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The association of smoking with hospitalization and mortality differs according to sex in patients with heart failure following myocardial infarction

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Running title: Smoking in high-risk myocardial infarction

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Abstract

Background: Smoking has been associated with higher morbidity and mortality following myocardial infarction (MI), but reports of the impact on morbidity and mortality for females and elderly patients experiencing MI complicated with left ventricular dysfunction or overt heart failure are limited.

Methods: In an individual patient data meta-analysis of high-risk MI patients, the association of smoking with hospitalizations and death were investigated. Weighted Cox proportional hazard modelling were used to study the risks of smoking on adjudicated endpoints among different sex and age categories.

Results: 28,735 patients from the CAPRICORN, EPHEBUS, OPTIMAAL and VALIANT trials were assessed. After weighting, smokers (N=18,148) were unfrequently women (29.2%) and a minority were above ≥ 80 years (9.8%). Smoking was significantly more associated with all-cause hospitalizations in women (hazard ratio (HR) 1.24; 95% confidence interval (CI) 1.16 - 1.32) than in men (HR=1.10; CI 1.05 - 1.16) resulting in a significant interaction between smoking and sex ($p=0.005$). Smoking was predictive of all-cause mortality homogenously across age categories (p for interaction=0.25) and sex (p for interaction=0.58).

Conclusions: The influence of smoking on morbidity differed according to sex following high-risk MI. The deleterious impact of smoking on hospitalization appeared particularly potent in women, which should further reinforce preventive strategies in females.

Keywords: Smoking; Age; Sex; Myocardial infarction; Hospitalization; Mortality; Heart failure; Cardiovascular diseases

Abbreviations

ACE	Angiotensin-converting enzyme
ARB	Angiotensin receptor blockers
CI	Confidence interval
CHD	Coronary heart disease
CV	Cardiovascular
HR	Hazard ratio
HF	Heart failure
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
PS	Propensity score
SD	Standard deviation

Introduction

Smoking is a major risk factor for coronary heart disease (CHD), cerebrovascular disease, and atherosclerotic cardiovascular disease.¹ It increases all-cause and cardiovascular mortality.² In patients with established CHD, persistent smoking increases the risk of reinfarction, sudden cardiac death and overall mortality.^{3,4}

In contrast, smokers have been observed to have lower mortality rates following acute myocardial infarction (MI) in unadjusted analysis; a phenomenon that is often termed “smoker’s paradox”.^{5,6} The reason for the “smoker’s paradox” has been coined to be caused by different age and co-morbidity between smokers and non-smokers; smokers are generally younger and have a different incidence of **relevant risk factors** such as obstructive airway disease, diabetes, hypertension, previous MI, and severe CHD.^{5,7,8} **Furthermore, recent publications focusing on sex differences in MI indicate that demographics and clinical risk factors differ between sexes and that the proportion of smokers are lower in women.**^{9,10} **Interestingly**, it has also been shown that female smokers are more likely to develop CHD,¹¹⁻¹³ **that smoking may be a stronger risk factor in women** and that they have increased risk of adverse events following MI compared with male smokers.^{9,14} **However, reports on the impact of smoking on risk for long-term outcomes and potential differences among sex and age categories in patients that experience a high-risk MI and if the smoker’s paradox is present after weighed analyses in such patients are limited.**

On the background of these aforementioned observations, **we examined the High-Risk MI Database Invitative dataset to explore and report additional information on smoking as a risk factor and focused our analyses on differences among sex and age categories in high-risk MI patients using weighed models.** **Our** primary aim was to test the hypothesis that smoking is associated with an increased risk of morbidity and mortality in a large study sample of patients experiencing a high-risk MI complicated with LV (left ventricular) dysfunction or overt heart failure (HF), and to evaluate risks associated with smoking among different sex and age subgroups.

Methods

The High-Risk Myocardial Infarction Database Initiative

The High-Risk MI Database was constructed by merging the captured information on individual patients from four large randomized clinical trials evaluating pharmacological intervention in high-risk patients following an acute MI complicated with signs of HF or LV dysfunction: VALIANT,¹⁵ OPTIMAAL,¹⁶ EPHEBUS,¹⁷ and CAPRICORN.¹⁸ All four trials recruited patients in the subacute phase following MI complicated with clinical evidence of HF or objective evidence of LV dysfunction. The trials evaluated randomised medication added to conventional management according to local routine practice in complicated acute MIs. VALIANT randomised patients to either an ACE inhibitor (captopril) or an angiotensin receptor blocker (ARB) (valsartan) or both. OPTIMAAL randomised patients to either an ACE inhibitor (captopril) or an ARB (losartan). EPHEBUS randomised patients to either placebo or an aldosterone antagonist (eplerenone). CAPRICORN randomised patients to either placebo or a beta-blocker (carvedilol). The sponsors of the original trials agreed to permit creation of the database on the condition that the patient's individual randomization with regard to the intervention was not included.¹⁹ The database contains detailed information on 28,771 patients with 5,111 deaths and 33,868 all-cause rehospitalizations representing 330,486 days spent following complicated MI. Thus, an analysis of this large database permits assessment of the effects of smoking on outcomes in a patient cohort at a particularly high risk of mortality and morbid events. For the present study, we analysed 28735 of these patients (36 out of 28771 were excluded due to missing data for smoking status). The trials were conducted in accordance with the Declaration of Helsinki and were approved by ethics committees. All patients signed informed consents.

Baseline data

Baseline patient information at the time of acute MI were registered, including demographics, clinical observations, past history, use of medications, and results of relevant blood tests. **Baseline data medications were recorded at the time of inclusion for each of the respective studies (patients were allowed to be included between 12 hours and 21 days after experiencing their MI).** Patients were at each site per protocol assessed for symptoms and signs of HF, and LV ejection fraction (LVEF) was determined by echocardiography, contrast ventriculography, or

radionucleotide ventriculography. **LVEF was obtained before inclusion and usually within the first days of admission.**

Outcomes

Clinical events and deaths that occurred during follow-up were sampled and all were by design adjudicated by independent endpoint committees.

Statistical analysis

Continuous variables are described as mean \pm standard deviation (SD), categorical variables as frequencies (percentages). Comparison of baseline characteristics according to smoking status was carried out using t-test for continuous variables and Fisher's exact test for categorical variables.

As recommended by the Joint Commission on Accreditation of Healthcare Organizations, smoking status was binary assessed as "smoker" (current/past smoker) and "never smoked".²⁰ Age was categorized into <60, 60-69, 70-79, and \geq 80 years and sex to male or female.

