

## Supplementary files

**Figure legends**

## Supplementary figure 1

Sex-specific relationship between percentage of target dose and all cause mortality risk in the subset of patients with heart failure with preserved ejection fraction for ACE inhibitors / ARBs (A) and beta-blockers (B)

## Supplementary figure 2

Sex-specific relationship between percentage of target dose and all cause mortality risk in the subset of patients with specific mention of heart failure in their diagnosis text for ACE inhibitors / ARBs (A) and beta-blockers (B), and using last recorded dosage for ACE inhibitors / ARBs (C) and beta blockers (D)

**Tables**

	Angiotensin-converting enzyme inhibitors / Angiotensin II receptor blockers		Beta-blockers	
	Women	Men	Women	Men
<b>Heart failure subtype</b>				
Reduced ejection fraction	128	250	126	219
Midrange ejection fraction	60	93	63	87
Preserved ejection fraction	210	126	162	70
Unrecorded ejection fraction	30	37	30	38

Supplementary Table 1 Overview of number of women and men included in each analysis based on heart failure subtype and medication group

	Heart failure specifically mentioned in the diagnosis text	Last observation carried forward	Heart failure with preserved ejection fraction (EF ≥ 40%)
	Adjusted HR (95%CI)	Adjusted HR (95%CI)	Adjusted HR (95%CI)
<b>Whole cohort</b>			
<b>Angiotensin-converting enzyme inhibitors/Angiotensin II receptors</b>			
< 50% of target dose	0.82 (0.60-1.12)	1.03 (0.78-1.37)	0.72 (0.47-1.10)
≥ 50% of target dose (ref)	1	1	1
<b>Beta-blockers</b>			
< 50% of target dose	1.21 (0.88-1.67)	1.08 (0.80-1.44)	0.91 (0.59-1.42)
≥ 50% of target dose (ref)	1	1	1
<b>Women</b>			
<b>Angiotensin-converting enzyme inhibitors/Angiotensin II receptors</b>			
< 50% of target dose	0.85 (0.53-1.35)	1.05 (0.69-1.61)	0.61 (0.33-1.12)
≥ 50% of target dose (ref)	1	1	1
<b>Beta-blockers</b>			
< 50% of target dose	1.31 (0.83-2.07)	0.87 (0.57-1.33)	0.83 (0.46-1.49)
≥ 50% of target dose (ref)	1	1	1
<b>Men</b>			
<b>Angiotensin-converting enzyme inhibitors/Angiotensin II receptors</b>			
< 50% of target dose	0.82 (0.54-1.24)	1.03 (0.71-1.50)	0.84 (0.45-1.57)
≥ 50% of target dose (ref)	1	1	1
<b>Beta-blockers</b>			

< 50% of target dose	1.11 (0.71-1.75)	1.31 (0.88-1.99)	1.04 (0.53-2.06)
≥ 50% of target dose (ref)	1	1	1

Supplementary Table 2      General and sex-specific hazard ratios for the relationship between percentage of target dose and all-cause mortality for sensitivity analyses in the subgroup of patients with heart failure specifically mentioned in their diagnosis text, using the last observed medication dosage instead of baseline, and using a different definition of HF<sub>r</sub>EF

CI = confidence interval, HR=hazard ratio

	Literature-based categories Adjusted HR (95% CI)	Cohort-based tertiles Adjusted HR (95% CI)	Quartiles Adjusted HR (95% CI)
<b>Whole cohort</b>			
<i>Angiotensin-converting enzyme inhibitors/Angiotensin II receptors</i>			
First category (ref)	1	1	1
Second category	0.98 (0.72-1.34)	0.86 (0.61-1.21)	1.04 (0.63-1.71)
Third category	1.01 (0.70-1.48)	0.90 (0.64-1.26)	1.01 (0.61-1.68)
Fourth category	na	na	1.04 (0.60-1.79)
<i>Beta-blockers</i>			
First category (ref)	1	1	1
Second category	0.92 (0.67-1.26)	1.70 (1.18-2.44)	1.29 (0.76-2.19)
Third category	1.11 (0.67-1.84)	0.97 (0.65-1.44)	1.10 (0.64-1.90)
Fourth category	na	na	1.43 (0.75-2.74)
<b>Women</b>			
<i>Angiotensin-converting enzyme inhibitors/Angiotensin II receptors</i>			
First category (ref)	1	1	1
Second category	0.83 (0.50-1.40)	0.95 (0.56-1.62)	1.10 (0.51-2.36)
Third category	1.12 (0.66-1.89)	1.05 (0.63-1.74)	0.92 (0.41-2.06)
Fourth category	na	na	1.16 (0.52-2.62)
<i>Beta-blockers</i>			
First category (ref)	1	1	1
Second category	0.97 (0.63-1.51)	2.25 (1.31-3.88)	2.13 (0.91-5.01)
Third category	0.62 (0.25-1.56)	1.06 (0.58-1.96)	1.72 (0.72-4.11)
Fourth category	na	na	1.58 (0.54-4.60)

<b>Men</b>			
<b><i>Angiotensin-converting enzyme inhibitors/Angiotensin II receptors</i></b>			
First category (ref)	1	1	1
Second category	1.05 (0.70-1.57)	0.79 (0.51-1.22)	1.00 (0.52-1.93)
Third category	0.90 (0.52-1.56)	0.79 (0.50-1.24)	1.04 (0.54-2.00)
Fourth category	na	na	0.92 (0.44-1.94)
<b><i>Beta-blockers</i></b>			
First category (ref)	1	1	1
Second category	0.86 (0.55-1.35)	1.29 (0.78-2.12)	0.82 (0.41-1.62)
Third category	1.61 (0.87-2.98)	0.91 (0.54-1.52)	0.74 (0.37-1.50)
Fourth category	na	na	1.27 (0.56-2.89)

Supplementary Table 3      General and sex-specific hazard ratios for the relationship between percentage of target dose and all-cause mortality using three different medication dosage categories

CI = confidence interval, HR=hazard ratio