Title: Evidence based therapy and its association with workforce detachment following first hospitalization for heart failure

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ABSTRACT

Background: The ability to work can be a marker of functional capacity and quality of life. We investigated the association between the use of evidence-based medicine (EBM) for heart failure (HF) and risk of workforce detachment.

Methods: We examined a nationwide cohort of patients in the workforce one year after first hospitalization for HF. EBM was defined as treatment with β-blockers and renin angiotensin system inhibitors. The fraction of target dose (0-1) for each drug was calculated. The sum of the fractions gave each patient a score between 0-2. Patients were stratified into 4 groups according to this score: Group 4: Score =2 (target dose of both drugs); Group 3: 1<score<2; Group 2: 0.5< score ≤1; Group 1: 0< score ≤ 0.5. The risk of subsequent workforce detachment was estimated in cause specific Cox-regression models.

Results: One year after first HF hospitalization 10185 patients were part of the workforce, 7561 (74%) were in treatment with at least one of the components of EBM. During a median follow-up of 727 days, 2698 individuals (36%) became detached from the workforce. Patients receiving more EBM had a significantly lower risk of workforce detachment compared with those receiving less EBM: Group 4 HR 0.87 [0.77-0.98], Group 3 HR 0.85 [0.77-0.94], and Group 2 HR 0.92 [0.83-1.02]), all compared to Group 1.

Conclusion: Patients in the workforce one year after first HF hospitalization and treated with target or near target doses of EBM was associated with a significantly lower risk of subsequent workforce detachment.

INTRODUCTION

Heart failure (HF) is a condition associated with considerable mortality and morbidity as well as reduced quality of life.[1-3] The advances in HF-specific device and pharmacological therapy has significantly improved life-expectancy in patients with HF[4, 5], which has led to an increased focus on factors in the everyday life of patients including the ability to work. Renin angiotensin system inhibitors (RASi) and β-blockers, in this study referred to as evidence-based medicine (EBM), are cornerstones in treatment of HF. HF guidelines includes specific recommendations on up-titration to 'target doses' which are considered as 'optimal medical therapy'.[6, 7] Information about the effectiveness of other doses, lower or higher is scarce. It is well established that a significant proportion of people with HF do not receive EBM and even if they do, many do not receive guideline-recommended 'target' doses.[8-10] The benefits of drugs and devices are usually evaluated on the basis of clinical outcomes such as mortality and hospitalization. Although these are undoubtedly important, they do not reflect the whole burden of heart failure on the individual and his or her family and care-givers or on society. A patients' ability to work reflects both the direct and indirect consequences and costs of HF. Beyond having a financial impact, employment status affects a patient's self-esteem, quality of life and can affect an individual's mental and physical well-being and potentially that of a spouse and other family members.[11, 12] Thus, use of EBM and its relation to employment status in patients with HF may provide additional information on the broader benefits of these drugs in younger patients living with HF.

In this nationwide study, we set out to assess the relationship between use of EBM and workforce detachment i.e. sickness leave, early retirement or any other economic support from the state due to reduced working capability. We hypothesized that lower use of EBM would be associated with a higher risk of workforce detachment in HF patients.

Methods

Data sources

All residents in Denmark have a unique personal identification number. By use of this number, Danish administrative and health registries can be linked at an individual level.[13] For the present study, we linked Danish registries which include information on hospitalizations, out-patient visits, all prescribed medications, education level and death with information on whether the patients received any kind of public welfare payments.[14, 15]

Study population and baseline variables

We studied patients with a first hospitalization for HF in the period of 1997-2014. Patients were included if they were between 18 and 60 years at time of first hospitalization and part of the workforce, i.e. employed or available for work one year after first HF hospitalization. Thus, baseline was set to one year after first HF hospitalization. Workforce status was determined by evaluation of a five-week period one year after discharge from first HF hospitalization. This evaluation method of work status has previously been described in detail.[16] . All residents in Denmark can receive state funded support. We classified patients who were not on paid sickness leave, had not taken early retirement or were receiving any support due to reduced working capability as able to work. Patients in the workforce one year after first HF hospitalization were grouped according to level of treatment with β-blockers and RASi at baseline by use of the following scheme: For each patient and each drug the fraction of the target dose (0-1) was calculated (Appendix 1). Subsequently the sum of the fractions was calculated for each patient. This gave each patient a score between 0-2. According to this number patients were stratified into 4 groups. group 4: Score = 2; group 3: 1< score <2; group 2: 0.5< score ≤ 1; group 1: 0< score ≤ 0.5; Supplementary Figure 1. The following sensitivity analyses were carried out: 1) An underlying assumption of our calculations is that β-blockers and RASi carry the same weight. To assess this, we compared patients in target dose of RASi and reduced dose of β-blockers with patients in target dose of β-blockers and reduced dose of RASi; and 2) Patients might have been down-titrated from target dose already during the first year or have had fluctuations in drug treatment. To assess the latter, we did an analysis where patients were grouped according to highest achieved dose of EBM within the first year rather than dose achieved at one year follow-up. 3) In addition to the main analysis we created a propensity score-matched population. The propensity score was estimated as each patient's probability of receiving low doses of EBM (group 1 and 2) or high doses (group 3 and 4) by multivariable logistic regression analysis conditional on the following baseline covariates: age, sex, educational level, calendar time, use of diuretics and MRA and comorbidities i.e. ischemic heart disease, atrial fibrillation, chronic kidney disease, COPD, diabetes, hypertension, stroke and cancer.