For patient outcome we evaluated all-cause hospitalization and all-cause death. To adjust for imbalance in baseline characteristics between smokers and never smoked patients, propensity score (PS)-based analyses were performed for assessment of risk for endpoints; the PS representing the likelihood of being a smoker was calculated for each patient using a logistic regression model. The variables included in the PS model were age, sex, interaction term between age and sex, body mass index, renal insufficiency, chronic obstructive airway disease, peripheral artery disease, diabetes, hypertension, Killip class (**I - no HF [no clinical signs of cardiac decompensation], II - HF [diagnostic criteria include rales, S3 gallop and venous hypertension], III - severe HF [frank pulmonary edema] and IV - cardiogenic shock [signs included hypotension of systolic pressure of 90 mmHg or less and evidence of peripheral vasoconstriction such as oliguria, cyanosis and diaphoresis]**)²¹, systolic blood pressure, diastolic blood pressure, diuretics and estimated glomerular filtration rate. Some variables had missing data and, in order to preserve maximum data completeness, 25 imputed datasets were generated using multiple imputation chained equations.²² We used the "across" method, which consists of generating PSs within each imputed dataset, and then to average the PS across datasets for each individual and use the averaged propensity scores in the

analyses.²³ Among PS-based techniques, an inverse probability treatment weighting was performed herein using stabilized weights.²⁴ These probabilities correspond to the inverse of the PS. Stabilized weights were obtained by multiplying inverse probability treatment weighting by the marginal probability. Weights were then trimmed at 99th percentile to ameliorate efficiency and reduce the influence of extreme weights. Balance of covariates between smokers and never smoked patients was assessed by calculating absolute standardized mean differences before and after weighting. For each variable, the absolute standardized mean difference represents the absolute difference between the mean values in the two groups divided by the common standard deviation. An absolute standardized mean difference less than 0.10 indicates a balance between the two groups.²⁵ Cox regression models using stabilized weights were then executed and different models were tested: model 1 included sociodemographic characteristics (age and sex), model 2 included variables of model 1 and clinical characteristics (Killip class III-IV, systolic blood pressure), co-morbidities (diabetes, hypertension, renal insufficiency, chronic obstructive airway disease and peripheral artery disease), and medication (diuretics), model 3 included variables of model 2 and estimated glomerular filtration rate <60 mL/min/1.73 m². Further, we also assessed interactions of smoking status with age and sex in these models; **a multiplicative interaction term was inserted in the multivariable model testing the interaction of smoking with sex (smoking*sex) and age (smoking*age)**. Hazard Ratios (HR) for smoker vs. never smoked (reference) are presented with their 95% confidence intervals (CI) as HR (CI 95%). Event occurrence in different groups are illustrated following weighted Kaplan-Meier analyses and differences between the weighted survival curves were analyzed using the robust log-rank test. **An outline of patients that were assessed is depicted in Figure 1.**

All analyses were performed using R software, version 4.0.2 (the R foundation for Statistical Computing). The two-tailed significance level was set at p-value <0.05 .

Results

28,735 patients from the CAPRICORN, EPHEBUS, OPTIMAAL and VALIANT trials were included for study, of which there were 18,235 smokers and 10,500 never smoked patients.

Baseline data

Patient demographics, findings on admission and medical history according to smoking status for the overall study sample are displayed in Table 1. A lesser proportion of smokers were females (17.3% versus 51.6%) and they were also younger (mean age of 62.6 ± 11.4 versus 69.1 ± 10.3). More smokers had a diagnosis of chronic obstructive airway disease (10.7% versus 4.1%) but fewer had a history of diabetes (22.7% versus 30.8%) and hypertension (48.6% versus 63.7%). Furthermore, renal insufficiency were less common among smokers (2.9% versus 3.9%) and mean estimated glomerular infiltration rate was higher (72.3 ± 20.6 versus 64.4 ± 19.9).

Available baseline data for different age and sex categories are presented in Table 2 and 3. Similar to above, the proportion of smoking females were lower for all age groups and the mean body mass index were lower across all categories. The same trend of less smokers having diabetes, hypertension and renal insufficiency were also found (Table 2). Similar findings were observed if evaluated according to sex, except for the comparison of mean body mass index in smokers versus never smoked males (Table 3).

Evaluation of outcomes

After weighting, 18,148 were assessed as smokers, of which 5,304 (29.2%) were women and 1,774 (9.8%) were above ≥ 80 years (Table S1). **The mean duration of follow-up was 23 ± 11 months (1.9 ± 0.9 years).** Weighted number of events according to smoking status are shown in Table S2.

When assessing the risk for all-cause hospitalizations, smoking was a clearly significant factor in all models and was associated with a 14% increased risk in the most adjusted model 3 (Table 4). The effect among different age categories was also significant in all groups and appeared strongest for the youngest patients. However, no statistically significant interaction between smoking and age were found. In contrast, the risk associated with smoking was increased by 24% for females compared to 10% for males in model 3, with a statistically significant interaction

between smoking and sex ($p=0.005$). Event curves and comparison of all-cause hospitalization for different groups are illustrated in Figure 2.

For prediction of death, smoking was also highly predictive of risk in the overall study sample with a 14% increase in the most adjusted model (Table 5). When stratified by age, the risk estimations were highest among younger patients with a 24% increase in <60 and 60-69 years categories while an association in patients ≥ 80 years was not present. Nonetheless, no interaction was found between smoking and age ($p=0.25$). Furthermore, males were observed to have a risk estimate of a 15% increase compared to 11% for females for mortality in model 3. In contrast to prediction of hospitalizations, no interaction between smoking and sex was found ($p=0.58$). Event curves and comparison for all-cause death for different groups are illustrated in Figure 3.

Discussion

This analysis presents several novel findings concerning the relationship between smoking and outcomes following MI, supplementing previous reports by presenting results of advanced weighted models on smoking for risk prediction among different age and sex groups from a study sample that included a substantial number of aged and female patients experiencing a high-risk MI. The impact of smoking on the risk of hospitalizations was particularly robust in females with a statistically significant interaction present. Furthermore, our results support an increased risk of adverse outcomes for smokers in the majority of the investigated age and sex groups. However, while the risk estimates differed among categories and appeared more strong for younger than elderly patients, no significant interactions with age were observed.

The “smoker’s paradox” is a classic example of Simpson’s paradox. The “smoker’s paradox” is attributed to the observation that smokers present with lower unadjusted mortality rates following acute MI.^{5, 6} The major reason for this phenomenon is generally attributed to smokers being younger with a lower burden of important comorbidities.^{5, 8, 26} **Interestingly, in our weighted models, smoking was associated with an increased risk of hospitalization and mortality in unadjusted analyses and this support that smoking is an important and significant risk factor for outcomes.** Moreover, the smoking-associated risk of CHD appears to be related to sex. A large-scale meta-analysis demonstrated a 25% increased risk of CHD in female smokers as compared with male smokers,¹¹ and others have found an increased risk of CHD for female smokers.^{12, 13} In addition to a smoking-associated increase in risk for CHD, sex appears to be an important predictor of outcome following MI.¹⁴ The present analyses confirms and extends on these prior observations by presenting risk estimates and evaluation of potential interactions associated with smoking among sex and age categories in weighted adjusted models for morbidity and mortality in patients experiencing a high-risk MI complicated by LV dysfunction or overt HF.

Smoking was a strong risk factor for hospitalization in our dataset, being associated with an increased risk among all age and sex groups and overall. Interestingly, female smokers experiencing a high-risk MI inherited a particularly strong risk for hospitalizations and there was an interaction present between smoking status and sex for hospitalizations. Although the youngest smoking patients seemed to

have the highest risk, no significant interaction was found between smoking and age for hospitalization.

