Association between beta-blocker use and mortality/morbidity in older patients with heart failure with reduced ejection fraction

A propensity score-matched analysis from the Swedish Heart Failure Registry

Short title: Beta-blockers in older patients with HFrEF

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Abstract

Background. Beta-blockers reduce mortality and morbidity in heart failure with reduced ejection fraction (HFrEF). However, patients older than 80 years are poorly represented in randomized controlled trials (RCTs). We assessed the association between beta-blocker use and outcomes in HFrEF patients ≥80 years.

Methods and results. We included patients with EF<40%, age ≥80 years from the Swedish HF Registry. The association between beta-blocker use, all-cause mortality and cardiovascular (CV) mortality/HF hospitalization was assessed by Cox proportional hazard models in a 1:1 propensity score (PS)-matched cohort. To assess consistency, the same analyses were performed in a positive control cohort with age <80 years. A negative control outcome analysis was run using hospitalization for cancer as endpoint.

Of 6,562 patients aged ≥80 years, 5640 (86%) received beta-blockers. In the matched cohort including 1,732 patients, beta-blocker use was associated with a significant reduction in risk of all-cause mortality (HR: 0.89; 95%CI: 0.79–0.99). Reduction in CV mortality/HF hospitalization was not significant (HR: 0.94; 95%CI: 0.85–1.05) due to the lack of association with HF hospitalization, whereas CV death was significantly reduced. After adjustment rather than matching for the PS in the overall cohort, beta-blocker use was associated with reduced risk of all outcomes. In patients aged <80 years, use of beta-blockers was associated with reduced risk of all-cause death (HR: 0.79, 95%CI: 0.68-0.92) and of the composite outcome (HR: 0.88, 95%CI: 0.77-0.99).

Conclusions. In HFrEF patients ≥80 years of age, use of beta-blockers was high and was associated with improved all-cause and CV survival.

Keywords: Heart Failure; Elderly; Beta-blocker; SwedeHF; Registry

Introduction

The aging of the general population has increased the prevalence of heart failure (HF) and the mean age of HF patients, which now exceeds 70 years in most developed countries.[1, 2] Although octogenarians represent up to one-third of the general HF population in Europe, they have been excluded from or are underrepresented in randomized controlled trials (RCTs), leading to uncertainty about the effect of therapies and optimal management of older patients with HF with reduced left ventricular ejection fraction (HFrEF).[2, 3] They are more frail, have more comorbidities and a higher risk of cardiovascular (CV) and non-CV events than younger HF patients.[4] Further issues concern lower tolerance to medications, altered pharmacokinetics and drug interactions due to polypharmacy that lead to undertreatment and high rates of discontinuation.[2, 4]

Beta-blockers reduce mortality/morbidity in patients with HFrEF,[5-8] and thus represent one of the cornerstones of HFrEF therapy. However, limited data on their efficacy/tolerability in older HFrEF patients is currently available.[9] The SENIORS trial tested the efficacy/safety of nebivolol in patients >70 years old, with findings supporting the use of beta-blockers in elderly.[10] However, no significant impact on mortality was observed and the trial included very few patients >80 years old.[10] A large meta-analysis of RCTs recently reported a significant effect of beta-blockers on mortality regardless of age, but with a minor attenuation of treatment effect for CV mortality in older age and almost no enrolled patient >80 years of age.[11]

We sought to assess the use of beta-blockers in HFrEF patients aged ≥80 years, and test their association with all-cause mortality and CV mortality/HF hospitalization in a large, contemporary, real-world HFrEF cohort.

Methods

Study population

The Swedish Heart Failure Registry (SwedeHF) has been previously described.[12] Briefly, patients with clinician-judged HF have been included in the registry since 11 May 2000. Approximately 80 variables are recorded at hospital discharge or after out-patient clinic visit.

For the current analysis, SwedeHF was linked to the National Patient Registry which provided the outcomes hospital admission for HF, syncope, cancer and additional baseline comorbidities, and the Causes of Death registry which provided date and cause of death. Variable definitions are reported in **Table S1**. Linkage with Statistics Sweden provided socioeconomic characteristics. This study with linking of the above registries was approved by a multisite ethics committee and complies with the Declaration of Helsinki.

*Patients (**Figure S1**)*

Patients registered between 11 May 2000 and 31 December 2015, with age ≥80 years, EF <40%, HF duration ≥3 months (similar to the inclusion criterion for HF trials testing beta-blockers), follow-up ≥1 day (i.e. patients who died during the hospitalization/visit linked with the registration in SwedeHF were excluded), and no missing data for beta-blocker use were considered for this analysis. We excluded patients receiving beta-blockers other than those recommended by HF guidelines (i.e. bisoprolol, carvedilol or metoprolol, **Table S2**).[13] If the same patient was registered more than once, we considered the first registration. End of follow-up was 31 December 2015.