Patients were followed for up to 4 years after first HF hospitalization. Thus during the study period no patients were old enough to receive ordinary retirement pension, which individuals in Denmark are eligible to from 65 years of age. History of comorbidities in the form of cancer, chronic kidney disease, chronic obstructive pulmonary disease (COPD), diabetes, stroke, ischemic heart disease, atrial fibrillation and hypertension was identified by a primary or secondary discharge diagnosis in relation to any hospitalization in the previous 10 years. Patients with diabetes mellitus were additionally identified by at least one filled prescription for glucose lowering drugs up to 180 days prior to 1 year after first HF hospitalization. Besides RASi and β-blockers we also assessed the use of mineralocorticoid receptor antagonists (MRA) and loop-diuretics, but the doses of these drugs were not included in the EBM score.

Outcome Measures

Patients alive and in the workforce one year after first hospitalization for HF were followed for an additional three years. The primary outcome was defined as three consecutive weeks of workforce detachment, i.e. paid sickness leave, early retirement or any other economic support from the state due to reduced working capability. Unemployed patients and patients receiving state educational grants, paid maternity leave, on vacation, on family medical leave or on some other leave of absence were classified as being part of the workforce as these social benefits are for persons who are capable of working. Furthermore we also assessed follow-up in outpatient clinics and re-hospitalization for HF.

Statistics

We used Kruskal-Wallis test for continuous variables and χ^2-test for categorical variables to test for differences between groups. We estimated cumulative incidence curves of workforce detachment with death as a competing risk by use of the Aalen-Johansen method.[17] Gray's test were used to test for unadjusted differences. Hazard ratios (HRs) for each treatment group were assessed for workforce detachment by use of cause specific Cox regression models. All analyses were adjusted for age, sex, educational level, calendar time, use of diuretics and MRA and comorbidities i.e. ischemic heart disease, atrial fibrillation, chronic kidney disease, COPD, diabetes, hypertension, stroke and cancer. Adjusted variables were chosen before any analyses was done and were based on clinical relevance and known prognostic importance in HF. For the propensity matched analysis a univariate hazard ratio was calculated as the other covariates were used to generate the propensity score. The proportional hazard assumption was tested by analyses of log (-log(survival)) curves. Age, sex, comorbidity and calendar time effects were tested for interactions with score groups on the outcome of workforce detachment. For all analyses, a two-sided p-value < 0.05 was considered statistically significant. All analyses were performed using SAS statistical software package, version 9.4 (SAS Institute, Cary, NC, USA) and R, version 3.2.2 (R development Core Team).

RESULTS

Baseline characteristics of the study population

A total of 24239 patients aged 18-60 with a first-time HF hospitalization between 1997 and 2014 were identified. Of these patients 10185 (42%) were in the workforce 1-year after first HF hospitalization. Among these, 7561 (74%) were treated with at least one of the components of EBM and these individuals formed the study population. Baseline characteristics according to EBM-score group are shown in Table 1. The proportion of men was higher among those receiving most EBM (84% men in group 4 and 77% men in group 1, $p<0.0001$) as were the use of diuretics (43% in group 4 and 34% in group 1, $p<0.0001$) and an MRA (40% in group 4 and 17% in group 1, $p<0.0001$). Hypertension was more frequent among patients in group 2 (group 2: 20% vs group 1: 17%, p=0.03). Comorbidities were otherwise evenly distributed between groups. There was no difference in age between the EBM- groups.

Workforce detachment

Patients were followed for up to 3 years with a median follow-up of 727 days (Q1-Q3 313-1095 days). During this period 2698 (36%) became detached from the workforce i.e. 1653 (61%) went on paid sick leave, 114 (4%) received support due to reduced working capabilities, 337 (12%) received disability pension and 594 (22%) had taken early retirement. Taking differences in follow-up time into account we found that the risk of workforce detachment was 41% [38-44%] in EBM group 4 (target dose therapy), 40% [38-42%] in group 3, 42% [40-45%] in group 2 and 43% [41-46%] in group 1; (Figure 1). The differences between groups were significant (Gray's test: P=0.02). The competing risk of death was low but was correlated to the level of treatment (group 4: 3% [2%-4%], group 3: 3% [2%-3%], group 2: 5% [4%-6%], group 1 6% [5%-7%]. In fully-adjusted cause specific Cox regression analyses, patients in groups 4 and 3 had significantly lower risks of workforce detachment compared with those in group 1: group 4 HR 0.87 [0.77-0.98] and group 3 HR 0.85 [0.77-0.94]. Patients in group 2 did not have a significantly different risk than those in group 1: HR 0.92 [0.83-1.02] (Figure 2). Other factors associated with a lower risk of workforce detachment included younger age, male gender and higher level of education. Use of diuretics and an MRA, as well as a history of COPD and cancer, was associated with higher likelihood of workforce detachment (Figure 2).