The observation of smoking impacting particularly strong on the risk for hospitalizations in women experiencing a high-risk MI has, to the best of our knowledge, rarely been described before. In general, women with a MI have a higher hospitalization rate following their event than men.²⁷ Furthermore, female survivors of an acute MI complicated by cardiogenic shock have an increased risk of admissions in the early post-discharge period.²⁸ Also, cardiac rehabilitation may decrease readmissions and participation in cardiac rehabilitation are significantly lower in women compared with men.²⁹ It is possible that the interaction that were found may be explained by unmeasured confounders. Nonetheless, reports explaining how smoking impacts on the observed excessive risk of hospitalizations among women that were smokers in our study appear unclear and warrants further investigation.

Similar to smokers more often experiencing hospitalizations after a high-risk MI, we observed that smoking significantly increased risk of death when assessing risk of mortality in the overall study sample. However, in contrast to hospitalizations, we found no interaction for sex when assessing the risk for mortality. Furthermore, even though the risk appeared strongest in younger patients and notably did not reach statistical significance for patients ≥ 80 years and were borderline for patients 70-79 years, no significant interaction between smoking status and age were found. Nonetheless, one may still argue that our findings do not confidently exclude that there may be subtle differences on the impact of smoking on outcomes among different age groups. For example, there may be an increased risk of unrelated deaths that may reduce the effects of smoking in the higher age-groups due to competing risk, with the consequence that the contribution of smoking on risk factor were diluted. As well, patients who are likely to suffer a smoking-related death may die earlier, and old smokers in our dataset could represent a selected sample of individuals more likely to resist negative effects of smoking; this may also explain the surprisingly low proportion of female smokers, especially in the oldest age categories, and the observed weaker association to mortality for female smokers. Also, old smokers may be considered “high risk” and more aggressively treated for risk factors. Nevertheless, our findings support that potential differences on the impact of smoking among age groups are limited in patients experiencing a high-risk MI.

Strengths and limitations

Our individual patient data meta-analysis design allowed for an adequate number of observations in assessing aged and female subgroups including adjustment for numerous confounders. Another major strength of the dataset is the adjudication of outcomes by independent committees, which reduce noise from potential differences between hospitals and investigators. In the analysis, patients were categorized as “present/past smokers” or “never-smokers”, which can be seen as a strength but also a limitation. The categorization of patients as “present/past smokers” or “never-smokers” was done to reduce the effects of patient and investigator related difficulties in acquiring the correct smoking-status at the time of inclusion into a trial and is in accordance with the recommendations by the Joint Commission on Accreditation of Healthcare Organizations.²⁰ However, many patients may feel guilt for smoking or have an initial ambition of becoming a non-smoker at the time they are asked; thus, in response to the question on smoking status they may incorrectly categorize themselves as past smokers. Moreover, the current database contains no consistent quantification of smoking exposure (cigarettes per day/pack-years), and there was no information on smoking status during follow-up. Therefore, we included current and ex-smokers into the same category as “present/past smokers”. A weakness of this categorization is an underestimation of the effects of current smoking on mortality, and it does not estimate the effects of smoking cessation.³⁰ Our results may consequently be considered a more conservative estimate than if a more detailed smoking status had been available; number of cigarettes consumed, number of years of exposure prior to inclusion, and smoking status and number of cigarettes consumed during follow-up. **Furthermore, information on type of revascularization and type of myocardial infarction could have further mitigated residual bias.** Finally, this study assessed data obtained through rigorous follow-up and repeated study-related outpatient visits. The intensive monitoring may influence the rate of hospitalizations compared with patients who are not participating in a clinical trial as they may experience an increased rate of hospitalizations due to the improved diagnostic sensitivity; alternatively, an increased study related follow-up may have reduced the number of hospitalizations following better compliance to therapy.

Conclusions

Smoking status provides important information for risk prediction of patients experiencing a high-risk MI complicated with LV dysfunction or overt HF. The impact of smoking on hospitalization appear particularly potent in women, which may further reinforce preventive strategies in females.

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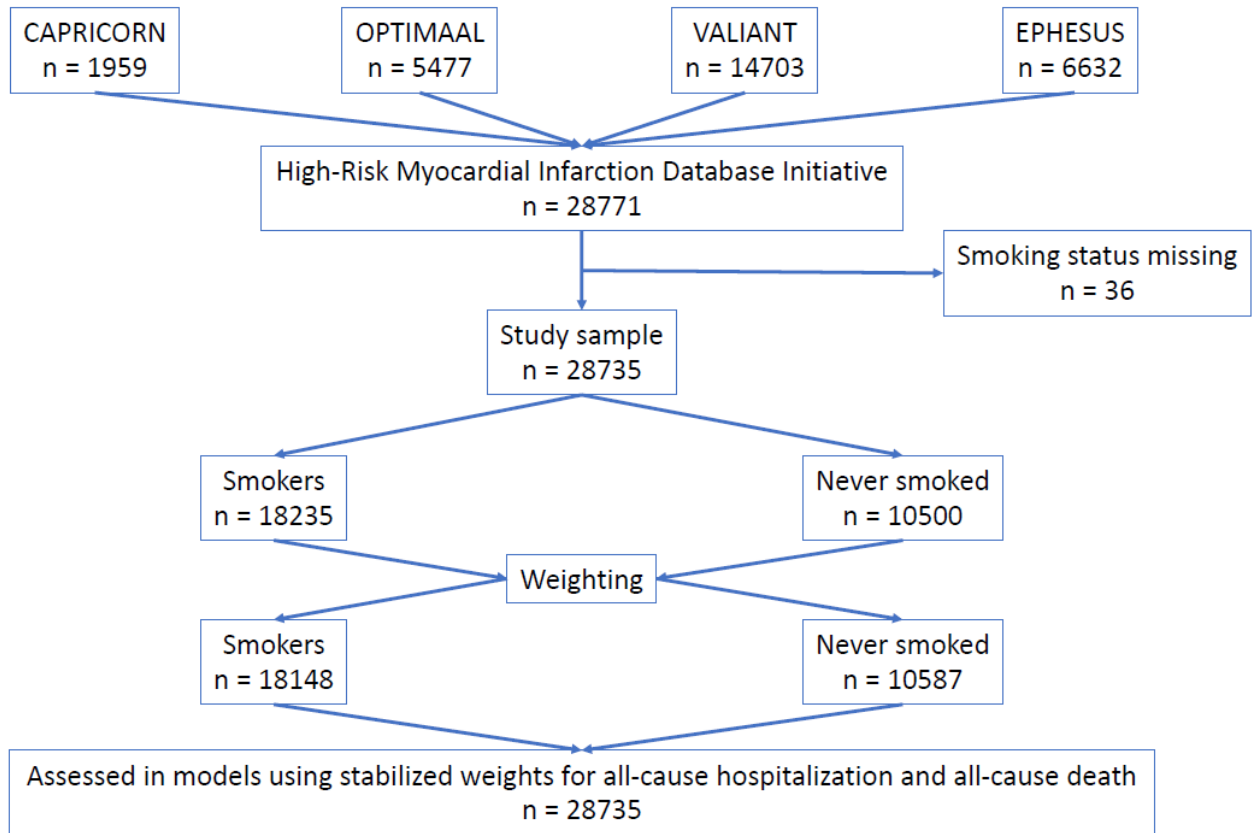
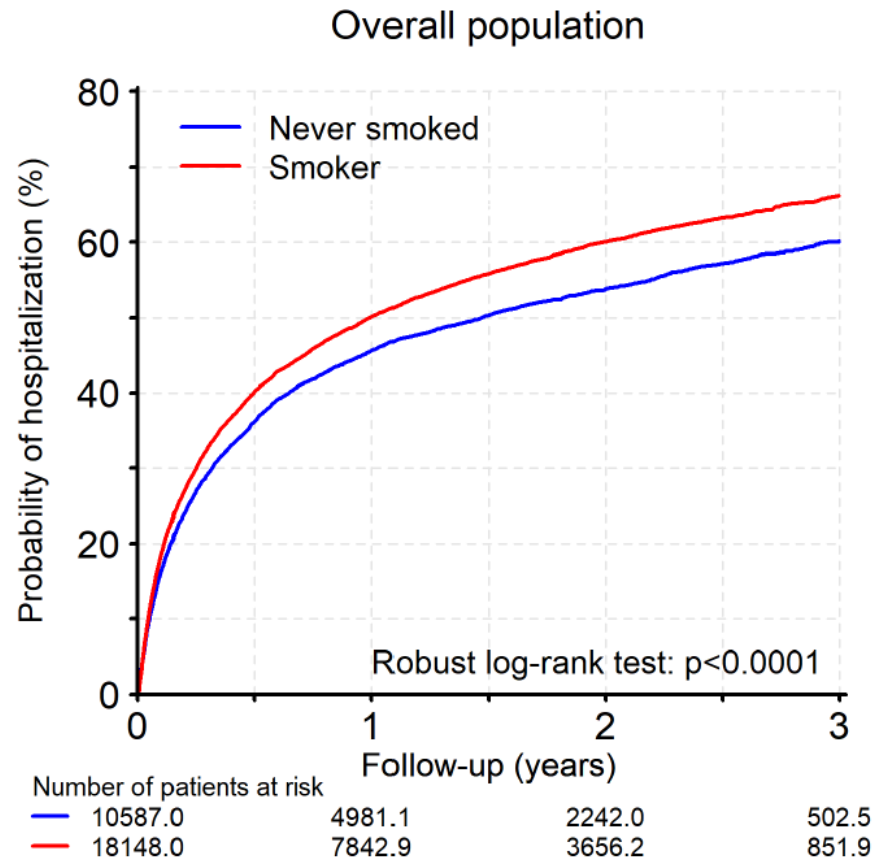
Figure legends**Figure 1. Overview of the study sample.**