Statistical analysis

Multiple imputation (R-package *mice;*[S1] 10 imputed datasets generated) was used to handle missing values in variables which were required for multivariable models. Variables included in

multiple imputation model are reported in **Table 1**, whereas **Table S3** shows the number of missing records per baseline variable. The propensity score (PS) for beta-blocker use was separately calculated in each imputed dataset by a logistic regression model including the clinically relevant variables reported in **Table 1** as covariates, and then averaged across the 10 imputed datasets.[14] Beta-blocker users and non-users were then matched 1:1 using the nearest neighbor method with caliper <0.01 and no replacement. The ability of the matching to balance baseline characteristics in beta-blocker users vs. non-users was assessed by absolute standard differences, with a value <10% considered as not significant. Non-linearity was assessed and variables were transformed accordingly if non-linearity was present.

The primary outcomes of this study were 5-year all-cause mortality and a 5-year composite of CV mortality and first HF hospitalization (with censoring for non-CV death). Secondary outcomes were 5-year CV mortality (with censoring for non-CV death), first HF hospitalization and hospitalization for syncope (with censoring for death). We used a Cox proportional hazard model to estimate the association between beta-blocker use and outcomes. Results are presented as hazard ratio (HR) with 95% confidence interval (CI) and survival estimates are visualized by the Kaplan-Meier method. The proportional hazards assumption was verified by assessment of the Schoenfeld residuals.

Matching reduced the sample size and may limit generalizability, therefore, a Cox proportional hazard models was fitted in the overall cohort adjusting, rather than matching, for the PS. A positive and negative control analysis was also performed. The positive control analysis consisted of a PS matched and adjusted Cox proportional hazard model in patients aged <80 years, while the negative control analysis consisted of a model fitted in patients aged ≥80 years with hospitalization for cancer as outcome, since this is not expected to be associated with beta-blocker use. All statistical analyses were performed in R software version 3.5.1.

Results

A total of 6,562 patients were ≥80 years of age and fulfilled the inclusion criteria. Among the overall cohort, 5,640 (86%) treated with beta-blockers and 922 (14%) were untreated. After PS matching, the analysis was restricted to 1,732 patients, 866 (50%) treated and 866 (50%) untreated.

Baseline characteristics

Median age of the overall cohort was 84 [interquartile range (IQR): 82-87] years, 34.7% were women. Of patients treated with beta-blockers, 21.1% received target dose, 36.4% received 50–99% of target dose and the remaining 42.5% received <50% of the target dose (definition of target dose reported in **Table S2**).

Treated and untreated patients differed for most of the baseline characteristics (**Table 1**). Those receiving beta-blockers were younger, more likely female and followed-up in specialist care, had less severe HF, higher body mass index (BMI), different pattern of comorbidities (less likely anaemic and with peripheral artery disease, more likely diabetic, with hypertension and ischemic heart disease) and higher use of pharmacological and device therapies except for mineralocorticoid receptor antagonists. Consequently, in the overall cohort PS were differently distributed across the study arms (**Figure 1**). After matching, there were no statistically significant differences in baseline characteristics between beta-blocker users and non-users (**Figure 1, Table 1**). Standardized differences were <10% for all variables, with the exception of N-terminal pro-B-type natriuretic peptide (NT-proBNP)(14.6%). Among the matched beta-blocker users, 19.0% received guideline recommended target dose, 33.4% received 50–99% of target dose, 33.4% between 25–49% of target dose and 14.2% received <25% of target dose.

Primary outcomes

All-cause mortality (**Figure 2A**)

In the overall cohort, over a median follow-up of 1.76 [IQR: 0.64-3.39] years, 4,658 (71%) patients died from any cause. The 5-year event rate was 32.2 per 100 patient-years for beta-blocker users vs. 42.8 per 100 patient-years for non-users, with a HR of 0.76 (95%CI: 0.71-0.83).

In the matched cohort the 5-year event rate for beta-blocker users was 36.7 vs. 41.8 per 100 patient-years for non-users, with a HR of 0.89 (95%CI: 0.79-0.99).

In the unmatched overall cohort a statistically significant association between beta-blocker use and 5-year all-cause mortality was confirmed adjusting rather than matching for PS, yielding a HR of 0.89 (95%CI: 0.82-0.97).

Composite outcome (CV mortality or HF hospitalization)(**Figure 2B**)

In the overall cohort, 4,701 (71.6%) patients experienced CV mortality or HF hospitalization. The 5-year event rate for beta-blocker users was 46.7 vs. 58.8 per 100 patient-years for non-users, with a HR of 0.83 (95%CI: 0.76-0.90).

