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Heart failure treatment up-titration and outcome and age: an analysis of BIOSTAT-CHF

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Aims

Several studies have shown that older patients with heart failure with reduced ejection fraction (HFrEF) are undertreated. The aim of this study was to evaluate the association of up-titration of angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB) and beta-blockers on outcome across the age spectrum in HFrEF patients.

Methods and results

We analysed HFrEF patients on sub-optimal doses of ACEI/ARB and/or beta-blockers from the BIOSTAT-CHF study stratified by age. Patients underwent a 3-month up-titration period. We used inverse probability weighting to adjust for the likelihood of successful up-titration to determine the association of achieved dose with mortality and/or heart failure hospitalisation, testing for an interaction with age. Over a median follow-up of 21 months in 1720 HFrEF patients (76.5% male, mean age 67 years), the primary outcome occurred in 558 patients. Increased percentage of target dose of ACEI/ARB and beta-blocker achieved at 3 months were both significantly associated with reduced incidence of the primary outcome, [ACEI-ARB: hazard ratio (HR) per 12.5% increase in dose: 0.92, 95% confidence interval (CI) 0.91–0.94, $P < 0.001$; beta-blocker: HR 0.98, 95% CI 0.95–1.00, $P = 0.046$], with a significant interaction with age seen for beta-blockers but not ACEI/ARB ($P = 0.034$ and $P = 0.22$, respectively).

Conclusions

Achieving higher doses of ACEI/ARB was associated with improved outcome regardless of age. However, achieving higher doses of beta-blockers was only associated with improved outcome in younger, but not in older patients.

Keywords

ACE inhibitor • Angiotensin receptor blocker • Beta-blocker • Up-titration • Elderly

Introduction

Increased life expectancy and improved management of acute cardiology conditions and comorbidities mean that the age of patients with heart failure with reduced ejection fraction (HFrEF) is steadily increasing.¹ With this has come a rise in the complexity

of HFrEF patients. Particularly in more developed countries, HFrEF is becoming a disease of the older, frailer patient, and these factors combine to increase mortality risk.^{2–4}

As well as having worse outcomes, older HFrEF patients are frequently undertreated compared to younger patients, often being on none or sub-optimal doses of angiotensin-converting

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enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB) and beta-blockers.^{5–9} Major HFrEF clinical trials from which guidelines are derived have often included few elderly patients, with the mean age in almost all landmark studies being <70 years, with some trials excluding older patients altogether.² Although post-hoc analyses of these trials have not reported significant treatment interactions with age for ACEI,¹⁰ ARB^{11,12} or beta-blockers,^{13–15} there have been very few trials specifically including older populations with HFrEF.¹⁶ In particular, there is very little information on the relationship between achieving target doses of heart failure (HF) medications and clinical outcomes. Clinicians may be particularly reluctant to up-titrate HF therapies to the maximally tolerated dose in older patients due to concerns varying from side-effects and polypharmacy to patient preference, cost and even 'therapeutic inertia'.

The aim of this study was to evaluate whether achieving target doses of ACEI/ARB and beta-blockers after a period of up-titration was associated with similar outcome in HFrEF patients who were undertreated at baseline regardless of age.

Methods

Study design

The cohort and study design of the BIOSTAT-CHF study have been described in detail previously.¹⁷ Briefly, an index cohort of 2516 patients with new-onset or worsening HF (left ventricular ejection fraction $\leq 40\%$ or elevated natriuretic peptides) on loop diuretics and on $\leq 50\%$ of target dose of ACEI/ARB and/or beta-blocker were recruited from 11 European countries between December 2010 and December 2012. Median follow-up was 21 months. Patients underwent a 3-month up-titration period where the treating clinicians were encouraged to up-titrate ACEI/ARB and beta-blockers to guideline-recommended target doses (online supplementary Table S1).¹⁸ Following this period, no further medication changes were mandated unless clinically indicated. Information on ACEI/ARB and beta-blocker doses were collected at 3 months. Patients attended for a visit at 9 months where clinical examination and electrocardiogram (ECG) was performed.