Figure 2. KM curves for all-cause hospitalizations.

Figure 2: KM curves for all-cause hospitalization

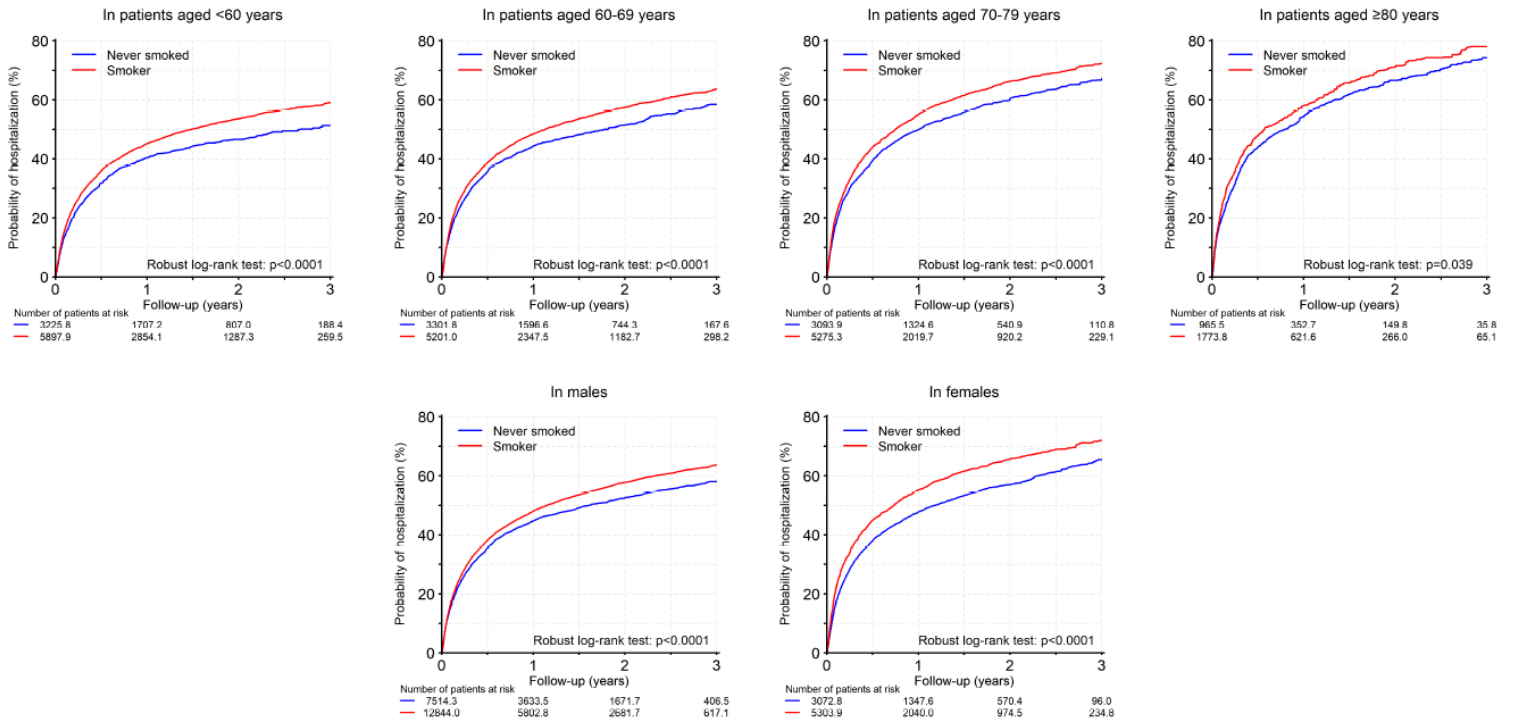


Figure 3. KM curves for all-cause death.