In the matched cohort the 5-year event rate for beta-blocker users was 54.4 vs. 58.2 per 100 patient-years in non-users, with a HR of 0.94 (95%CI: 0.85-1.05).

Conversely, the PS-adjusted Cox regression model fitted in the overall cohort yielded to a statistically significant association between beta-blocker use and reduced risk of the composite outcome, with a HR of 0.90 (95%CI: 0.83-0.97).

Secondary outcomes

CV mortality (**Figure S2A**)

In the overall cohort the event rates for 5-year CV mortality in beta-blocker users vs. non-users were 23.2 vs. 32.0 per 100 patient-years, respectively. The crude HR was 0.74 (95%CI: 0.67-0.81).

In the matched cohort the 5-year event rates were 26.2 vs. 31.1 per 100 patient-years for beta-blocker users vs. non-users, yielding a HR of 0.86 (95%CI: 0.75-0.97).

In the overall cohort, adjusting rather than PS matching, beta-blocker use was consistently associated with a statistically significant reduction in CV mortality, with a HR of 0.87 (95%CI 0.79-0.95).

HF hospitalization (**Figure S2B**)

In the overall cohort the event rates for 5-year risk of HF hospitalization were 33.8 vs. 40.4 per 100 patient-years for beta-blocker users vs. non-users, respectively. The crude HR was 0.87 (95%CI: 0.79-0.96).

In the matched cohort the 5-year event rates were 38.5 vs. 41.0 per 100 patient-years for beta-blocker users vs. non-users, with a HR of 0.94 (95%CI: 0.83-1.07).

Conversely, the PS-adjusted association between beta-blocker use and HF hospitalization in the overall cohort showed a statistically significant HR of 0.90 (95%CI: 0.82-0.99).

*Safety outcome (**Figure S2C**)*

In the overall cohort the 5-year event rates for hospitalization for syncope in beta-blocker users vs. non-users were 1.3 vs. 1.2 per 100 patient-years, respectively. The crude HR was 1.09 (95%CI: 0.69-1.71).

In the matched cohort the 5-year event rates were 1.7 vs. 1.2 per 100 patient-years for beta-blocker users vs. non-users, respectively, with a HR of 1.04 (95%CI: 0.69-1.58).

Consistently with the PS-matched analysis, in the PS-adjusted analysis the HR for the association between beta-blocker use and risk of hospitalization for syncope was 1.03 (95%CI: 0.65–1.64).

*Subgroup analysis (**Figure 3**)*

The association between beta-blocker use, all-cause mortality and the composite outcome was further investigated in clinically relevant subgroups (**Figure 3**). There were no significant interactions between beta-blocker use and any variable defining the subgroups of interest (including atrial fibrillation).

Positive control analysis

Primary outcomes (**Figure 2C-2D**)

In the positive control analysis, we tested the association between beta-blocker use and outcomes in patients <80 years of age (n=13,351). Of them, 12,458 (93.3%) were treated with beta-blockers. Baseline characteristics of the overall and the matched cohorts aged <80 years are summarized in **Table S4**.

In beta-blocker users vs. non-users, 5-year event rates were 11.0 vs. 16.8 per 100 patient-years for all-cause mortality, and 23.5 vs. 31.9 per 100 patient-years for the composite outcome, respectively. The crude HR for all-cause mortality was 0.66 (95%CI: 0.60-0.73), whereas the HR for the composite outcome was 0.77 (95%CI: 0.70-0.84).

After PS matching, the positive control analysis was restricted to 1,662 patients, including 831 (50%) beta-blocker users. The 5-year event rate for all-cause mortality was 12.1 per 100 patient-years for beta-blocker users vs. 15.5 per 100 patient-years for non-users, while the 5-year event rate for the composite outcome was 25.2 vs. 30.0 per 100 patient-years, respectively. The HR for all-cause mortality was 0.79 (95%CI: 0.68-0.92), and 0.88 (95%CI: 0.77-0.99) for the composite outcome. There was no statistically significant interaction between beta-blocker use and atrial fibrillation for both outcomes.

Similar results were reported when we adjusted rather than PS-matched in the overall cohort. The HR for all-cause mortality was 0.89 (95%CI: 0.80–0.99) and 0.86 (95%CI: 0.78–0.94) for the composite outcome.

Secondary outcomes

In the overall cohort the 5-year event rates for CV mortality in beta-blocker users vs. non-users were 7.2 vs. 11.3 per 100 patient-years, respectively. The crude HR was 0.65 (95%CI: 0.57–0.73).

In the matched cohort the 5-year event rates were 8.0 vs. 10.3 per 100 patient-years for beta-blocker users vs. non-users, yielding a HR of 0.79 (95%CI: 0.66–0.94). The PS-adjusted analysis resulted in a HR of 0.84 (95%CI: 0.75–0.96).

