ESC guidelines adherence is associated with improved survival in patients from the Norwegian Heart Failure Registry

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Aims
To assess the adherence to heart failure (HF) guidelines for angiotensin-converting enzyme-I (ACE-I), angiotensin II receptor blockers (ARB), and β-blockers and the possible association of ACE-I or ARB, β-blockers, and statins with survival in the large contemporary Norwegian Heart Failure Registry.

Methods and results
The study included 5761 outpatients who were diagnosed with HF of any aetiology (mean left ventricular ejection fraction 32% ± 11%) from January 2000 to January 2010 and followed up until death or February 2010. Adherence to treatment according to the guidelines was high. Cox regression analysis to identify risk factors for all-cause mortality, after adjustment for many factors, showed that ACE-I ≥ 50% of target dose, use of beta-blockers, and statins were significantly related to improved survival (P = 0.003, P < 0.001, and P < 0.001, respectively). Propensity scoring showed the same benefit for these variables.

Conclusions
Both multivariable and propensity scoring analyses showed survival benefits with β-blockers, statins, and adequate doses of ACE-I in this contemporary HF cohort. This study stresses the importance of guidelines adherence, even in the context of high levels of adherence to guidelines. Moreover, respecting the recommended target doses of ACE-I appears to have a crucial role in survival improvement and, in the multivariate Cox regression analysis, ARB treatment was not significantly associated with a lower all-cause mortality.

Keywords
Heart failure • Guidelines • ACE-I • Beta blockers

Introduction
Chronic heart failure (CHF) is a common clinical syndrome with important health and socioeconomic impacts. Although substantial progress has been made in the last decades with pharmacological and non-pharmacological treatments, CHF remains associated with high morbidity and mortality.1

The incidence of CHF increases with age. The population aged 60 or over is expected to rise from 264 million in 2009 to 416 million in 2050 in the developed world.2 Several large randomized controlled trials (RCTs) have shown that angiotensin-converting enzyme-I (ACE-I)3 and β-blockers4 improve survival in patients with HF. Statin treatment has been associated with better survival in observational studies in patients with CHF,5 but no survival benefit in two large RCTs6,7 has been shown. Adherence to pharmacological treatment guidelines in patients with CHF is often less than optimal,8 although it is associated with improved survival.9 This study sought to assess the level of adherence to HF guidelines for ACE-I, angiotensin II receptor blockers (ARB), and β-blockers in the contemporary
Norwegian Heart Failure Registry. We also assessed the possible association between ACE-I or ARB, β-blockers, and statins and overall survival.

Methods

Study sample

Patients from 22 outpatient hospital HF clinics enrolled in The Norwegian Heart Failure Registry that had adequate survival data between January 2000 and January 2010 were assessed. The data were collected at visits to outpatient HF clinics that were run by specially trained nurses in cooperation with cardiologists. At the first visit, all relevant medical history, physical examination data, blood chemistry results, and management regimens were recorded in the web-based database. The patients were followed up until they were considered stable and their treatment was optimized. This last visit was the starting point for collection of mortality which was obtained until March 2010 from the Norwegian Death Register administered by Statistics Norway. All patients gave their written informed consent. The study complies with the Declaration of Helsinki. The study was approved by the Regional Committees for Medical and Health Research Ethics and the Norwegian Data Inspectorate.

Guidelines adherence level

The proportions of patients treated with a renin angiotensin system inhibitor (renin–angiotensin system inhibitor (RASI), ACE-I, and/or ARB) and a β-blocker after treatment optimization were assessed. Angiotensin II receptor blockers treatment is recommended by guidelines to be a possible alternative in patients intolerant to ACE-I treatment; hence we considered the exposition to either one of the RASI as a single binary variable. The definition of the indication for RASI that we used was left ventricular ejection fraction (LVEF) ≤ 40%, serum potassium ≤ 5.0 mmol/L, and creatinine ≤ 220 μmol/L for β-blockers, LVEF ≤ 40% and heart rate ≥ 50, according to the ESC guideline.

Dose equivalents

The doses of the different ACE-I were recorded in the registry, but not the doses of ARB. We calculated dose equivalents for ACE-I and β-blockers. Expressed as a percent, the dose equivalent (DE) was calculated as the dose of the medication divided by its respective maximal recommended target. These target doses were defined as, for ACE-I: 150 mg for captopril, 40 mg for enalapril, 40 mg for lisinopril, and 10 mg for ramipril; for β-blockers: 10 mg for bisoprolol, 50 mg for carvedilol, and 200 mg for metoprolol. For atenolol, the HF guidelines do not specify a target dose and we used 100 mg, the maximal suggested dose for hypertension or angina. For molecules recorded as ‘other’, the information was considered as missing. For sotalol, the information was also considered as missing because it is most often used as an antiarrhythmic, rather than an HF β-blocker medication and may be associated with inherent higher risk. For loop diuretics, we calculated a bumetanide equivalent by dividing the doses of furosemid by 40. Renal function calculated as the eGFR was assessed by the Modification of Diet in Renal Disease (MDRD) formula.