Figure 3: KM curves for all-cause death

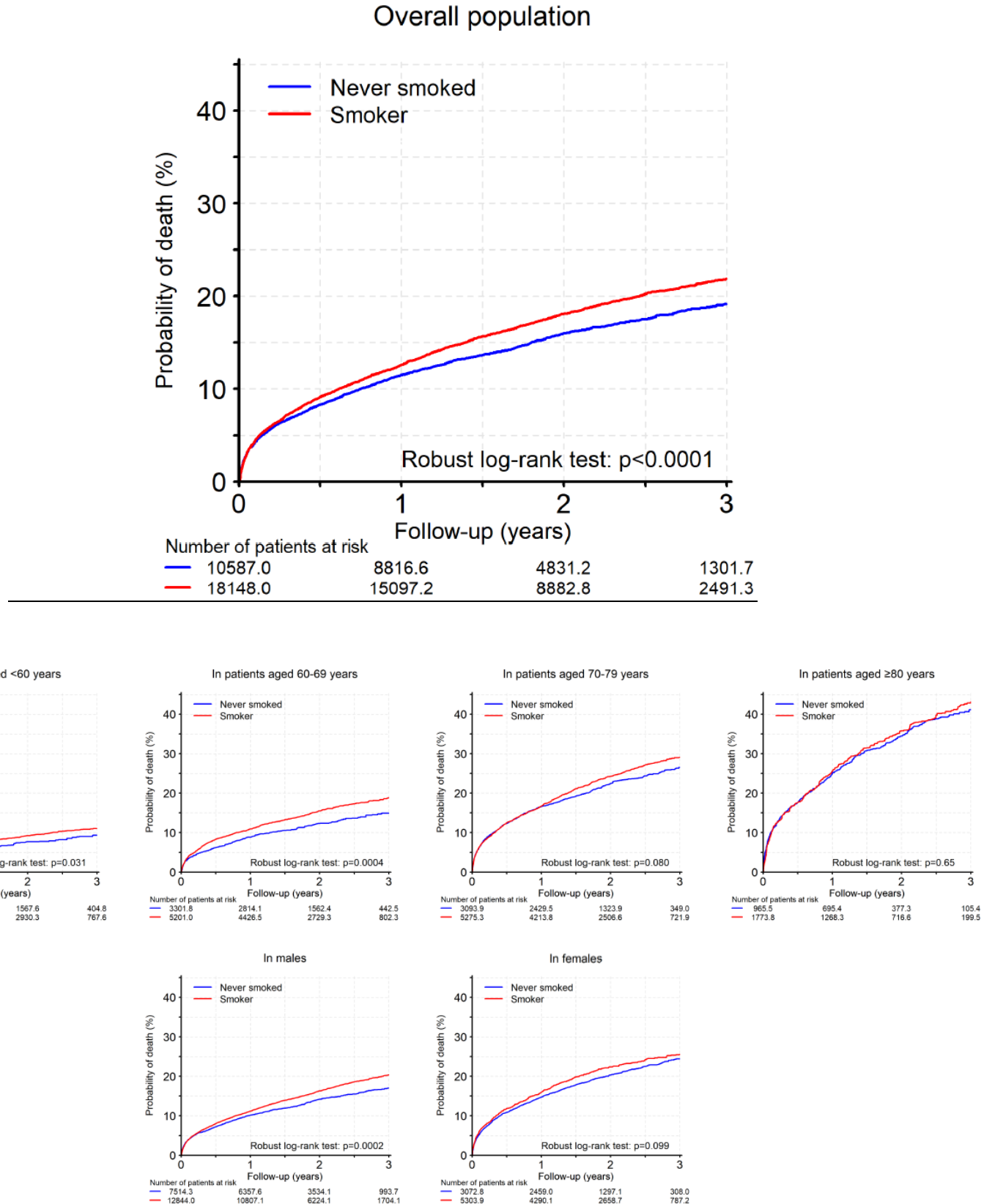


Table 1: Baseline characteristics according to smoking status overall

<u>Variables</u>	<u>Smoker (n=18235)</u>	<u>Never smoked (n=10500)</u>	<u>p-value*</u>
<u>Age (years)</u>	<u>62.6 ± 11.4</u>	<u>69.1 ± 10.3</u>	<u><0.0001</u>
<u>Female</u>	<u>3153 (17.3 %)</u>	<u>5418 (51.6 %)</u>	<u><0.0001</u>
<u>Weight (kg)</u>	<u>80.5 ± 15.6</u>	<u>76.6 ± 15.1</u>	<u><0.0001</u>
<u>BMI (kg/m²)</u>	<u>27.4 ± 4.5</u>	<u>27.7 ± 4.6</u>	<u><0.0001</u>
<u>Renal insufficiency</u>	<u>528 (2.9 %)</u>	<u>408 (3.9 %)</u>	<u><0.0001</u>
<u>COPD</u>	<u>1954 (10.7 %)</u>	<u>435 (4.1 %)</u>	<u><0.0001</u>
<u>Peripheral artery disease</u>	<u>1697 (9.3 %)</u>	<u>658 (6.3 %)</u>	<u><0.0001</u>
<u>Diabetes</u>	<u>4145 (22.7 %)</u>	<u>3229 (30.8 %)</u>	<u><0.0001</u>
<u>Hypertension</u>	<u>8869 (48.6 %)</u>	<u>6688 (63.7 %)</u>	<u><0.0001</u>
<u>Obesity (BMI > 30 kg/m²)</u>	<u>4161 (23.4 %)</u>	<u>2672 (26.0 %)</u>	<u><0.0001</u>
<u>Killip class III-IV</u>	<u>3232 (17.8 %)</u>	<u>2188 (20.9 %)</u>	<u><0.0001</u>
<u>Systolic BP (mmHg)</u>	<u>120.2 ± 16.3</u>	<u>124.5 ± 17.6</u>	<u><0.0001</u>
<u>Diastolic BP (mmHg)</u>	<u>71.5 ± 10.8</u>	<u>73.3 ± 11.3</u>	<u><0.0001</u>
<u>LVEF (%)</u>	<u>34.0 ± 8.4</u>	<u>34.3 ± 8.1</u>	<u>0.016</u>
<u>ACEI/ARB</u>	<u>8154 (56.1 %)</u>	<u>5041 (57.8 %)</u>	<u>0.012</u>
<u>Beta-blockers</u>	<u>11351 (66.5 %)</u>	<u>6451 (66.5 %)</u>	<u>0.90</u>
<u>Diuretics</u>	<u>7823 (42.9 %)</u>	<u>5164 (49.2 %)</u>	<u><0.0001</u>
<u>eGFR (mL/min/1.73m²)</u>	<u>72.3 ± 20.6</u>	<u>64.4 ± 19.9</u>	<u><0.0001</u>
<u>Hemoglobin (g/dL)</u>	<u>13.5 ± 1.6</u>	<u>13.1 ± 1.6</u>	<u><0.0001</u>
<u>Sodium (mmol/L)</u>	<u>139.2 ± 3.5</u>	<u>139.5 ± 3.9</u>	<u><0.0001</u>

<u>Variables</u>	<u>Smoker</u> <u>(n=18235)</u>	<u>Never smoked</u> <u>(n=10500)</u>	<u>p-value</u> *
<u>BMI: body mass index; COPD: chronic obstructive pulmonary disease; BP: blood pressure; LVEF: left ventricular ejection fraction; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blockers; eGFR: estimated glomerular filtration rate.</u>			
<u>*p-value from t-test for continuous variables or Fisher's exact test for categorical variables.</u>			

Table 2: Baseline characteristics according to smoking status in different age categories