For HF hospitalization the event rates for beta-blocker users vs. non-users were 20.2 vs. 26.2 per 100 patient-years. The crude HR was 0.80 (95%CI: 0.73–0.88).

In the matched cohort the 5-year event rates were 21.6 vs. 25.0 per 100 patient-years for beta-blocker users vs. non-users, yielding a HR of 0.90 (95%CI: 0.79–1.03). Conversely, when we adjusted rather than PS-matched in the overall cohort, beta-blocker use was associated with reduced risk of HF hospitalization, with an HR of 0.84 (95%CI: 0.75–0.96).

Negative control analysis

In the matched cohort aged ≥80 years, 5-year event rates for hospitalization for cancer were 2.7 vs. 2.6 per 100 patient-years for beta-blocker users vs. non-users, respectively, yielding an HR of 1.04 (95%CI: 0.69-1.58).

The PS-adjusted model in the overall cohort yielded an HR of 0.97 (95%CI: 0.70–1.36).

Corresponding HRs in the cohort aged <80 years were 1.21 (95%CI: 0.81–1.79), and 1.26 (95%CI: 0.92–1.72), respectively.

Discussion

Among HFrEF patients aged ≥80 years included in SwedeHF, 86% were treated with a beta-blocker as compared to 93% of those aged <80 years. Beta-blocker use was associated with reduced risk of all-cause mortality and CV death regardless of age, suggesting that the survival benefit from this treatment is not impaired by older age. In patients aged ≥80 years, use of beta-blockers was not significantly associated with the composite outcome of CV mortality and HF hospitalization. This was mainly due to the lack of a significant association with HF hospitalization in the elderly population. Conversely, in patients aged <80 years, beta-blocker use was significantly associated with reduced risk of CV death or HF hospitalization. PS-matching limited the sample size and thus the statistical power of our analysis. When we adjusted rather than matched for PS in the overall cohort, beta-blocker use was also associated with a statistically significant reduction in risk of the composite outcome and of HF hospitalization alone. In both PS-matched and adjusted analyses, beta-blocker use was not associated with an increased risk of hospitalization for syncope and the negative control outcome (i.e. hospitalization for cancer), regardless of age.

Beta-blocker use in HFrEF patients aged ≥80 years

In our real-world population, 86% of patients ≥80 years of age received beta-blockers as compared to 93% in the younger subgroup, confirming the feasibility of beta-blocker treatment in older age. Previous studies have reported more underuse,[15-17] but their inpatient setting may explain the lower use of beta-blockers as compared with our cohort.

According to the current HF guidelines, beta-blockers are recommended in HFrEF regardless of age.[18] However, beta-blocker use has been reported to be less and discontinuation rates higher in older patients due to concerns regarding tolerance and efficacy,[2, 19-23] although dedicated studies showed good tolerability supporting their use in the elderly.[24, 25] In a meta-analysis of 11 RCTs, older age has

not been shown to be associated with higher likelihood of beta-blocker therapy discontinuation, but the lower median age (64 years) compared to real-world populations may contribute to explain this finding.[11] Indeed, in the CHAMP-HF registry, beta-blockers were less likely uptitrated in older patients.[26]. Consistently with previous studies showing underdosing of beta-blockers in the overall HF population,[22, 27, 28] we observed that only 19% of patients ≥80 years received target doses and 47.6% received <50% of the target dose. Potential reasons for beta-blocker underuse in the older population may be related to safety concerns and in particular potential hypotensive or bradyarrhythmic events.[29] However, in our study the risk of hospitalization for syncope, which may be a consequence of hypotension or bradiarrhythmia, was similar regardless of the use of beta-blockers. Further potential reasons for underuse in older patients may be related to misconceptions regarding risk in patients with respiratory disorders, as well as comorbidities, frailty, polypharmacy, less specialist care, and social circumstances.[2] Finally, age per se may explain the observed underuse of beta-blockers and other HF drugs in elderly. Indeed, RCTs lacked representative samples of older patients which may have lead clinicians to limit the use of beta-blockers in octogenerians.[9]

Association between beta-blocker use and outcomes in HFrEF patients aged ≥80 years