Follow-up in outpatient clinics and re-hospitalization for HF

The proportion of patients followed up in an outpatient clinic within 3 years was 67% in group 4 (target dose therapy), 59% in group 3, 50% in group 2 and 46% in group 1; ($P<0.0001$). During 3 years of follow-up the risk of rehospitalization for HF was 50% [47%-53%] in group 4, 48% [46%-50%] in group 3, 44% [41%-46%] in group 2, 40% [37%-42%] in group 1; $P<0.0001$.

Sensitivity analyses

1) In analyses comparing patients in target dose of RASi and reduced dose of β-blockers with patients in target dose of β-blockers and reduced dose of RASi we found no differences in workforce detachment (39% [37%-42%] vs 41% [36%-46%]; Gray's test: P=0.64; Supplementary Figure 2). 2) Patients were stratified according to highest achieved doses of EBM during 1 year after first HF hospitalization which led to 363 (5% of the total study population) extra patients in the target dose group (group 4). This resulted in a risk of workforce detachment of 40% [38%-43%] in group 4, 41% [39%-44%] in group 3, 42% [40%-44%] in group 2 and 43% [40%-46%] in group 1 (Gray's test: P=0.03; Supplementary Figure 3). 3) A propensity score-matched population of 3114 matched pairs of patients in low dose of EBM (Group 1 and 2) and patients in high dose of EBM (Group 3 and 4) was identified. In cause-specific Cox regression analysis of the propensity score-matched population we found that patients in the high dose of EBM group had a significantly lower risk of workforce detachment compared with those in the low dose group (HR 0.86 [0.79-0.93]; P=0.0003).

Discussion

In this nationwide study, we examined the association between use of EBM and workforce detachment. Among 7561 patients in the workforce one year after first HF hospitalization and treated with EBM, up-titration to target or near target doses of EBM was achieved in 3538 (47%) patients and was associated with a lower likelihood of workforce detachment during long-term follow-up. Younger age, male sex and a higher level of education were also associated with a lower risk of workforce detachment. Conversely, use of diuretics and an MRA, as well as history of COPD and cancer, were associated with higher likelihood of workforce detachment.

Beta-blockade and inhibition of the renin-angiotensin system have been shown to reduce all-cause mortality and hospitalizations in pivotal landmark trials and are thus the fundamental building blocks of HF treatment.[18, 19] In addition to these well-documented benefits, intensity of treatment may have other consequences for a patient's well-being and life-style. In the current study, we demonstrated that up-titration to target or near target doses of EBM was associated with a lower risk of long-term workforce detachment following a first hospitalization for HF. So far there has been conflicting results regarding the benefit of full up-titration of EBM.[20-22] Our results should be interpreted with some caution, as the inability to up-titrate EBM could be due to intolerance of larger doses because of more severe cardiac as well as non-cardiac underlying disease. This is, however, not a likely explanation in our study as comorbidities were evenly distributed across score groups and use of diuretics and MRAs were more common among patients in the groups with a higher treatment score. In our analyses, we found that the use of diuretics was associated with higher risk of workforce detachment, which is in accordance with the fact that diuretic dose is a marker of severity of HF.[23, 24] We also found that use of MRA was associated with higher risk of workforce detachment but again this may be because MRA use is a marker of greater severity, especially as during most of the period of this study MRAs were only indicated for patients in New York Heart Association (NYHA) functional classes III and IV.

The majority of patients in our study were not treated with target doses of EBM, which is in line with other real-world cohorts.[25-27] Adverse effects such as hypotension and renal insufficiency which often are dose-dependent can explain why some patients do not tolerate up-titration to target doses of EBM. Still, if the vast majority, as in our study, does not receive EBM in target doses this cannot, in our view, be fully explained by adverse effects, particularly not in a population of younger patients with HF. Other reasons for suboptimal treatment could be the individual patient´s lack of adherence to treatment arising from insufficient understanding of the pathophysiology and seriousness of the disease as well as, or in conjunction with, the stresses of everyday life amplified by the knowledge of having to accept and live with this condition. Therefore, efforts to improve patients' understanding of heart failure as well as helping them develop strategies to incorporate taking their medication reliably during their daily routine may be valuable. However a Danish population study of adherence among patients in the primary care setting has shown a high compliance to cardiovascular drugs.[28] Thus other explanations for suboptimal treatment such as underuse and the inability to complete up-titration among physicians prescribing EBM might be in play, as has been previously described. [29, 30] The reasons for this underperformance are most likely complex but exaggerated concerns for side-effect and failure to recognize the serious prognosis associated with HF, particularly if untreated, could be part of the explanation.

In our study, men were more likely to receive target or near target doses of EBM than women. Similar findings have been reported in other studies.[31, 32] Although the majority of patients in clinical trials are men there is no evidence suggesting that women should have less effect of β-blockers and RASi. Thus it is important to implement EBM in all patients irrespective of gender. We also found that women were more likely to become detached from the workforce than men. Although our data do not enable us to examine exact reasons for this difference, one could speculate that men may be under greater pressure than women to keep their job for economic reasons, and working status may be more important to the male than female identity. The motivation to keep working might also change with age. Older patients closer to retirement age might be more willing to leave the workforce due to lack of necessity and not because of poor performance status.

