availability Statement**

The data underlying this article will be shared on reasonable request to the corresponding author.

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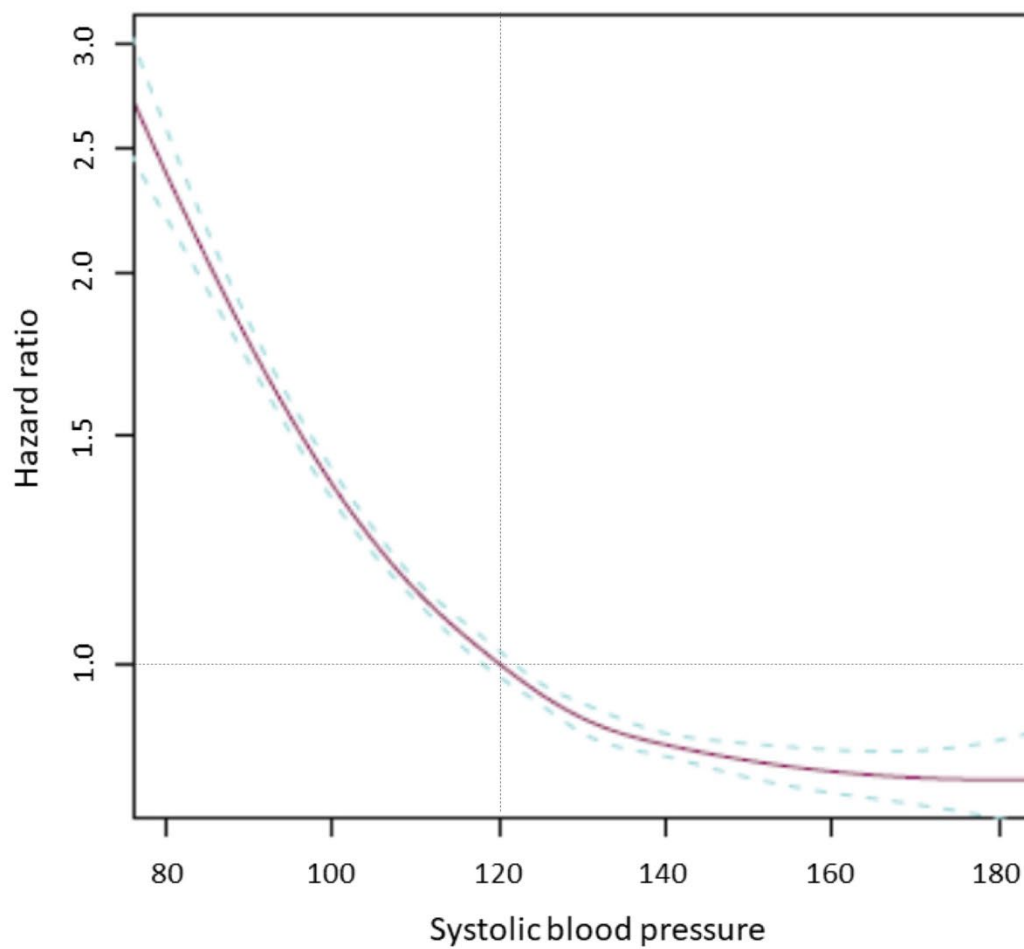
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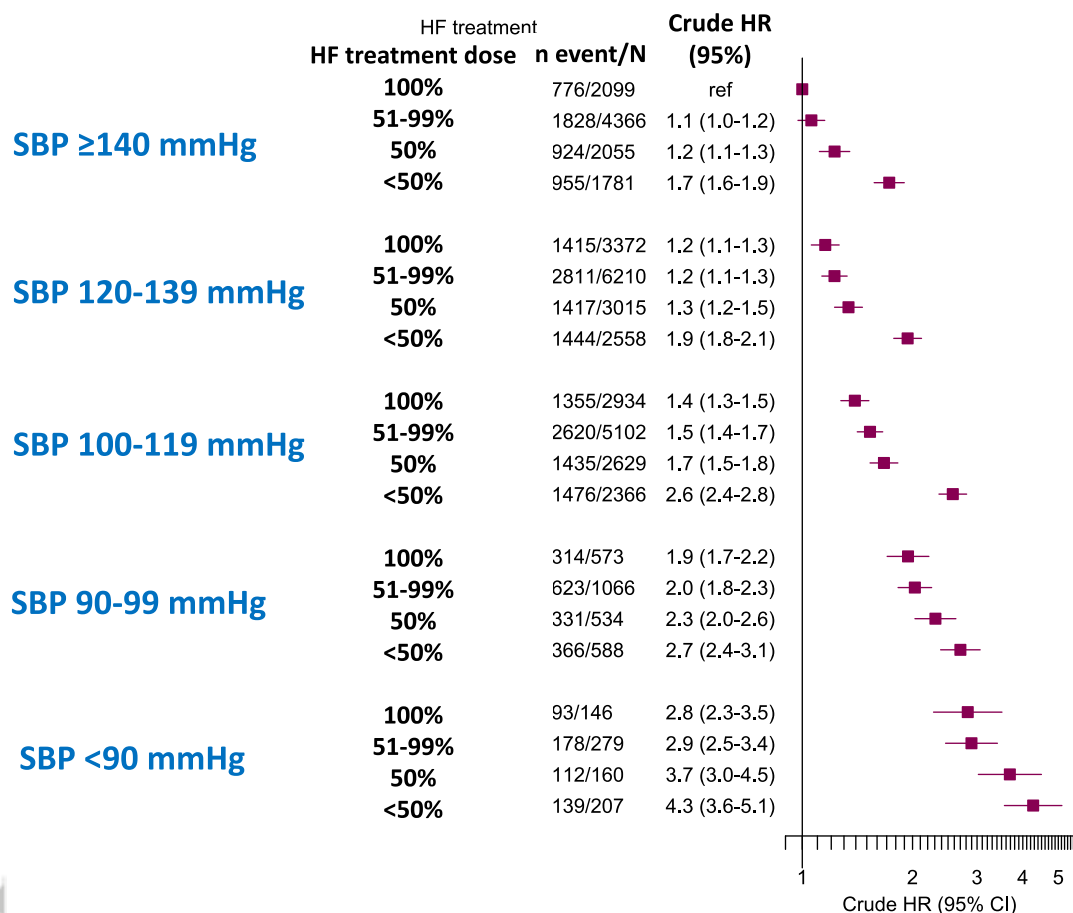
## Figures