The advances in medical management of HF and the aging of the general population has drastically modified the shape of the HF population worldwide. Currently, most patients with HF in developed countries are ≥70 years of age, which underlines the significance of our analysis given the uncertainty of beta-blocker safety and efficacy in the elderly.[1, 2, 15]. Patients aged ≥80 years have been excluded or largely underrepresented in RCTs due to several reasons, such as less use of specialist care or comorbidities more likely affecting older patients which represent exclusion criteria in RCTs. Potential efficacy/tolerability of beta-blockers in the elderly can only be extrapolated from the results of RCTs enrolling younger populations with a mean age ranged 58-64 years.[5-8] The only study

designed to assess the efficacy of beta-blockers in older HF patients was the SENIORS trial (inclusion criteria≥70 years, mean age=76 years), which showed a significant reduction in the risk of death or CV rehospitalization, but non-significant effect on survival, in patients receiving beta-blockers vs. not.[10] Notably, most of the patients enrolled were <80 years old and 36% had EF >35%.[10] It is unclear whether the older age of patients enrolled in the SENIORS vs. other RCTs may explain the lower impact of nebivolol on mortality compared to other beta-blockers. A recent meta-analysis of RCTs testing beta-blockers in patients with HFrEF and sinus rhythm showed a significant benefit in terms of all-cause mortality that was consistent across age groups.[11] Similar results were observed for HF hospitalization, albeit with a minor attenuation of beta-blocker effect in older patients.[11]

The present analysis of SwedeHF, which includes one of the largest octogenarian cohorts worldwide, showed that beta-blocker use was significantly associated with improved survival in both patients aged ≥80 years and in those aged <80 years, but with slightly less favorable HR in older vs. younger patients. We observed that the HR reported in our elderly cohort was the same as in the SENIORS trial, although in our analysis the association between beta-blocker use and mortality was statistically significant.[10] This may be explained by the two-fold higher mortality rates in our real-world cohort as compared with the SENIORS trial and thus higher statistical power. The less favorable HR for mortality in older vs. younger patients observed in our study may also be explained by death from a natural or a non-CV cause competing with the benefits of the treatment. The HR for mortality in our positive control was higher than in RCTs, which may be due to the enrollment of a contemporary cohort of HFrEF patients, more likely to receive other guideline recommended HFrEF treatments as compared to more than 10 years ago when RCTs were run. Moreover, although including patients aged <80 years, our positive-control cohort was older and with more comorbidities as compared with RCTs. Finally, in our matched cohort aged ≥80 years we could not observe a significant reduction in risk of the composite of CV death and HF hospitalization associated with beta-blockers. Indeed, although the

risk of CV death was significantly reduced in treated vs. untreated patients, the risk of HF hospitalization was not. In the matched positive control cohort of patients aged <80 years, beta-blocker use was associated with reduced risk of the composite of CV death and HF hospitalization, of CV death alone but again not of HF hospitalization. This lacking association in the matched cohort might be explained by PS-matching reducing the sample size and the power of our analysis, and thus masking any significant association between beta-blocker use and risk of HF hospitalization. Indeed in the analyses fitted in the overall cohort where we adjusted, rather than matched, for PS, we observed a significant reduction in risk of the composite outcome and of HF hospitalization alone in treated vs. untreated patients.

Limitations

Although SwedeHF collects many variables allowing for an extensive adjustment using PS-matching, that was further strengthened by a negative control outcome analysis, we cannot rule out potential unmeasured confounders. SwedeHF includes patients from different Swedish hospitals and primary care clinics, and thus we cannot exclude a confounding role linked with potential regional differences in care. For PS calculation, we did not consider NT-proBNP levels and BMI due to the high proportion of missing data, but several patient characteristics which are proxies of NT-proBNP and BMI (e.g. diuretic use, NYHA class, comorbidity burden) were included. Additionally, in SwedeHF, most of the patients received beta-blockers, which led to a great reduction of sample size and statistical power after matching. Beta-blocker use was defined at baseline and potential cross-over throughout the follow-up may have diluted the association with outcomes. Additionally, whether patients received beta-blockers before the enrolment in SwedeHF but then interrupted because of tolerance/adherence issues or worsening health/harms related to comorbid conditions was unknown. In our cohort comorbidity and frailty burden was lower compared to other real-world studies,[3, 30] which may limit

generalizability of our findings. Finally, due to the high proportion of patients not receiving target dose of beta-blockers, we might have underestimated the magnitude of the association between beta-blocker and outcomes.

Conclusions

In HFrEF patients aged ≥80 years, the use of beta-blockers was high, although lower than in those aged <80 years, and was associated with reduced risk of all-cause and CV mortality but not with increased risk of hospitalization for syncope. Our analysis supports current guidelines recommendation on beta-blocker therapy in HFrEF patients regardless of age.

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Conflict of interest

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Figure legends

Figure 1. Kernel density plot reporting the propensity score distribution in the overall (n = 6,562) and matched (n = 1,720) cohort of patients ≥80 years of age by treatment arm.

Figure 2. Kaplan-Meier curves of association between beta-blocker use and all-cause mortality and the composite outcome (cardiovascular mortality or heart failure hospitalization). (A) and (B) patients aged ≥80 years. (C) and (D) patients aged <80 years (positive control analysis).