A sensitivity analysis comparing patients in target dose RASi and suboptimal β-blocker dose compared with patients in target dose β-blockers and suboptimal RASi dose showed no significant differences in subsequent workforce detachment. This suggests that it is acceptable for RASi and β-blockers to carry the same weight in our score system and hence grouping of patients. Patients grouped according to highest achieved dose of EBM within the first year rather than dose achieved at one year follow-up showed very minor differences from the main analyses. Thus down-titration or fluctuation in EBM doses did not seem to confound our findings. However patients down-titrated from target dose seemed to do at least as good, if not better, than patients in target dose at one year follow-up.
We found that a higher proportion of patients in group 3 and 4 were followed in an outpatient clinic but they also had the highest risk of rehospitalization. This might be due to some selection in outpatient clinics of patients most affected by their HF.

Strengths and limitations

This study covers all patients admitted to a hospital with HF in Denmark independent of race, socioeconomic status and private healthcare insurance. We were able to combine weekly updated information of patients' occupational status and data on vital status and hospitalizations. Thus, we had an unselected cohort with detailed information on work status with almost no persons lost to follow-up. The main limitation of our study is the lack of clinical important information such as NYHA functional class and left ventricular ejection fraction. Thus, we were not able in our analyses to stratify our patients by severity of HF or by left ventricular ejection fraction. We tried to exclude patients with preserved ejection fraction by only including patients who received at least some dose of EBM. However, some patients may have had a normal left ventricular ejection fraction, a group in which there is no evidence for the benefit of ACEI/ARBs and betablockers and comparatively weak evidence for the use of MRAs. Our estimates of medical doses are based on strength and frequency of redeemed prescriptions, and may allow some margin of error, particularly immediately after initiation of treatment. Finally, our study is observational. This means that the effect of unmeasured clinical variables and unidentified confounders cannot be excluded and that our findings represent associations and not necessarily causal connections.

Conclusion

Up-titration of EBM defined as β-blockers and RASi to target or near-target doses within one year of first HF hospitalization was associated with a lower likelihood of subsequent workforce detachment. Less than half of patients treated with EBM and in the workforce 1 year after first HF hospitalization were taking target or near target doses of EBM. Further studies are warranted to examine whether initiatives to improve up-titration of EBM in patients with HF to the highest tolerated doses of medication might improve quality of life and decrease workforce detachment.

Clinical perspectives

In our opinion, using workforce detachment as an outcome adds important information on the consequences of living with HF. As such, it can be relevant to have workforce detachment as an additional quality of life metric in HF studies.

Translational outlook

Workforce detachment as an additional quality metric could generate new and useful knowledge of the socioeconomic impact of HF and be of potential benefit for the individual patient.

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Table Novelty of this study

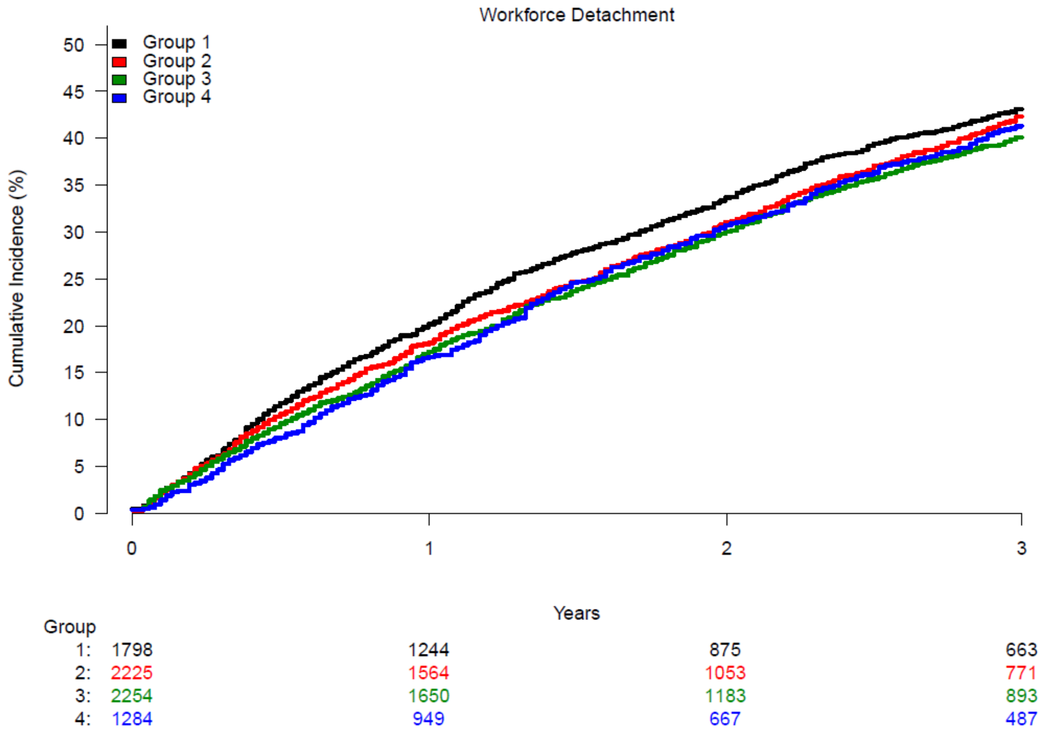
What is known
• Among patients of working age with a first hospitalization for HF, two thirds have returned to the workforce within one year. • Younger age, male sex, higher income, and higher level of education are associated with an increased likelihood of return to work after HF hospitalization. • Comorbidities such as stroke, diabetes, cancer, chronic obstructive pulmonary disease, and chronic kidney disease are associated with higher risk of detachment from the workforce 1 year after heart failure hospitalization.
What this study adds
• The current study examined the relationship between use of guideline-recommended medical treatment following first HF hospitalization and long-term risk of workforce detachment. • Even among patients alive and in the workforce 1 year after HF hospitalization only half received target or near target doses of evidence based medicine • Up-titration to target or near target doses of evidence-based medicine following HF hospitalization was associated with a lower likelihood of workforce detachment.