For this analysis, we only included patients meeting the current definition of HFrEF (left ventricular ejection fraction $< 40\%$) and surviving the initial 3-month up-titration period. Patients were stratified into older (≥ 70 years) and younger (< 70 years) age groups. Target doses of ACEI/ARB and beta-blocker were taken from the European Society of Cardiology guidelines at the time the study was designed.¹⁹ Outcomes assessed were all-cause mortality and/or HF hospitalisation combined and mortality alone.

Statistical analysis

Normally distributed continuous data are reported as mean $\pm$ standard deviation, while non-parametric data are reported as median with interquartile range in brackets. Categorical data are reported as number with percentage in brackets. Comparisons between continuous variables were made using independent *t*-tests, while chi-square tests were made for comparisons between categorical variables, with post-hoc correction for tests including more than two groups.

Multivariable linear regression was used to determine associations between baseline variables including age and percentage of target dose

achieved at the end of the up-titration period. All variables significantly associated ($P < 0.05$) with successful up-titration in univariable analysis were included in a multivariable model. Pearson correlation and linear regression were used to evaluate the association between heart rate at 9 months with dose of beta-blocker achieved adjusted for baseline heart rate. The primary analysis was the association between the percentage of target dose achieved (per 12.5% dose increase) and the primary outcome of mortality and/or HF hospitalisation and its interaction with age as a continuous variable in a model adjusted for the likelihood of up-titration using inverse probability weighting as described previously.²⁰ Multivariable analyses were also performed using age as a categorical variable with cut-offs of above and below 70. Finally, patients were stratified into four groups according to percentage of target dose achieved (0%, 1–49%, 50–99% and $\geq 100\%$) and associations with the primary outcome assessed in patients above and below 70 years old assessed using Kaplan–Meier models. Sensitivity analyses were performed adjusting for the BIOSTAT-CHF risk prediction model, a validated model developed within this cohort which includes variables most strongly associated with outcome including age.²¹ All tests were two-sided and a *P* value < 0.05 was considered significant throughout. All tests were performed using R version 3.5.1.

Results

Baseline characteristics

In total 1720 patients with HFrEF surviving to the end of the 3-month up-titration period were included (76.5% male, mean age 67.2 ± 11.9 years). A total of 765 patients (44.5%) were aged ≥ 70 years. Baseline characteristics are summarised in Table 1. Older patients were more likely to be female and had a higher prevalence of comorbidities such as myocardial infarction, atrial fibrillation and hypertension. Older patients were less likely to have had HF device therapy. Older patients had higher systolic blood pressure but lower diastolic blood pressure, heart rate and body mass index, worse renal function and higher N-terminal pro-B-type natriuretic peptide.

Heart failure treatment at baseline

Dosages of ACEI/ARB and beta-blockers at baseline are summarised in Figure 1. As per design of the BIOSTAT-CHF study, the majority of patients were receiving less than 50% of target dose of ACEI/ARB and beta-blocker at baseline. Older patients were significantly more likely than younger patients to not be prescribed any dose of ACEI/ARB (28.9% vs. 23.3%, $P = 0.007$) or beta-blocker (17.8% vs. 13.5%, $P = 0.021$) at baseline.

Up-titration of heart failure therapies at follow-up

ACEI/ARB and beta-blocker dosage data were obtained at 3 months. For both groups of medications there were significant differences in dosages attained at follow-up (Figure 1). Older patients were significantly less likely to achieve $\geq 50\%$ of target dose of ACEI/ARB than younger patients (51.6% vs. 57.6%, $P = 0.016$). There was no significant difference in the likelihood of