Figure 3. The association between beta-blocker use, all-cause mortality and the composite of CV mortality and HF hospitalization in prespecified subgroups in the matched cohort ≥80 years of age. Legend: NYHA, New York Heart Association; eGFR, estimated glomerular filtration rate (calculated by MDRD formula); COPD: Chronic obstructive pulmonary disease; HR, hazard ratio; CI, confidence interval.

Table 1. Baseline characteristics of patients ≥80 years old in the overall and matched cohort

	Overall cohort			Matched cohort		
	Beta-blocker non-users	**Beta-blocker users**	**p-value**	**Beta-blocker non-users**	**Beta-blocker users**	**Absolute standardized difference***
n	922 (14%)	5640 (86%)		866 (50%)	866 (50%)	
Age (years, mean (SD))[a, b]	85.4 (4.2)	84.6 (3.6)	<0.001	85.2 (4.0)	85.3 (3.8)	1.1%
Sex = Female (%)[a, b]	30.5	35.4	0.004	30.9	31.5	1.2%
Location = Out-patient (%)[a, b]	36.7	40.2	0.052	37.5	34.9	5.5%
Follow-up location = Specialty (%)[a, b]	36.6	47.0	<0.001	38.5	39.2	1.5%
NYHA class (%)[a, b]			<0.001			3.8%
NYHA-I	5.7	3.5		4.8	4.0	
NYHA-II	31.9	37.6		33.3	33.4	
NYHA-III	51.7	51.8		52.0	52.6	
NYHA-IV	10.7	7.1		9.9	10.0	
EF = 30 - 39% (%)[a, b]	55.3	53.8	0.385	55.5	54.0	3.8%
Clinical measures						
BMI (kg/m^2, mean (SD))	24.3 (4.2)	25.1 (4.3)	0.001	24.4 (4.2)	24.5 (4.0)	2.9%
SBP (mmHg, mean (SD))	124.8 (19.8)	124.7 (20.1)	0.862	124.9 (19.7)	123.9 (20.5)	4.9%
DBP (mmHg, mean (SD))	69.3 (11.5)	70.4 (11.3)	0.008	69.3 (11.6)	70.0 (11.3)	6.0%
MAP (mmHg, mean (SD))[a, b]	87.8 (12.5)	88.5 (12.5)	0.122	87.8 (12.6)	87.9 (12.6)	1.0%
Heart Rate (bpm, median [IQR])[a, b]	72.0 [63.0, 82.0]	72.0 [64.0, 82.0]	0.611	72.0 [63.0, 82.0]	71.0 [63.0, 82.0]	4.7%
<60 bmp	14.4%	12.2%		14.6%	11.6%	
eGFR (mL/min/1.73m^2, median [IQR])[b]	45.3 [34.2, 59.6]	44.5 [33.5, 58.0]	0.222	44.9 [34.1, 59.4]	45.1 [33.6, 59.0]	1.4%
>60	24.9%	22.3%		24.4	23.4	
30-60	57.3%	59.2%		57.8	57.8	
<30	17.9%	18.5%		17.9	18.8	
NT-proBNP (pg/L, median [IQR])	4773.5 [2106.3, 10454.8]	5228.5 [2410.0, 11805.3]	0.195	4761.0 [2143.5, 9926.0]	5711.0 [2456.5, 13234.5]	14.6%
Smoking (%)[a, b]			0.966			7.6%
never	51.6	52.0%		50.6	52.5	
former	44.2	43.7%		45.0	44.5	
current	4.2	4.3%		4.4	3.0	
Medical history (%)						