Table 1 Baseline characteristics of patients in the workforce one year after first HF hospitalization according to groups: group 4: Score = 2; group 3: 1< score <2; group 2: 0.5< score ≤ 1; group 1: 0< score ≤ 0.5 (n=7561).

	Group 1	Group 2	Group 3	Group 4
No. Patients	1798	2225	2254	1284
Age, median (IQR)	53 (47-57)	53 (48-57)	53 (47-57)	52 (46-57)
Male	1380 (77%)	1778 (80%)	1819 (81%)	1074 (84%)
Additional HF therapy				
Diuretics	613 (34%)	809 (36%)	885 (39%)	555 (43%)
MRA	301 (17%)	549 (25%)	737 (33%)	519 (40%)
Highest education Level				
Basic school <10 yrs	546 (30%)	668 (30%)	613 (27%)	384 (30%)
High school, +3yrs	79 (4%)	105 (5%)	118 (5%)	61 (5%)
Vocational Education	727 (40%)	929 (42%)	980 (43%)	551 (43%)
Short/medium higher, +2-4 yrs	269 (15%)	311 (14%)	360 (16%)	191 (15%)
Long higher, +≥5 yrs	92 (5%)	119 (5%)	120 (5%)	68 (5%)
Unknown	85 (5%)	93 (4%)	63 (3%)	29 (2%)
Comorbidity (%)				
Ischemic heart disease	399 (22%)	460 (21%)	439 (19%)	237 (18%)
Atrial fibrillation	173 (10%)	251 (11%)	221 (10%)	123 (10%)
Cancer	45 (3%)	48 (2%)	58 (3%)	32 (2%)
COPD	75 (4%)	79 (4%)	52 (2%)	30 (2%)
Diabetes	100 (6%)	149 (7%)	127 (6%)	58 (5%)
Hypertension	300 (17%)	435 (20%)	376 (17%)	215 (17%)
Chronic kidney disease	33 (2%)	42 (2%)	37 (2%)	11 (1%)
Stroke	37 (2%)	63 (3%)	45 (2%)	25 (2%)

IQR – Interquartile range;
MRA - mineralocorticoid receptor antagonists;
COPD - chronic obstructive pulmonary disease;

Figure 1 Risk of workforce detachment with death as competing risk among patients in treatment with EBM and in the workforce one year after first HF hospitalization (n=7561). Time zero is 365 days after discharge from first HF hospitalization.