Variables	<60 years			60-69 years			70-79 years			≥80 years		
	Smoker (n=7306)	Never smoked (n=1844)	p-value*	Smoker (n=5398)	Never smoked (n=3120)	p-value*	Smoker (n=4424)	Never smoked (n=3981)	p-value*	Smoker (n=1107)	Never smoked (n=1555)	p-value*
Age (years)	51.2 ± 6.0	52.6 ± 5.6	<0.0001	64.5 ± 2.9	64.9 ± 2.8	<0.0001	74.1 ± 2.8	74.3 ± 2.8	<0.0001	83.0 ± 2.8	83.6 ± 3.1	<0.0001
Female	975 (13.3 %)	531 (28.8 %)	<0.0001	964 (17.9 %)	1429 (45.8 %)	<0.0001	935 (21.1 %)	2401 (60.3 %)	<0.0001	279 (25.2 %)	1057 (68.0 %)	<0.0001
Weight (kg)	84.1 ± 16.5	84.2 ± 17.1	0.87	80.2 ± 14.8	79.3 ± 14.1	0.004	77.1 ± 13.7	74.1 ± 13.3	<0.0001	72.0 ± 13.0	68.5 ± 12.9	<0.0001
BMI (kg/m ²)	28.0 ± 4.8	28.9 ± 5.2	<0.0001	27.4 ± 4.4	28.3 ± 4.5	<0.0001	26.7 ± 4.1	27.3 ± 4.3	<0.0001	25.3 ± 3.7	25.8 ± 4.2	0.003
Renal insufficiency	75 (1.0 %)	26 (1.4 %)	0.17	154 (2.9 %)	108 (3.5 %)	0.12	232 (5.2 %)	181 (4.5 %)	0.14	67 (6.1 %)	93 (6.0 %)	0.93
COPD	453 (6.2 %)	38 (2.1 %)	<0.0001	658 (12.2 %)	116 (3.7 %)	<0.0001	678 (15.3 %)	203 (5.1 %)	<0.0001	165 (14.9 %)	78 (5.0 %)	<0.0001
Peripheral artery disease	421 (5.8 %)	61 (3.3 %)	<0.0001	544 (10.1 %)	168 (5.4 %)	<0.0001	585 (13.2 %)	315 (7.9 %)	<0.0001	147 (13.3 %)	114 (7.3 %)	<0.0001
Diabetes	1391 (19.0 %)	536 (29.1 %)	<0.0001	1372 (25.4 %)	988 (31.7 %)	<0.0001	1133 (25.6 %)	1304 (32.8 %)	<0.0001	249 (22.5 %)	401 (25.8 %)	0.055
Hypertension	3220 (44.1 %)	989 (53.6 %)	<0.0001	2711 (50.2 %)	2065 (66.2 %)	<0.0001	2381 (53.8 %)	2691 (67.6 %)	<0.0001	557 (50.3 %)	943 (60.6 %)	<0.0001
Obesity (BMI > 30 kg/m ²)	2016 (28.0 %)	618 (34.1 %)	<0.0001	1258 (23.9 %)	900 (29.3 %)	<0.0001	776 (18.1 %)	928 (23.8 %)	<0.0001	111 (10.5 %)	226 (15.2 %)	0.0006
Killip class III-IV	986 (13.5 %)	245 (13.3 %)	0.85	989 (18.4 %)	572 (18.4 %)	1.00	988 (22.4 %)	990 (25.0 %)	0.005	269 (24.4 %)	381 (24.6 %)	0.89
Systolic BP (mmHg)	117.0 ± 15.0	120.5 ± 16.5	<0.0001	120.9 ± 16.1	124.1 ± 17.3	<0.0001	123.5 ± 17.2	125.9 ± 17.8	<0.0001	124.6 ± 17.6	126.1 ± 18.5	0.036
Diastolic BP (mmHg)	72.4 ± 10.7	74.6 ± 11.3	<0.0001	71.8 ± 10.7	74.5 ± 11.0	<0.0001	70.5 ± 11.0	73.1 ± 11.1	<0.0001	68.7 ± 11.2	70.0 ± 11.9	0.002
LVEF (%)	34.4 ± 8.0	34.3 ± 7.8	0.44	33.8 ± 8.4	34.5 ± 7.9	0.0008	33.5 ± 8.9	34.2 ± 8.1	0.004	33.2 ± 9.2	34.0 ± 8.8	0.073
ACEI/ARB	3464 (56.0 %)	995 (61.9 %)	<0.0001	2361 (56.5 %)	1477 (57.1 %)	0.60	1879 (56.4 %)	1918 (57.7 %)	0.27	450 (53.8 %)	651 (54.0 %)	0.96
Beta-blockers	4995 (73.9 %)	1250 (75.1 %)	0.30	3258 (64.7 %)	1990 (69.5 %)	<0.0001	2496 (59.3 %)	2321 (63.0 %)	0.0007	602 (56.3 %)	890 (60.0 %)	0.061
Diuretics	2468 (33.8 %)	715 (38.8 %)	<0.0001	2403 (44.5 %)	1370 (43.9 %)	0.59	2288 (51.7 %)	2174 (54.7 %)	0.008	664 (60.0 %)	905 (58.2 %)	0.36
eGFR (mL/min/1.73m ²)	81.6 ± 19.5	76.2 ± 20.5	<0.0001	71.0 ± 18.7	67.1 ± 18.6	<0.0001	62.9 ± 17.9	60.8 ± 18.7	<0.0001	56.4 ± 17.4	54.5 ± 16.7	0.004
Hemoglobin (g/dL)	13.8 ± 1.5	13.5 ± 1.7	<0.0001	13.5 ± 1.5	13.3 ± 1.6	<0.0001	13.2 ± 1.6	12.9 ± 1.6	<0.0001	13.0 ± 1.5	12.6 ± 1.6	<0.0001
Sodium (mmol/L)	139.2 ± 3.6	139.5 ± 3.6	0.030	139.3 ± 3.6	139.8 ± 4.0	<0.0001	139.3 ± 3.4	139.5 ± 3.9	0.035	139.0 ± 3.7	139.2 ± 3.8	0.43

BMI: body mass index; COPD: chronic obstructive pulmonary disease; BP: blood pressure; LVEF: left ventricular ejection fraction; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blockers; eGFR: estimated glomerular filtration rate.

*p-value from t-test for continuous variables or Fisher's exact test for categorical variables.

Table 3: Baseline characteristics according to smoking status and gender

Variables	Male			Female		
	Smoker (n=15082)	Never smoked (n=5082)	p-value *	Smoker (n=3153)	Never smoked (n=5418)	p-value *
Age (years)	62.1 ± 11.4	66.2 ± 10.7	<0.0001	65.2 ± 11.1	71.7 ± 9.2	<0.0001
Weight (kg)	82.4 ± 14.9	81.9 ± 14.2	0.020	71.5 ± 15.6	71.6 ± 14.1	0.71
BMI (kg/m ²)	27.3 ± 4.3	27.3 ± 4.1	0.55	27.6 ± 5.7	28.0 ± 5.1	0.0005
Renal insufficiency	458 (3.0 %)	225 (4.4 %)	<0.0001	70 (2.2 %)	183 (3.4 %)	0.002
COPD	1524 (10.1 %)	214 (4.2 %)	<0.0001	430 (13.6 %)	221 (4.1 %)	<0.0001
Peripheral artery disease	1420 (9.4 %)	281 (5.5 %)	<0.0001	277 (8.8 %)	377 (7.0 %)	0.002
Diabetes	3318 (22.0 %)	1285 (25.3 %)	<0.0001	827 (26.2 %)	1944 (35.9 %)	<0.0001
Hypertension	7187 (47.7 %)	2739 (53.9 %)	<0.0001	1682 (53.3 %)	3949 (72.9 %)	<0.0001
Obesity (BMI > 30 kg/m ²)	3267 (22.2 %)	1050 (21.1 %)	0.12	894 (29.2 %)	1622 (30.7 %)	0.18
Killip class III-IV	2541 (16.9 %)	825 (16.3 %)	0.34	691 (22.0 %)	1363 (25.3 %)	0.0007
Systolic BP (mmHg)	120.2 ± 16.1	122.0 ± 16.4	<0.0001	120.1 ± 17.0	126.7 ± 18.4	<0.0001
Diastolic BP (mmHg)	72.1 ± 10.6	73.3 ± 10.8	<0.0001	68.9 ± 11.5	73.4 ± 11.8	<0.0001
LVEF (%)	33.9 ± 8.3	34.0 ± 7.9	0.53	34.5 ± 9.0	34.6 ± 8.2	0.89
ACEI/ARB	6849 (56.4 %)	2432 (59.2 %)	0.002	1305 (54.7 %)	2609 (56.6 %)	0.13
Beta-blockers	9377 (66.8 %)	3267 (69.9 %)	<0.0001	1974 (65.1 %)	3184 (63.4 %)	0.14
Diuretics	6317 (41.9 %)	2158 (42.5 %)	0.47	1506 (47.8 %)	3006 (55.5 %)	<0.0001
eGFR (mL/min/1.73m ²)	73.7 ± 20.2	69.4 ± 19.4	<0.0001	65.5 ± 20.9	59.6 ± 19.2	<0.0001
Hemoglobin (g/dL)	13.7 ± 1.5	13.6 ± 1.6	0.003	12.6 ± 1.5	12.5 ± 1.5	0.003
Sodium (mmol/L)	139.2 ± 3.5	139.6 ± 3.6	<0.0001	139.4 ± 3.5	139.5 ± 4.1	0.20