**Figure 1:** Shape of the association between systolic blood pressure and cardiovascular death/First Heart Failure Hospitalization.



**Figure 2:** Association of Heart Failure (HF) treatment dose and systolic blood pressure categories with the primary endpoint of cardiovascular death/First HF hospitalization.

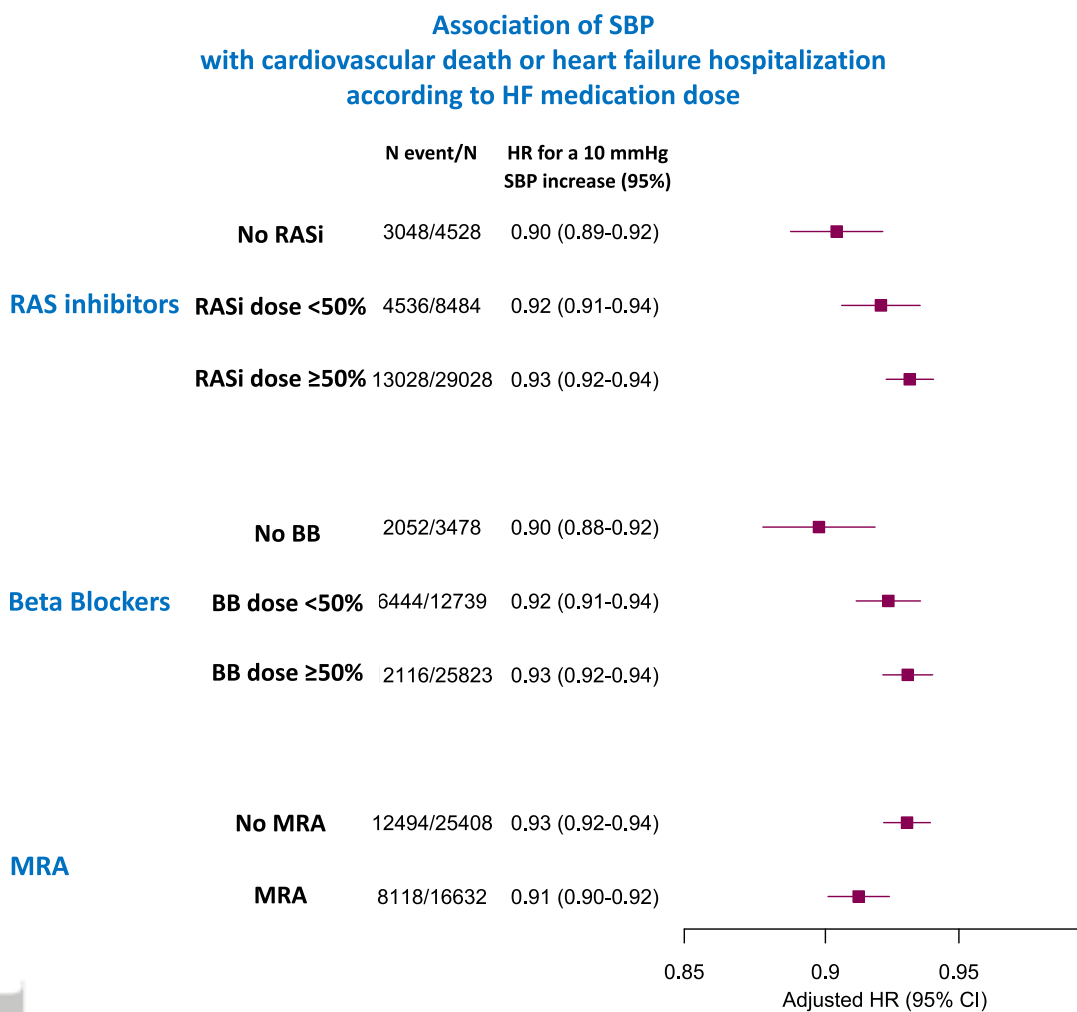
### Association of SBP categories with cardiovascular death or heart failure hospitalization according to HF medication dose



Legend: HR and 95% CI from a Cox model using the treatment variable combining data for ACE-I/ARB, beta-blockers, and mineralcorticoid antagonists are provided.

HR, Hazard ratio; MRA, mineralcorticoid antagonist; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralcorticoid receptor antagonist; RAS, Renin Angiotensin System.