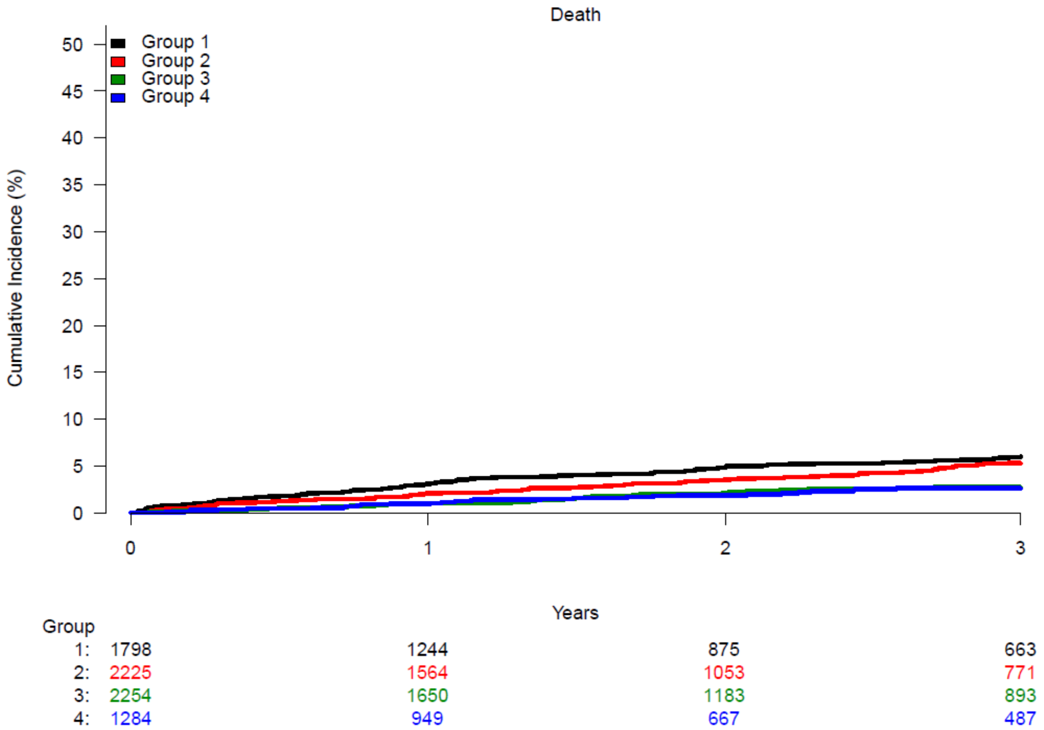
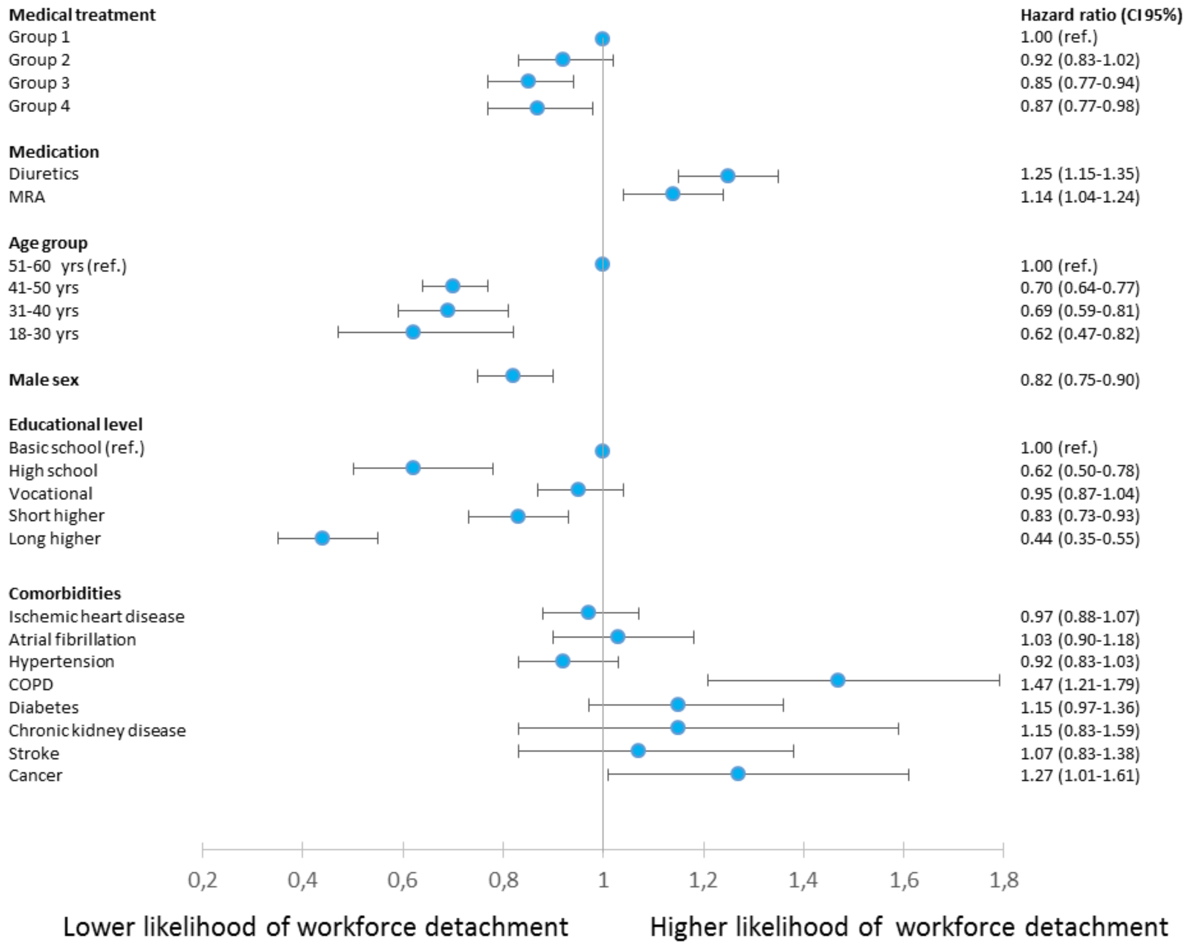