Atrial fibrillation [a, b]	65.5	68.4	0.088	65.9	67.1	2.4%
Anemia [a, b]	50.0	44.7	0.003	48.7	49.8	2.1%
COPD [a, b]	15.2	15.9	0.641	15.7	13.3	6.9%
Dilated Cardiomyopathy [a, b]	10.1	9.8	0.797	9.6	11.3	5.7%
Diabetes [a, b]	21.9	28.9	<0.001	22.6	22.5	0.3%
Hypertension [a, b]	58.8	69.2	<0.001	60.9	62.1	2.6%
Ischemic heart disease [a, b]	66.8	74.4	<0.001	68.4	70.2	4.0%
Peripheral artery disease [a, b]	16.3	13.3	0.016	16.3	16.2	0.3%
Stroke and/or TIA [a, b]	19.3	20.1	0.604	19.7	19.4	0.9%
Valvular disease [a, b]	40.9	38.5	0.178	41.2	40.9	0.7%
Cancer in the previous 3 years [a, b]	14.1	12.9	0.346	14.0	14.8	2.3%
Dementia	2.4	2.6	0.828	2.4	2.4	0.1%
Procedures (%)						
Coronary revascularization [a, b]	32.8	37.1	0.012	33.6	34.2	1.2%
Devices (CRT or ICD) [a, b]	3.3	5.5	0.008	3.5	2.5	5.4%
Pacemaker (CRT-D, CRT-P or pacemaker)	19.2	19.5	0.137	19.2	20.6	3.7%
Medication use (%)						
RAS-inhibitors [a, b]	72.4	81.7	<0.001	75.5	73.7	4.1%
MRA [a, b]	32.3	32.5	0.958	32.8	34.9	4.4%
Digoxin [a, b]	15.6	17.1	0.281	15.8	17.6	2.1%
Diuretics [a, b]	89.9	91.0	0.321	90.6	90.0	2.1%
Statins [a, b]	31.4	44.4	<0.001	33.4	35.0	3.4%
Anticoagulants [a, b]	34.5	42.3	<0.001	36.0	36.6	1.3%
Anti-platelets [a, b]	50.9	53.0	0.256	52.4	50.6	3.6%
Nitrates [a, b]	24.2	28.0	0.018	24.9	26.5	3.5%
Social economic characteristics (%)						
Marital status [a, b]			0.723			2.3%
Married	45.7	47.0		46.9	45.7	
Single	15.8	15.2		15.1	15.5	
Widowed	38.5	37.8		38.0	38.8	
Education level [a, b]			0.867			3.3%
Compulsory school	57.9	57.4		57.3	58.9	
Secondary school	30.5	31.3		31.2	30.0	

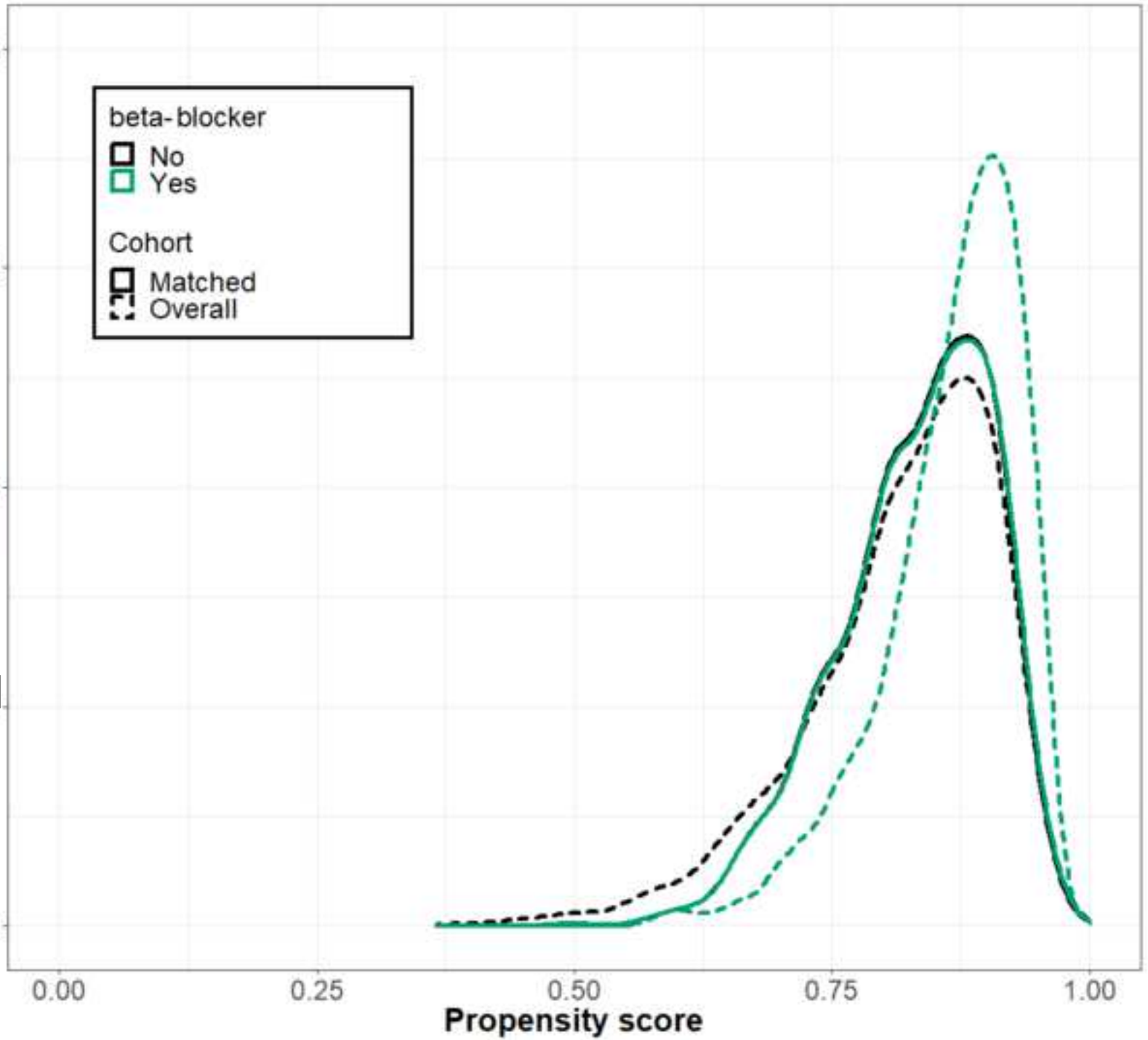
University	11.6	11.3		11.5	11.1	
Income > median [a, b]	42.2	42.8	0.763	42.7	41.6	2.3%