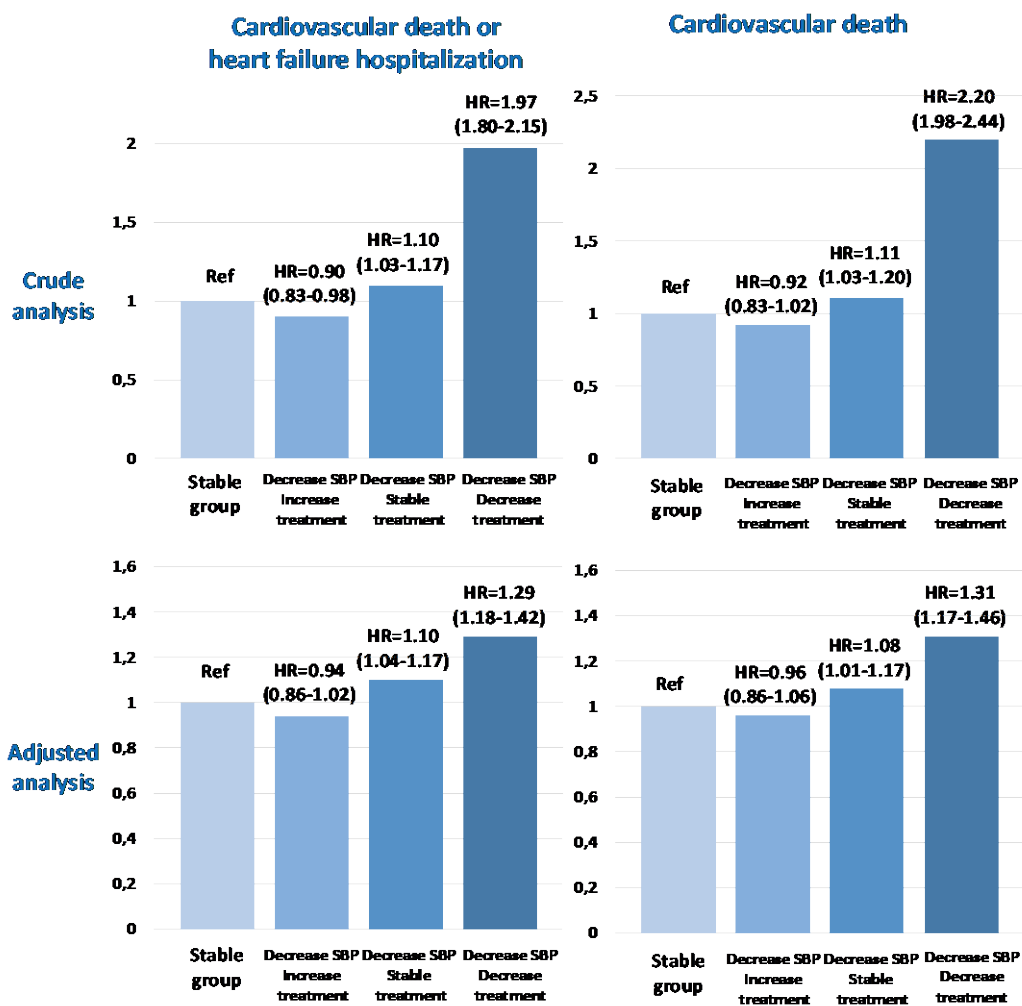
**Figure 3:** Association of systolic blood pressure (SBP) with the primary endpoint of cardiovascular death/First Heart Failure Hospitalization according to the dose of Heart Failure medication (ACE-I/ARB, beta-blockers, and mineralcorticoid antagonists)



Legend: Adjusted HR are provided.

HR, Hazard ratio; MRA, mineralcorticoid antagonist; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralcorticoid receptor antagonist; RAS, Renin Angiotensin System.

**Figure 4:** Association of systolic blood pressure (SBP) changes during follow-up with outcome according to treatment dose changes.



## Figure legends

**Figure 1:** Shape of the association between systolic blood pressure and cardiovascular death/First Heart Failure Hospitalization.

**Figure 2:** Association of Heart Failure (HF) treatment dose and systolic blood pressure categories with the primary endpoint of cardiovascular death/First HF hospitalization.

Legend: HR and 95% CI from a Cox model using the treatment variable combining data for ACE-I/ARB, beta-blockers, and mineralcorticoid antagonists are provided.

HR, Hazard ratio; MRA, mineralcorticoid antagonist; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralcorticoid receptor antagonist; RAS, Renin Angiotensin System.

**Figure 3:** Association of systolic blood pressure (SBP) with the primary endpoint of cardiovascular death/First Heart Failure Hospitalization according to the dose of Heart Failure medication (ACE-I/ARB, beta-blockers, and mineralcorticoid antagonists)

Legend: Adjusted HR are provided.

HR, Hazard ratio; MRA, mineralcorticoid antagonist; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralcorticoid receptor antagonist; RAS, Renin Angiotensin System.

**Figure 4:** Association of systolic blood pressure (SBP) changes during follow-up with outcome according to treatment dose changes.