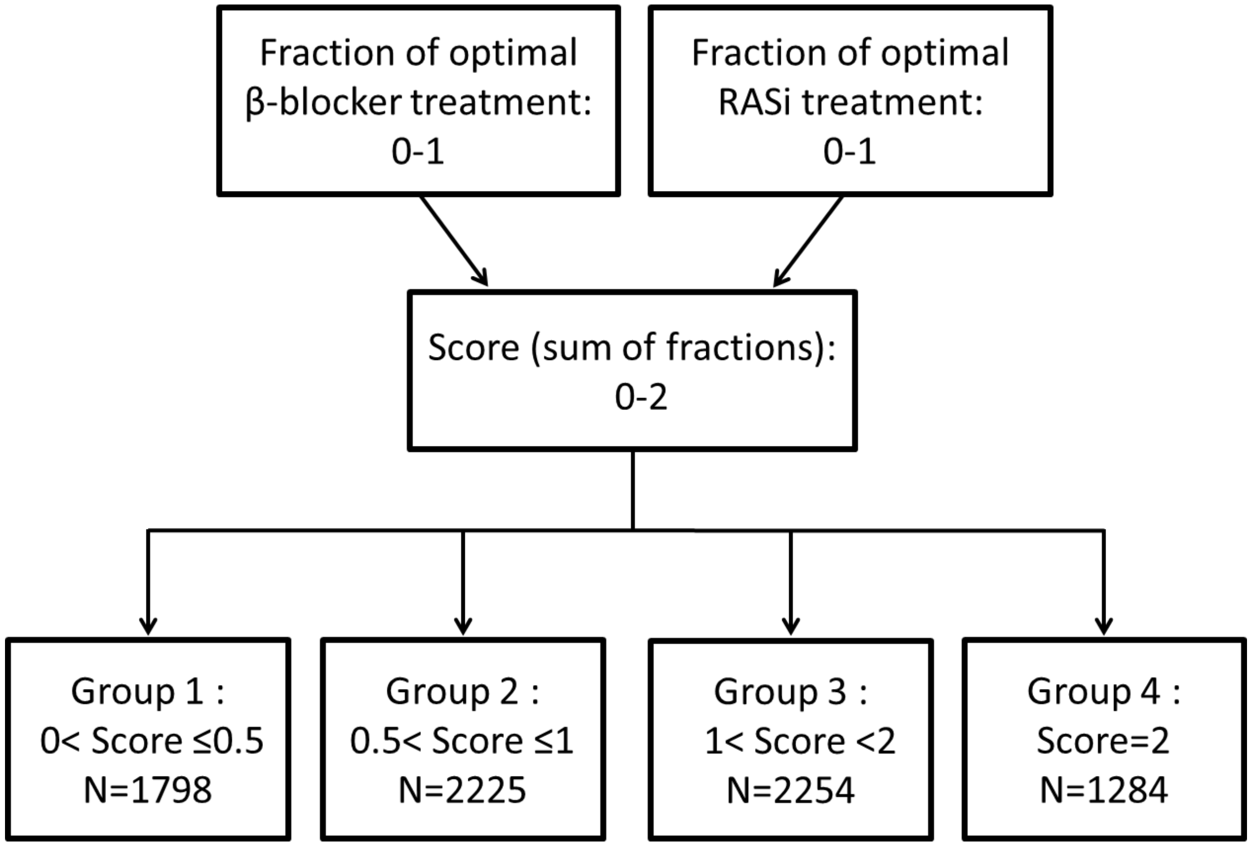
Figure 2 Multiple cause specific Cox regression model of factors associated with workforce detachment among patients in treatment with EBM and in the workforce one year after first HF hospitalization (n=7561).



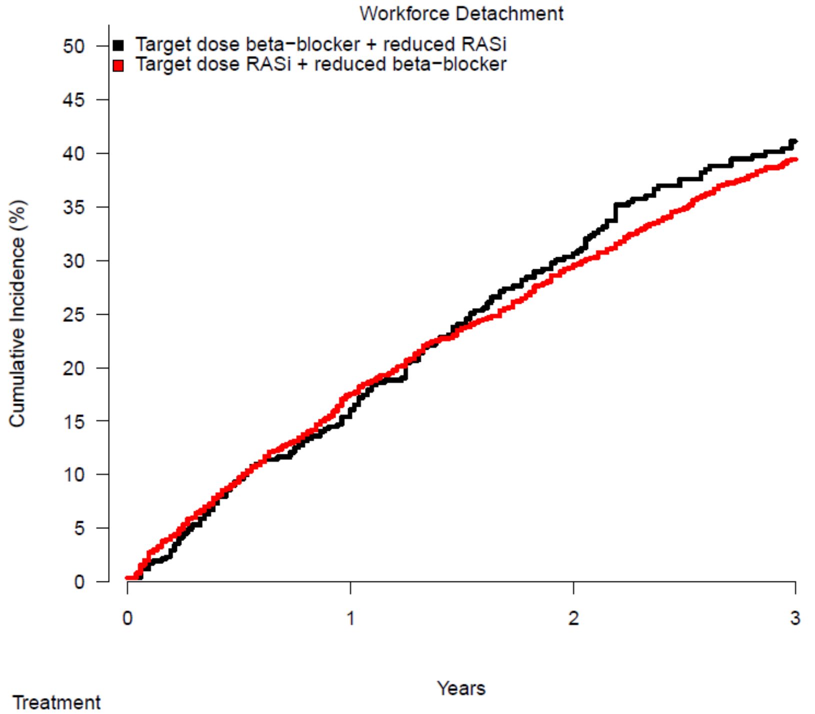
MRA - mineralocorticoid receptor antagonists;

COPD - chronic obstructive pulmonary disease;