BMI: body mass index; COPD: chronic obstructive pulmonary disease; BP: blood pressure; LVEF: left ventricular ejection fraction; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blockers; eGFR: estimated glomerular filtration rate.

Variables	Male			Female		
	Smoker (n=15082)	Never smoked (n=5082)	p-value*	Smoker (n=3153)	Never smoked (n=5418)	p-value*

*p-value from t-test for continuous variables or Fisher's exact test for categorical variables.

Table 4: Univariable and multivariable weighted Cox models for smoking status with all-cause hospitalization.

Effect of smoking	Univariable		Model 1		Model 2		Model 3	
	HR (CI 95%)	p-value	HR (CI 95%)	p-value	HR (CI 95%)	p-value	HR (CI 95%)	p-value
Overall effect	1.16 (1.12 - 1.21)	<0.0001	1.16 (1.12 - 1.21)	<0.0001	1.16 (1.12 - 1.21)	<0.0001	1.14 (1.10 - 1.19)	<0.0001
Effect in subgroups								
Age								
<60 years	1.20 (1.10 - 1.31)	<0.0001	1.20 (1.10 - 1.31)	<0.0001	1.20 (1.10 - 1.30)	<0.0001	1.18 (1.08 - 1.28)	0.0002
60-69 years	1.15 (1.07 - 1.23)	0.0001	1.15 (1.07 - 1.23)	0.0001	1.13 (1.06 - 1.22)	0.0004	1.12 (1.04 - 1.20)	0.002
70-79 years	1.16 (1.09 - 1.23)	<0.0001	1.16 (1.09 - 1.24)	<0.0001	1.16 (1.09 - 1.24)	<0.0001	1.15 (1.08 - 1.23)	<0.0001
>80 years	1.13 (1.01 - 1.26)	0.034	1.13 (1.01 - 1.26)	0.036	1.14 (1.01 - 1.28)	0.028	1.13 (1.00 - 1.27)	0.042
	Interaction	0.81	Interaction	0.82	Interaction	0.80	Interaction	0.82
Sex								
Male	1.13 (1.08 - 1.19)	<0.0001	1.13 (1.07 - 1.18)	<0.0001	1.12 (1.06 - 1.17)	<0.0001	1.10 (1.05 - 1.16)	<0.0001
Female	1.24 (1.17 - 1.33)	<0.0001	1.25 (1.17 - 1.33)	<0.0001	1.26 (1.18 - 1.34)	<0.0001	1.24 (1.16 - 1.32)	<0.0001
	Interaction	0.017	Interaction	0.015	Interaction	0.004	Interaction	0.005

Model 1 is adjusted on age and gender (n = 28735 obs.).

Model 2 is adjusted on age, gender, Killip class (III-IV vs. I-II), systolic BP, comorbidities (diabetes, hypertension, renal insufficiency, COPD, peripheral artery disease) and medication use (diuretics) (n = 28557 obs.).

Model 3 includes variables of model 2a and eGFR <60 mL/min/1.73 m² (n = 27473 obs.).

Table 5: Univariable and multivariable weighted Cox models for smoking status with all-cause death.

<u>Effect of smoking</u>	<u>Univariable</u>		<u>Model 1</u>		<u>Model 2</u>		<u>Model 3</u>	
	<u>HR (CI 95%)</u>	<u>p-value</u>	<u>HR (CI 95%)</u>	<u>p-value</u>	<u>HR (CI 95%)</u>	<u>p-value</u>	<u>HR (CI 95%)</u>	<u>p-value</u>
Overall effect	1.15 (1.07 - 1.23)	<0.0001	1.14 (1.07 - 1.22)	0.0001	1.14 (1.06 - 1.22)	0.0002	1.14 (1.06 - 1.22)	0.0003
<u>Effect in subgroups</u>								
<u>Age</u>								
<60 years	1.23 (1.00 - 1.51)	0.045	1.23 (1.00 - 1.51)	0.046	1.22 (0.99 - 1.49)	0.059	1.24 (1.00 - 1.53)	0.049
60-69 years	1.27 (1.11 - 1.46)	0.0006	1.27 (1.11 - 1.46)	0.0007	1.23 (1.07 - 1.41)	0.003	1.24 (1.08 - 1.42)	0.003
70-79 years	1.10 (0.99 - 1.21)	0.082	1.10 (0.99 - 1.21)	0.080	1.10 (1.00 - 1.23)	0.061	1.10 (0.99 - 1.22)	0.084
>80 years	1.04 (0.89 - 1.21)	0.64	1.04 (0.89 - 1.20)	0.65	1.05 (0.90 - 1.22)	0.54	1.03 (0.88 - 1.20)	0.73
	<u>Interaction</u>	<u>0.17</u>	<u>Interaction</u>	<u>0.17</u>	<u>Interaction</u>	<u>0.37</u>	<u>Interaction</u>	<u>0.25</u>
<u>Sex</u>								
Male	1.18 (1.08 - 1.28)	0.0003	1.17 (1.07 - 1.28)	0.0004	1.15 (1.06 - 1.26)	0.002	1.15 (1.05 - 1.26)	0.002
Female	1.09 (0.98 - 1.21)	0.12	1.09 (0.98 - 1.22)	0.11	1.12 (1.00 - 1.25)	0.048	1.11 (0.99 - 1.24)	0.072
	<u>Interaction</u>	<u>0.28</u>	<u>Interaction</u>	<u>0.32</u>	<u>Interaction</u>	<u>0.65</u>	<u>Interaction</u>	<u>0.58</u>

Model 1 is adjusted on age and gender (n = 28735 obs.).

Model 2 is adjusted on age, gender, Killip class (III-IV vs. I-II), systolic BP, comorbidities (diabetes, hypertension, renal insufficiency, COPD, peripheral artery disease) and medication use (diuretics) (n = 28557 obs.).