Table 1 Baseline data

	<70 years (n = 955)	≥70 years (n = 765)	P-value
Age (years)	58.7 ± 8.5	77.8 ± 5.2	<0.001
Male sex	789 (82.6)	527 (68.9)	<0.001
Ischaemic cardiomyopathy	404 (42.3)	385 (50.3)	<0.001
HF hospitalisation within last 12 months	309 (32.4)	263 (34.4)	0.40
Previous MI	340 (35.6)	328 (42.9)	0.002
Previous CABG	127 (13.3)	151 (19.7)	<0.001
History of atrial fibrillation	339 (35.5)	377 (49.3)	<0.001
Diabetes	286 (29.9)	258 (33.7)	0.10
Previous stroke	67 (7.0)	73 (9.5)	0.07
History of hypertension	525 (55.0)	493 (64.4)	0.001
Device therapy			<0.001
Pacemaker	19 (2.0)	80 (10.5)	
ICD	115 (12.0)	46 (6.0)	
CRT	91 (9.5)	76 (9.9)	
BMI (kg/m ²)	28.6 ± 5.7	26.7 ± 4.7	<0.001
Heart rate (bpm)	81 ± 20	78 ± 17	<0.001
Systolic blood pressure (mmHg)	122 ± 21	126 ± 21	0.001
Diastolic blood pressure (mmHg)	81 ± 13	78 ± 12	<0.001
Dyspnoea VAS score	50.8 ± 22.7	46.1 ± 23.3	0.026
NYHA class III–IV	288 (30.1)	268 (35.0)	0.52
QRS duration (ms)	112 ± 30	125 ± 35	<0.001
LVEF (%)	26.4 ± 6.9	28.6 ± 6.5	<0.001
Urea (mmol/L)	14.6 ± 12.3	16.3 ± 11.2	0.006
Creatinine (μmol/L)	105 ± 52	120 ± 48	<0.001
NT-proBNP (ng/L)	3772 [938–6606]	4805 [1354–8256]	<0.001
ACEI/ARB (any dose)	733 (76.8)	544 (71.1)	0.007
Beta-blocker (any dose)	826 (86.5)	629 (82.2)	0.021
MRA	608 (63.7)	364 (47.6)	<0.001
Loop diuretic	955 (100)	764 (99.9)	0.91

Values are given as mean ± standard deviation, n (%), or median [interquartile range].

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; CRT, cardiac resynchronisation therapy; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; VAS, visual analogue scale.

Bold indicates $P < 0.05$.

achieving ≥50% of target dose of beta-blocker between older and younger patients (37.0% vs. 35.4%). Reasons for failure to reach target dose were broadly similar between the two age groups and are reported in online supplementary Table S2.

Baseline variables associated with achieved dose are reported in online supplementary Table S3. Increased age was significantly associated with lower achieved dose of beta-blocker [odds ratio (OR) per 10-year increase in age 0.98, 95% confidence interval (CI) 0.97–0.99, $P < 0.001$] but not ACEI/ARB (OR 0.98, 95% CI 0.97–1.00, $P = 0.07$). Other baseline variables significantly associated with treatment up-titration were body mass index, systolic blood pressure and serum creatinine (ACEI/ARB), country of recruitment and baseline heart rate (beta-blocker). Estimated glomerular filtration rate was more strongly associated with achieved dose in older patients, though the association remained significant in younger patients also (≥70 years: OR 1.03, 95% CI 1.02–1.04, $P < 0.001$; <70 years: OR 1.01 per 10 mL/min/1.73 m² increase, 95% CI 1.00–1.02, $P = 0.042$). All other variables showed no interaction with age.

ECG heart rate data were available at 9 months in 1345 individuals (769 <70 years, 576 ≥70 years). There was no significant

difference in achieved heart rate between older and younger patients (<70 years: 72.5 ± 14.6 bpm, ≥70 72.0 ± 14.6 bpm, $P = 0.51$). There was however a significant difference in the relationship between achieved dose of beta-blocker and achieved heart rate at 9 months between older and younger patients. As a continuous variable, in younger patients, each 12.5% of target dose of beta-blocker achieved was associated with a 0.7 bpm decrease in ECG heart rate ($P < 0.001$), whereas in older patients there was no significant association between achieved dose and achieved ECG heart rate (0.004 bpm decrease per 12.5% of target dose of beta-blocker, $P = 0.99$; interaction P -value between older and younger patients 0.018) (online supplementary Figure S1).

Association between achieved dose and outcome and interaction with age

Over the median follow-up period of 21 months, the primary outcome occurred in 558 patients [273 patients <70 years old (28.6%) and in 285 patients ≥70 years old (37.3%)].

Increased percentage of target dose of ACEI/ARB achieved at 3 months was significantly associated with reduced incidence of

the primary outcome [hazard ratio (HR) per 12.5% increase in dose 0.92, 95% CI 0.91–0.94, $P < 0.001$] and mortality alone (ACEI/ARB HR per 12.5% increase in dose 0.89, 95% CI 0.86–0.92, $P < 0.001$). There was no significant interaction with age (primary endpoint interaction P -value 0.22, mortality $P = 0.054$) (Figure 2; online supplementary Figure S2).