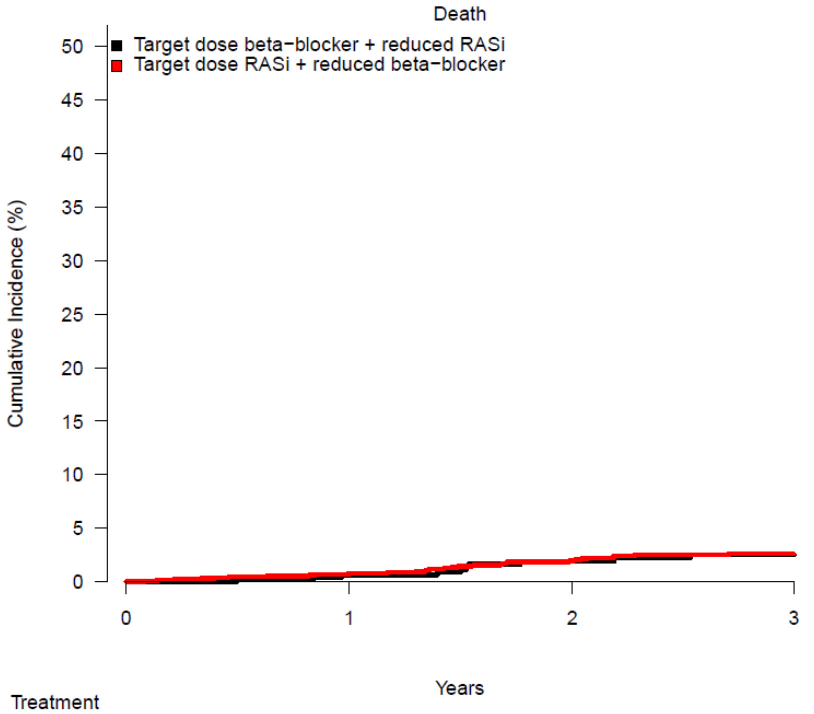
Supplementary figure 1 Illustration on how patients were grouped according to level of treatment with β-blockers and RASi



Supplementary Figure 2 Risk of workforce detachment with death as competing risk among patients in target dose of RASi and reduced of β-blockers compared with patients in target dose of β-blockers and reduced dose of RASi (n=1860). Time zero is 365 days after discharge from first HF hospitalization.



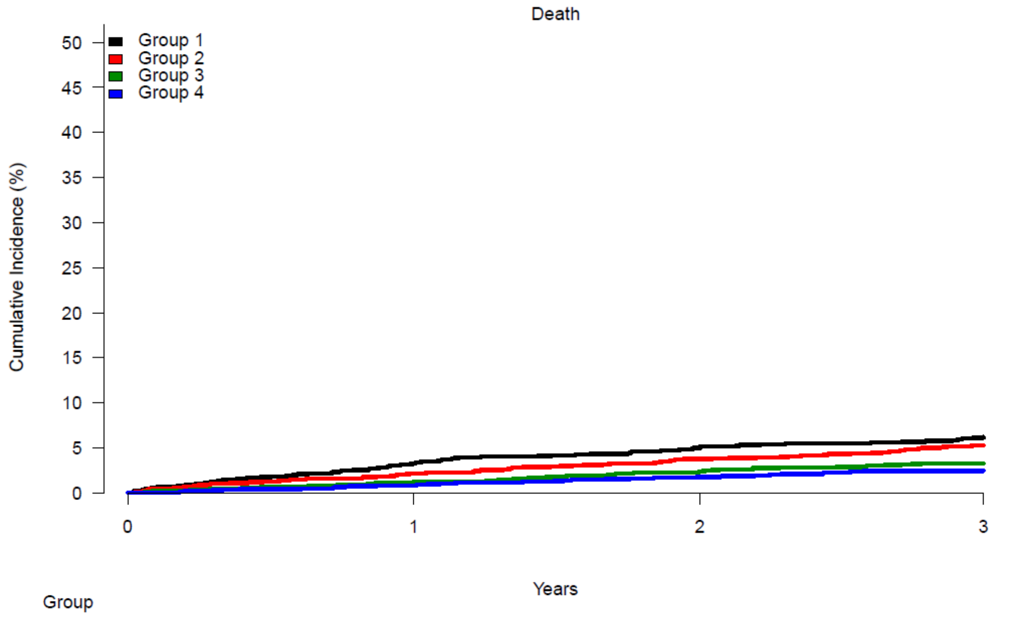
Treatment				
Target dose beta−blocker + reduced RASi:	514	370	241	168
Target dose RASi + reduced beta−blocker:	1346	1015	763	599



Treatment				
Target dose beta−blocker + reduced RASi:	514	370	241	168
Target dose RASi + reduced beta−blocker:	1346	1015	763	599

Supplementary Figure 3 Risk of workforce detachment with death as competing risk among patients in treatment with EBM and in the workforce one year after first HF hospitalization (n=7561). Patients are stratified by highest achieved doses during one year after first HF hospitalization. Time zero is 365 days after discharge from first HF hospitalization.

Group				
1:	1513	1042	738	557
2:	2220	1555	1047	780
3:	2181	1597	1146	860
4:	1647	1213	847	617



Group				
1:	1513	1042	738	557
2:	2220	1555	1047	780
3:	2181	1597	1146	860
4:	1647	1213	847	617

Appendix 1 Target doses of β-blockers and RASi.

	Target dose (mg)
β-blockers	
Metoprolol	200
Carvedilol	50
Bisoprolol	10
RASi	
Ramipril	10
Enalapril	20
Trandolapril	4
Perindopril	4/5
Losartan	150
Candesartan	32
Valsartan	320