NYHA: New York heart association; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MAP: Mean arterial pressure; eGFR: Estimated glomerular filtration rate (calculated by CKD-epi formula); COPD: Chronic obstructive pulmonary disease; TIA: Transient ischemic attack; CRT: Cardiac resynchronization therapy; ICD: Implantable cardioverter defibrillator; RAS-inhibitor: Renin-angiotensin-system inhibitor; MRA: Mineralocorticoid receptor antagonist; SD: Standard deviation; IQR: Interquartile range.

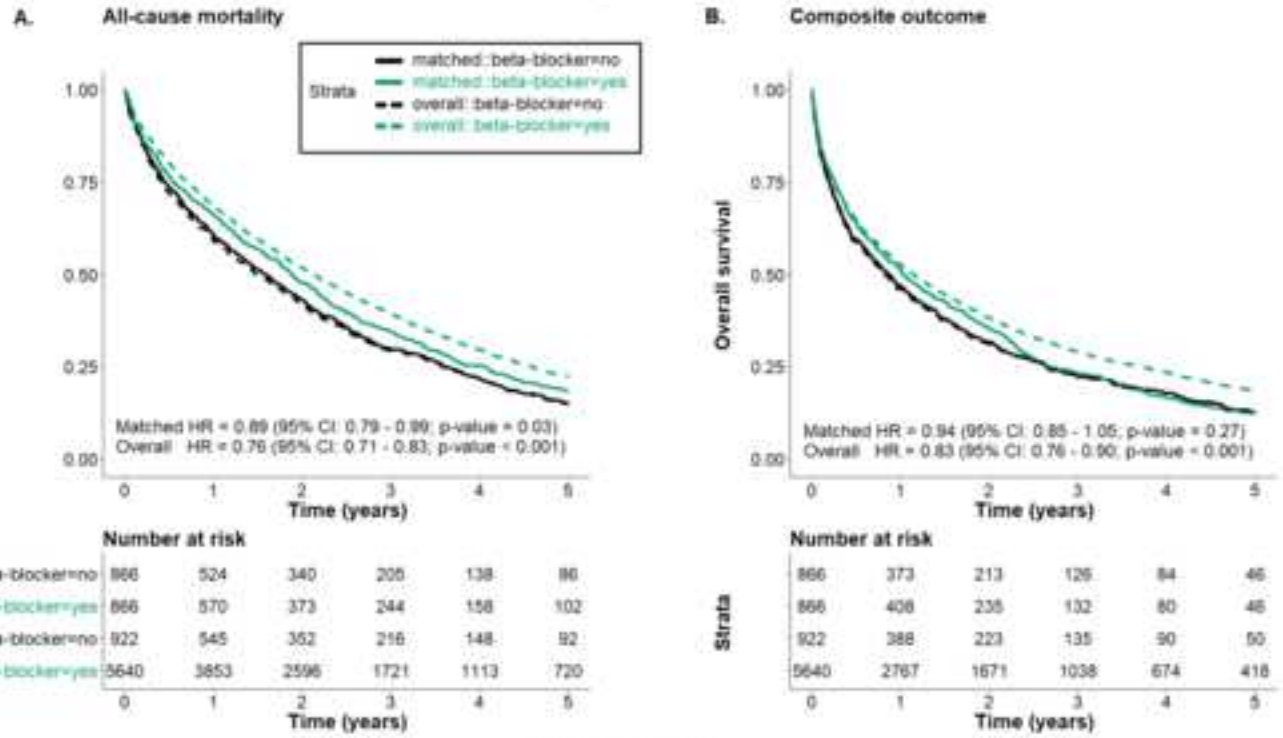
[a] = variables included in multiple imputation together with index year, duration of HF, the composite outcome, and beta-blocker use (yes/no);

[b] = variables included to estimate the propensity score together with index year and duration of HF.

* = Absolute standardized differences are defined as the difference in means, proportions or ranks divided by the mutual standard deviation



≥ 80 years



< 80 years