Increased percentage of target dose of beta-blocker achieved at 3 months was also associated with reduced incidence of both the primary outcome (HR per 12.5% increase in dose 0.98, 95% CI 0.95–1.00, $P = 0.046$) and mortality alone (HR per 12.5% increase in dose 0.92, 95% CI 0.89–0.96, $P < 0.001$); however, in contrast to ACEI/ARB, there was a significant interaction between age and the percentage of target dose of beta-blocker achieved for both the primary outcome ($P = 0.034$) and mortality ($P < 0.001$) (Figure 2; online supplementary Figure S2).

A similar pattern was also seen when the cohort was dichotomised according to age. Each 12.5% increase in ACEI/ARB dose achieved at 3 months was associated with a reduced incidence of the primary outcome in patients <70 (HR 0.91, 95% CI 0.88–0.94, $P < 0.001$) and ≥ 70 (HR 0.94, 95% CI 0.92–0.97, $P < 0.001$, interaction P -value 0.07). In contrast, increased achieved

dose of beta-blocker was only associated with reduced incidence of the primary outcome in younger patients (<70 : HR 0.95, 95% CI 0.92–0.98, $P = 0.003$; ≥ 70 : HR 1.01, 95% CI 0.98–1.04, $P = 0.65$, interaction P -value 0.014). Similar results were found when mortality was analysed alone (Figure 3).

The association between target dose achieved after the up-titration period and outcomes are summarised in Table 2 and Figure 4. After adjustment for likelihood of up-titration using inverse probability weighting, there was a similar relationship between dose of ACEI/ARB achieved and outcomes across age groups, higher achieved dose being associated with reduced incidence of the primary outcome (interaction P -value 0.20). While an association between higher achieved beta-blocker dose and lower risk of the primary outcome was also seen in younger patients, with achieving target dose not being associated with improved outcome compared to lower doses (interaction P -value 0.009). Similar patterns were seen for mortality alone (online supplementary Table S4).

These patterns also remained when adjusted for the BIOSTAT-CHF risk prediction model (online supplementary Tables S5 and S6).

Figure 2 Association between achieved angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB) and beta-blocker dose and the primary outcome across the age spectrum. The adjusted hazard ratio (red line) and 95% confidence interval (shaded area) for incidence of the primary outcome per 12.5% increase in ACEI/ARB and beta-blocker dose and the interaction with age as a continuous variable.

Figure 3 Association between achieved angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB) and beta-blocker dose and the primary outcome stratified by age. The adjusted hazard ratio and 95% confidence interval for outcomes per 12.5% increase in ACEI/ARB and beta-blocker dose in patients <70 and ≥70 years old. HF, heart failure.

Discussion

The most important finding of this study is that while higher achieved doses of ACEI/ARB were associated with similarly improved outcome in HFrEF patients regardless of age, there appeared to be an interaction with age in the relationship between achieved beta-blocker dose and outcome. While there was a clear

association between achieving target dose of beta-blocker and improved outcome in younger patients, there did not appear to be any incremental benefit in attaining target dose of beta-blockers in older patients compared to intermediate doses. We also showed, as has been previously reported, that older patients had a higher prevalence of comorbidities and were less likely to be established on guideline-recommended HF treatment. Additionally, despite

Table 2 Association between achieved dose following up-titration and mortality and/or heart failure hospitalisation (adjusted for likelihood of up-titration using inverse probability treatment weighting)

	<70 years			≥70 years			Interaction P-value
	No. patients	HR (95% CI)	P-value	No. patients	HR (95% CI)	P-value	
ACEI/ARB							
>100%	239	ref.		166	ref.		0.20
50–99%	311	1.23 (0.97–1.56)	0.09	229	0.99 (0.78–1.26)	0.96	
1–49%	338	1.61 (1.29–2.01)	<0.001	279	1.44 (1.16–1.78)	<0.001	
0	67	2.62 (1.94–3.55)	<0.001	91	1.78 (1.35–2.34)	<0.001	
Beta-blocker							
>100%	106	ref.		86	ref.		0.009
50–99%	247	0.98 (0.72–1.32)	0.89	185	0.81 (0.61–1.06)	0.13	
1–49%	551	1.24 (0.96–1.60)	0.10	437	0.84 (0.67–1.07)	0.16	
0	51	1.68 (1.12–2.52)	0.012	57	0.93 (0.63–1.38)	0.72	

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; HR, hazard ratio.
 Bold indicates $P < 0.05$.

encouragement to up-titrate HF medications in all patients, older patients remained less likely to be prescribed optimal doses of ACEI/ARB.