**Table 1. Baseline characteristics by different medication classes**

Variables	RAS inhibitors dose				Beta-blockers dose				MRA		
	No RASi	<50%	≥50%	p-value	No BB	<50%	≥50%	p-value	No	Yes	p-value
n	4528	8484	29028		3478	12739	25823		25408	16632	
Male sex, n (%)	3050 (67)	5806 (68)	20876 (72)	<0.001	2437 (70)	8747 (69)	18548 (72)	<0.001	17765 (70)	11967 (72)	<0.001
Age (years), Mdn (IQR)	81.0 [74.0, 87.0]	77.0 [68.0, 83.0]	72.0 [63.0, 80.0]	<0.001	79.0 [71.0, 85.0]	77.0 [67.0, 83.0]	73.0 [64.0, 80.0]	<0.001	75.0 [66.0, 83.0]	73.0 [64.0, 80.0]	<0.001
Outpatient setting, n(%)	1499 (33)	4567 (54)	19435 (67)	<0.001	1752 (50)	6977 (55)	16772 (65)	<0.001	14952 (59)	10549 (63)	<0.001
Follow-up, HF unit, n (%)	1513 (37)	4780 (59)	16451 (59)	<0.001	1400 (43)	6936 (58)	14408 (58)	<0.001	13045 (54)	9699 (61)	<0.001
Body mass index (kg/m <sup>2</sup> ), Mdn (IQR)*	24.7 [21.9, 28.2]	25.4 [22.7, 28.7]	26.4 [23.5, 30.1]	<0.001	24.8 [22.0, 28.3]	25.2 [22.5, 28.6]	26.6 [23.6, 30.2]	<0.001	25.8 [23.0, 29.2]	26.4 [23.3, 30.2]	<0.001
Left ventricular EF <30%, n (%)	2026 (44)	4167 (49)	14111 (49)	<0.001	1486 (43)	6144 (48)	12674 (49)	<0.001	11357 (45)	8947 (54)	<0.001
Current smoker, n (%)	312 (9)	803 (12)	3474 (15)	<0.001	291 (11)	1320 (13)	2978 (14)	<0.001	2827 (14)	1762 (13)	0.146
Duration of Heart Failure >6 months, n (%)	3048 (69)	4848 (58)	14813 (52)	<0.001	2110 (62)	6452 (52)	14147 (56)	<0.001	12909 (52)	9800 (60)	<0.001
<b>Clinical examination</b>											
NYHA class, n (%)**				<0.001				<0.001			<0.001
I	126 (4)	388 (6)	2572 (11)		233 (10)	886 (9)	1967 (9)		2011 (10)	1075 (8)	
II	857 (30)	2497 (40)	11544 (49)		944 (39)	4192 (44)	9762 (47)		9034 (47)	5864 (45)	
III	1476 (52)	2931 (47)	8628 (37)		1046 (43)	3822 (41)	8167 (40)		7368 (38)	5667 (43)	
IV	404 (14)	350 (6)	685 (3)		192 (8)	513 (5)	734 (4)		860 (5)	579 (4)	
Systolic BP (mmHg), Mdn (IQR)	120.0 [108.0,	120.0 [105.0,	123.0 [110.0,	<0.001	120.0 [110.0,	120.0 [110.0,	120.0 [110.0, 140.0]	<0.001	123.0 [110.0, 140.0]	120.0 [109.0, 134.0]	<0.001
Systolic BP, n (%)				<0.001				<0.001			<0.001
<90 mmHg	141 (3)	265 (3)	386 (1)		81 (2)	307 (2)	404 (2)		426 (2)	366 (2)	
90-99 mmHg	381 (8)	806 (9)	1574 (5)		248 (7)	1033 (8)	1480 (6)		1436 (6)	1325 (8)	
100-119 mmHg	1505 (33)	3008 (36)	8518 (29)		1047 (30)	4161 (33)	7823 (30)		7387 (29)	5644 (34)	