Model 3 includes variables of model 2a and eGFR <60 mL/min/1.73 m² (n = 27473 obs.).

Table S1: Balance of baseline characteristics according to smoking status before and after weighting

Variables	Before weighting			After weighting		
	Smoker	Never smoked	ASMD*	Smoker	Never smoked	ASMD*
Sum of weights	18235	10500		18148.0	10587.0	
Age (years)	62.6 ± 11.4	69.1 ± 10.3	0.593	65.0 ± 11.6	65.0 ± 11.6	0.003
Female	3153 (17.3%)	5418 (51.6%)	0.774	5303.9 (29.2 %)	3072.8 (29.0 %)	0.004
Weight (kg)	80.5 ± 15.6	76.6 ± 15.1	0.258	79.2 ± 15.8	79.0 ± 15.2	0.012
BMI (kg/m ²)	27.4 ± 4.5	27.7 ± 4.6	0.061	27.4 ± 4.7	27.4 ± 4.4	0.001
Renal insufficiency	528 (2.9%)	408 (3.9%)	0.055	595.9 (3.3 %)	339.8 (3.2 %)	0.004
COPD	1954 (10.7%)	435 (4.1%)	0.253	1519.3 (8.4 %)	880.9 (8.3 %)	0.002
Peripheral artery disease	1697 (9.3%)	658 (6.3%)	0.114	1466.5 (8.1 %)	794.6 (7.5 %)	0.021
Diabetes	4145 (22.7%)	3229 (30.8%)	0.182	4611.8 (25.4 %)	2657.2 (25.1 %)	0.007
Hypertension	8869 (48.6%)	6688 (63.7%)	0.307	9652.7 (53.2 %)	5535.8 (52.3 %)	0.018
Obesity (BMI > 30 kg/m ²)	4161 (23.4%)	2672 (26.0%)	0.061	4326.7 (24.5 %)	2448.3 (23.6 %)	0.021
Killip class III-IV	3232 (17.8%)	2188 (20.9%)	0.080	3414.5 (18.9 %)	1975.1 (18.7 %)	0.004
Systolic BP (mmHg)	120.2 ± 16.3	124.5 ± 17.6	0.251	121.5 ± 16.9	121.4 ± 16.7	0.007
Diastolic BP (mmHg)	71.5 ± 10.8	73.3 ± 11.3	0.164	72.0 ± 11.1	71.9 ± 11.0	0.010
LVEF (%)	34.0 ± 8.4	34.3 ± 8.1	0.036	34.1 ± 8.5	34.1 ± 8.0	0.000
ACEI/ARB	8154 (56.1%)	5041 (57.8%)	0.034	7944.5 (55.9 %)	5145.0 (58.6 %)	0.056
Beta-blockers	11351 (66.5%)	6451 (66.5%)	0.002	11237.3 (65.8 %)	6651.0 (68.4 %)	0.056
Diuretics	7823 (42.9%)	5164 (49.2%)	0.126	8169.6 (45.0 %)	4770.3 (45.1 %)	0.001
eGFR (mL/min/1.73m ²)	72.3 ± 20.6	64.4 ± 19.9	0.391	69.2 ± 20.8	69.2 ± 20.5	0.001
Hemoglobin (g/dL)	13.5 ± 1.6	13.1 ± 1.6	0.290	13.4 ± 1.6	13.3 ± 1.6	0.045
Sodium (mmol/L)	139.2 ± 3.5	139.5 ± 3.9	0.084	139.2 ± 3.5	139.5 ± 3.7	0.078

BMI: body mass index; COPD: chronic obstructive pulmonary disease; BP: blood pressure; LVEF: left ventricular ejection fraction; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blockers; eGFR: estimated glomerular filtration rate.

*ASMD: absolute standardized mean difference.

Table S2: Weighted number of events according to smoking status

	<u>Outcome = Death</u>		<u>Outcome = Hospitalization</u>	
	<u>N_{death}/N (%)</u>		<u>N_{hospitalization}/N (%)</u>	
	<u>Smoker</u>	<u>Never smoked</u>	<u>Smoker</u>	<u>Never smoked</u>
<u>Overall</u>	<u>3411/18148 (18.8%)</u>	<u>1715/10587 (16.2%)</u>	<u>10389/18148 (57.2%)</u>	<u>5444/10587 (51.4%)</u>
<u>Age</u>				
<u><60 years</u>	<u>552/5898 (9.4%)</u>	<u>245/3226 (7.6%)</u>	<u>3042/5898 (51.6%)</u>	<u>1465/3226 (45.4%)</u>
<u>60-69 years</u>	<u>842/5201 (16.2%)</u>	<u>414/3302 (12.5%)</u>	<u>2894/5201 (55.6%)</u>	<u>1651/3302 (50.0%)</u>
<u>70-79 years</u>	<u>1345/5275 (25.5%)</u>	<u>705/3094 (22.8%)</u>	<u>3276/5275 (62.1%)</u>	<u>1745/3094 (56.4%)</u>
<u>>80 years</u>	<u>672/1774 (37.9%)</u>	<u>351/966 (36.3%)</u>	<u>1177/1774 (66.3%)</u>	<u>583/966 (60.4%)</u>
<u>Sex</u>				
<u>Male</u>	<u>2182/12844 (17.0%)</u>	<u>1085/7514 (14.4%)</u>	<u>7075/12844 (55.1%)</u>	<u>3796/7514 (50.5%)</u>
<u>Female</u>	<u>1229/5304 (23.2%)</u>	<u>630/3073 (20.5%)</u>	<u>3314/5304 (62.5%)</u>	<u>1648/3073 (53.6%)</u>
<u>Age & Sex</u>				
<u><60 years - Male</u>	<u>454/4908 (9.3%)</u>	<u>208/2727 (7.6%)</u>	<u>2475/4908 (50.4%)</u>	<u>1219/2727 (44.7%)</u>
<u>60-69 years - Male</u>	<u>588/3801 (15.5%)</u>	<u>286/2423 (11.8%)</u>	<u>2063/3801 (54.3%)</u>	<u>1210/2423 (49.9%)</u>
<u>70-79 years - Male</u>	<u>822/3283 (25.0%)</u>	<u>409/1876 (21.8%)</u>	<u>1991/3283 (60.7%)</u>	<u>1066/1876 (56.8%)</u>
<u>>80 years - Male</u>	<u>318/852 (37.4%)</u>	<u>182/488 (37.3%)</u>	<u>546/852 (64.1%)</u>	<u>301/488 (61.7%)</u>
<u><60 years - Female</u>	<u>98/990 (9.9%)</u>	<u>37/499 (7.5%)</u>	<u>567/990 (57.2%)</u>	<u>246/499 (49.4%)</u>
<u>60-69 years - Female</u>	<u>255/1400 (18.2%)</u>	<u>129/879 (14.6%)</u>	<u>831/1400 (59.4%)</u>	<u>441/879 (50.2%)</u>
<u>70-79 years - Female</u>	<u>523/1993 (26.2%)</u>	<u>296/1218 (24.3%)</u>	<u>1285/1993 (64.5%)</u>	<u>679/1218 (55.8%)</u>
<u>>80 years - Female</u>	<u>354/922 (38.4%)</u>	<u>169/478 (35.3%)</u>	<u>631/922 (68.4%)</u>	<u>282/478 (59.0%)</u>