There have been few randomised trials in HFrEF specifically focusing on the elderly, and there are very few reports of the association between dose achieved and outcomes. There have been no trials using ACEI/ARB specifically in older HFrEF patients, however subgroup analyses of the pivotal randomised trials did not demonstrate any interaction with age. Our finding that ACEI/ARB are associated with improved outcome in older patients is also consistent with other observational studies.^{7,22} In the two largest randomised trials comparing low vs. high-dose of ACEI/ARB, patients assigned to higher doses had significantly improved outcome compared to those with lower dose, and there was no interaction with age, with older patients (>65 years) having similar outcome to younger patients.^{23,24} Our findings are consistent with these results.

Although randomised trials have not clearly shown an interaction between HF treatment and age, most trials have included very few patients over 70, and most subgroup analyses have a younger age stratification (e.g. 65 years). The key point for our study was therefore to examine patients over 70 years old, and also to specifically study up-titration of medications. There have been specific beta-blocker trials in elderly HFrEF patients. In SENIORS, nebivolol caused a significant reduction in the primary outcome in patients ≥70 years old.¹⁶ In clinical trials of older HFrEF patients, however, there has been some evidence to suggest that there may not be incremental benefit from achieving target doses of beta-blocker compared to intermediate doses. In SENIORS, patients reaching 50% of target dose of nebivolol (5 mg) had a similar outcome to those reaching the target dose of 10 mg.²⁵ Other beta-blocker trials in general HFrEF populations have demonstrated a similar lack of dose–response relationship. In MERIT-HF, outcomes were similar between patients reaching low or high-dose beta-blockers compared to placebo,²⁶ while in CIBIS II, the greatest benefit vs. placebo was seen in the mid-dose

bisoprolol group.²⁷ In HF-ACTION, the best outcomes were at intermediate beta-blocker doses, with more events at lower or target doses.²⁸ Although these were post-hoc analyses, they do suggest that attainment of target doses of beta-blocker may not provide incremental benefit over mid-range doses.

Our finding that the association between achieving target dose and outcome was different in older patients compared to younger is intriguing, particularly given the small magnitude of effect that age had on likelihood of achieving target dose. Although trials in HFrEF patients have not clearly demonstrated this, it has been postulated that mid-range beta-blocker doses might be optimal in older patients because they typically have a decrease in cardiovascular responsiveness to beta-adrenergic stimulation, acting as an intrinsic beta-blockade, reflected by lower resting heart rate in older patients.^{29–31} This might explain why we did not find a consistent association in our study between achieved beta-blocker dose and heart rate in older patients, in contrast to younger patients. It has been suggested that heart rate reduction might be more important than achieved beta-blocker dose in HFrEF. In CIBIS-ELD, achieved heart rate rather than beta-blocker dose (carvedilol or bisoprolol) was significantly associated with outcome.³² A separate post-hoc analysis of CIBIS-ELD suggested that reaching target dose may simply be a reflection of patients who have failed to respond to beta-blocker treatment (i.e. no heart rate reduction) and will continue to do so.³³ These findings have been replicated in other HFrEF studies and it is suggested that achieved heart rate has more influence on prognosis than dose.^{34,35} The higher prevalence of atrial fibrillation^{7,36,37} may also diminish any beneficial effects of beta-blockers in older patients – several large studies have established that beta-blockers may not be as effective in patients in atrial fibrillation.³⁸

Despite the increasing age of HF patients, individuals included in the most recent large HFrEF outcome trials are still relatively young, with a mean age <65 years.^{39,40} In practice, ‘real-world’ HF patients often differ from those in trials, being older with more comorbidities,⁴¹ and our study provides important information on

Figure 4 Percentage of target dose achieved and the primary outcome. Kaplan–Meier curves showing the association between achieved dose of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB) and beta-blocker and the primary outcome in patients <70 and ≥70 years old. Curves include the initial 3-month up-titration period.

older patients that may be more reflective of clinical practice. Several studies have previously shown that as one might expect, older HFrEF patients are frailer, sicker and have more comorbidities than younger patients.^{41,42} Our study parallels these results in a multi-national, European setting.