120-139 mmHg	1504 (33)	2828 (33)	10823 (37)		1215 (35)	4368 (34)	9572 (37)		9294 (37)	5861 (35)	
≥140 mmHg	997 (22)	1577 (19)	7727 (27)		887 (26)	2870 (23)	6544 (25)		6865 (27)	3436 (21)	
Diastolic BP (mmHg), Mdn(IQR)	70.0 [60.0, 80.0]	70.0 [60.0, 80.0]	72.0 [65.0, 80.0]	<0.001	70.0 [60.0, 80.0]	70.0 [60.0, 80.0]	72.0 [65.0, 80.0]	<0.001	70.0 [65.0, 80.0]	70.0 [63.0, 80.0]	<0.001
Mean BP (mmHg), Mdn (IQR)	86.7 [78.3, 96.7]	86.7 [77.3, 95.0]	90.0 [81.7, 100.0]	<0.001	88.3 [79.3, 97.7]	86.7 [78.7, 96.7]	90.0 [81.7, 99.7]	<0.001	90.0 [81.3, 100.0]	87.3 [80.0, 96.7]	<0.001
Heart rate /p.m, Mdn(IQR)	76.0 [67.0, 88.0]	73.0 [64.0, 84.0]	70.0 [62.0, 81.0]	<0.001	74.0 [64.0, 84.0]	70.0 [62.0, 81.0]	72.0 [64.0, 83.0]	<0.001	72.0 [63.0, 83.0]	71.0 [63.0, 82.0]	<0.001
<b>Laboratory results</b>											
Haemoglobin (g/L), Mdn (IQR)	125.0 [113.0,	130.0 [118.0,	136.0 [124.0,	<0.001	130.0 [118.0,	132.0 [120.0,	135.0 [123.0, 147.0]	<0.001	133.0 [120.5, 145.0]	135.0 [123.0, 147.0]	<0.001
Potassium, (mEq/L), Mdn (IQR)***	4.1 [3.8, 4.5]	4.2 [3.9, 4.5]	4.2 [4.0, 4.5]	<0.001	4.2 [3.9, 4.5]	4.2 [3.9, 4.5]	4.2 [4.0, 4.5]	<0.001	4.2 [3.9, 4.5]	4.3 [4.0, 4.6]	<0.001
CEFR, (mL/min), Mdn (IQR)	39.6 [26.3, 57.9]	53.1 [37.2, 72.5]	65.9 [49.7, 83.1]	<0.001	56.2 [40.1, 75.4]	59.8 [42.5, 79.0]	62.1 [44.6, 80.8]	<0.001	59.5 [41.2, 79.3]	62.9 [47.1, 80.8]	<0.001
NT-proBNP (pg/mL), Mdn (IQR)****	6570.0 [2841.5,	3554.0 [1560.0,	2340.0 [984.0,	<0.001	2989.5 [1085.0,	2946.0 [1164.0,	2712.0 [1163.0,	<0.001	2907.0 [1196.8,	2673.5 [1120.0,	<0.001
	16200.0]	8335.0]	5271.0]		7767.5]	7197.0]	6092.5]		7010.0]	5907.0]	
<b>Treatment</b>											
Diuretic, n (%)	3967 (88)	6939 (82)	21858 (75)	<0.001	2675 (77)	9725 (76)	20364 (79)	<0.001	19027 (75)	13737 (83)	<0.001
ACE-in, n (%)	0 (0)	3826 (45)	22515 (78)	<0.001	1792 (51)	8018 (63)	16531 (64)	<0.001	15952 (63)	10389 (62)	0.515
ARB, n (%)	0 (0)	4658 (55)	6513 (22)	<0.001	817 (23)	3046 (24)	7308 (28)	<0.001	6358 (25)	4813 (29)	<0.001
ACE-I or ARB, n (%)	0 (0)	8484 (100)	11064 (100)	<0.001	2609 (75)	11064 (87)	23839 (92)	<0.001	22310 (88)	15202 (91)	<0.001
MRA, n (%)	1430 (32)	2784 (33)	12418 (43)	<0.001	1118 (32)	4331 (34)	11183 (43)	<0.001	0 (0)	16632 (100)	<0.001
Beta-blocker, n (%)	3659 (81)	7598 (90)	27305 (94)	<0.001	0 (0)	12739 (100)	25823 (100)	<0.001	23048 (91)	15514 (93)	<0.001