We also found that older patients were less likely to be on guideline-recommended treatments at baseline. This has been reported previously in older studies,^{6,43} and would appear to remain the case despite the increasing management of HF patients by specialists.^{9,44} By design, patients included in BIOSTAT-CHF were undertreated at baseline, and perhaps more interestingly, despite the protocol encouraging treating clinicians to up-titrate ACEI/ARB and beta-blocker therapy, older patients remained less likely to be on ACEI/ARB following the up-titration period. This is similar to the analysis from CHAMP-HF, which reported that older age was significantly associated with reduced likelihood of up-titration of HF therapies.⁴⁵ Given that we found a strong association between achieved dose of ACEI/ARB and improved outcome, clinicians should look to take advantage of opportunities

to up-titrate these therapies wherever possible, even in older individuals.

Limitations

Our study does have some limitations. This is a post-hoc analysis of a non-randomised study. It is important to note that although BIOSTAT-CHF was an observational study, it did include a 3-month up-titration period, which did therefore provide an extra stimulus to up-titrate therapy which may not have been completely reflective of ‘real-world’ practice. Despite our use of inverse probability weighting, the study design does not permit definitive determination of causality. Our use of inverse probability weighting and a sensitivity analysis using the BIOSTAT-CHF risk score does provide some further confidence in the results. We could not completely account for changes in medications between visits, and did not collect data on non-cardiovascular hospitalisations during which medications might have changed. Although we analysed drugs according to their class, each drug has its own specific pharmacokinetic and

pharmacodynamic profile which might provide unique results. At the time the BIOSTAT-CHF study was designed, mineralocorticoid receptor antagonist (MRA) use was only recommended in the guidelines for 'severely symptomatic HF',¹⁹ and so the majority of patients were not on an MRA at baseline and up-titration was not mandated.⁴⁶ Similarly, the study time period pre-dated the introduction of newer therapies such as sacubitril/valsartan and ivabradine into HF treatment guidelines. Finally, we did not collect any more detailed information on reasons for failure to achieve target doses which could provide more granularity on this issue.

Conclusion

In this multi-centre European cohort study, we found that older HFrEF patients were significantly less likely to be prescribed guideline-recommended HF therapies, and despite encouragement to up-titrate treatment, were less likely to attain optimal doses of ACEI/ARB compared to younger patients. There was a similar association with improved outcome with attaining target dose of ACEI/ARB in older and younger patients; however, the association of achieving target dose of beta-blocker and improved outcome appeared to reduce with age. Clinicians should continue to use opportunities to up-titrate HF therapies to their patients' maximally-tolerated doses.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Target doses from European Society of Cardiology heart failure guidelines at time of study design (2008).

Table S2. Reasons for failure to achieve target dose.

Table S3. Variables significantly associated with percentage achieved dose of ACE inhibitor/angiotensin receptor blocker and beta-blocker in multivariable analysis.

Table S4. Association between achieved dose following up-titration and mortality only (adjusted for likelihood of up-titration using inverse probability treatment weighting).

Table S5. Association Between achieved dose following up-titration and mortality/heart failure hospitalisation (adjusted for likelihood of up-titration using inverse probability treatment weighting and BIOSTAT-CHF risk model).

Table S6. Association between achieved dose following up-titration and mortality only (adjusted for likelihood of up-titration using inverse probability treatment weighting and the BIOSTAT-CHF risk score for prediction of mortality).

Figure S1. Association Between achieved beta-blocker dose and achieved heart rate in older vs. younger patients. Mean heart rate (and standard error) at follow-up stratified by percentage of target dose of beta-blocker achieved and age. There was a significant correlation between beta-blocker dose and achieved heart rate in younger but not older patients.

Figure S2. Association between achieved ACE inhibitor/angiotensin receptor blocker and beta-blocker dose and the primary outcome across the age spectrum.

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