...an, n (%)	620 (14)	1233 (15)	4366 (15)	0.047	407 (12)	1118 (9)	4694 (18)	<0.001	3431 (13)	2788 (17)	<0.001
Platelet inhibitor, n (%)	2166 (48)	3756 (44)	12848 (44)	<0.001	1571 (45)	6665 (52)	10534 (41)	<0.001	11938 (47)	6832 (41)	<0.001
...agulant, n (%)	1685 (37)	3930 (46)	13303 (46)	<0.001	1154 (33)	4416 (35)	13348 (52)	<0.001	10660 (42)	8258 (50)	<0.001
Statin, n (%)	1701 (38)	4046 (48)	15041 (52)	<0.001	1250 (36)	6230 (49)	13308 (52)	<0.001	12227 (48)	8561 (51)	<0.001
Nitrat...n (%)	919 (20)	1247 (15)	3460 (12)	<0.001	488 (14)	1656 (13)	3482 (13)	0.208	3536 (14)	2090 (13)	<0.001
...CD, n (%)	399 (9)	988 (12)	3126 (11)	<0.001	178 (5)	911 (7)	3424 (13)	<0.001	1931 (8)	2582 (16)	<0.001
<b>Medical history</b>											
...ension, n (%)	2905 (64)	4959 (58)	17285 (59)	<0.001	1930 (55)	7126 (56)	16093 (62)	<0.001	14851 (58)	10298 (62)	<0.001
Diabetes, n (%)	1396 (31)	2417 (28)	7793 (27)	<0.001	855 (25)	3145 (25)	7606 (29)	<0.001	6695 (26)	4911 (29)	<0.001
...ic heart disease, n (%)	3058 (67)	5201 (61)	15753 (54)	<0.001	1976 (57)	7763 (61)	14273 (55)	<0.001	14489 (57)	9523 (57)	0.646
Previous MI, n (%)	2409 (53)	4058 (48)	12016 (41)	<0.001	1497 (43)	6184 (48)	10802 (42)	<0.001	11254 (44)	7229 (43)	0.096
Previous PCI, n (%)	856 (19)	1821 (21)	5956 (20)	0.003	540 (15)	2737 (21)	5356 (21)	<0.001	5039 (20)	3594 (22)	<0.001
...us CABG, n (%)	1357 (30)	2610 (31)	7664 (26)	<0.001	871 (25)	3589 (28)	7171 (28)	0.001	6697 (26)	4934 (30)	<0.001
Peripheral artery disease, n (%)	636 (14)	901 (11)	2394 (8)	<0.001	384 (11)	1242 (10)	2305 (9)	<0.001	2392 (9)	1539 (9)	0.591
Atrial fibrillation, n (%)	2866 (63)	4894 (58)	15024 (52)	<0.001	1802 (52)	5626 (44)	15356 (59)	<0.001	13581 (53)	9203 (55)	<0.001
...ous stroke-TIA, n (%)	1131 (25)	1758 (21)	4664 (16)	<0.001	778 (22)	2362 (18)	4413 (17)	<0.001	4780 (19)	2773 (17)	<0.001
Valvular disease, n (%)	1484 (33)	1752 (21)	4570 (16)	<0.001	875 (25)	2520 (20)	4411 (17)	<0.001	4480 (18)	3326 (20)	<0.001
COPD, n (%)	734 (16)	1249 (15)	3513 (12)	<0.001	516 (15)	1551 (12)	3429 (13)	<0.001	3272 (13)	2224 (13)	0.146

Categorical variables are presented with n (%) and continuous variables with median [q1-q3]

MRA, mineralcorticoid antagonist; HF, heart failure; EF, ejection fraction; NYHA, New York heart association; cl, clearance; BP, blood pressure; NT-proBNP, N-terminal pro B-type natriuretic peptide; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralcorticoid receptor antagonist; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery by-pass graft; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; RAS, Renin Angiotensin System; TIA, transient ischemic attack; IQR, interquartile range; mdn, median; b.p.m., beats per minute.

\* 39% had missing value; \*\* 23% had missing value; \*\*\* 21% had missing value; \*\*\*\* 49% had missing value