Statistical analysis

Differences in means for continuous variables were calculated with the Student t-test. Differences in proportions between groups were calculated by the χ² test. A P-value of < 0.05 was considered statistically significant. We estimated and compared median survival with the Kaplan–Meier estimator and the log-rank test. The simultaneous associations between patient characteristics and time to death were estimated using Cox regression analysis. Variables with a P-value of < 0.10 in univariable Cox models were included in the final multivariable model with the exception of selected variables of clinical relevance that were forced into the models. Hazard ratios (HRs) are presented with 95% confidence intervals. Propensity score (PS) models were developed for each treatment using logistic regression. The PS represents the probability of assignment to a particular treatment conditional on observed baseline characteristics. All variables with a P-value of ≤ 0.2 in univariable logistic regression models were included in the final PS models. We used the PS as an adjusting covariate in Cox regression analyses to correct for confounding of the treatment-survival association by patients’ baseline characteristics. The statistical analyses were performed using IBM SPSS 21.0.

Results

The study included 5761 patients (1653 women, 29%). Baseline characteristics of the study population are presented in Table 1. Mean age was 70.2 ± 12 years and the mean LVEF at entry was 32 ± 11% (646 missing values, 11.2%). Median duration since first HF diagnosis was 4 months; 72% of patients had their first diagnosis of HF within 12 months before entry. The main cause of HF was coronary heart disease (CHD) for 3187 patients (55.3%). There were 1962 deaths (34.1%) during follow-up. The mean survival for patients who died was 30.5 ± 22.8 months.

Medical treatment

Baseline characteristics of patients according to treatment with RASI, β-blockers, and statins after treatment optimization are shown in Table 1.

Renin angiotensin system inhibitors

After treatment optimization, 89.8% were treated with either an ACE-I (71.8%) or an ARB (19.5%). Among patients with an LVEF of ≤ 40%, 91.1% took either an ACE-I or an ARB. At entry, 67% of the patients fulfilled the HF guidelines indication criteria for RASI and 93% were treated.

β-Blockers

After treatment optimization, 86.0% patients were treated with β-blockers; among patients with an LVEF of ≤ 40%, 88.0% took β-blockers. At entry, 72% patients fulfilled the guidelines adherence indication criteria for β-blockers and 89% were treated.

Renin angiotensin system inhibitor and β-blocker combination therapy

After treatment optimization, 78.5% patients were treated with combination therapy including both a RASI and a β-blocker; 11.3% had a RASI but no β-blocker, 7.6% only a β-blocker, and 3% neither had a RASI nor a β-blocker. Among patients with an LVEF of ≤ 40%, 81% used the combination therapy. Among the patients who met the indication criteria for both RASI and β-blockers (n = 3727), 1.6% received none, 9.5% only a RASI, 5.3% only a β-blocker, and 83.6% received the combination therapy.

Statins

Statins were prescribed to 56.1% of the patients with CAD as the main reason for HF.
Table 1  Baseline characteristics of the outpatients with heart failure according to treatment at the final titration of treatment

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 5761)</th>
<th>Using ACE-I or ARB</th>
<th>Using β-blockers</th>
<th>Using statins</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n = 583)</td>
<td>Yes (n = 5160)</td>
<td>No (n = 798)</td>
<td>Yes (n = 4953)</td>
</tr>
<tr>
<td><strong>P-value</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>70.2 (12.0)</td>
<td>74.7 (10.9)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>1653 (29)</td>
<td>201 (35)</td>
<td>0.001</td>
<td>0.96</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>73 (15)</td>
<td>73 (16)</td>
<td>0.31</td>
<td>0.25</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>126 (23)</td>
<td>127 (24)</td>
<td>0.25</td>
<td>NA</td>
</tr>
<tr>
<td>NYHA class III or IV</td>
<td>2948 (52)</td>
<td>360 (63)</td>
<td>&lt;0.001</td>
<td>0.82</td>
</tr>
<tr>
<td>CHD as main cause for HF</td>
<td>3187 (61)</td>
<td>305 (61)</td>
<td>0.74</td>
<td>NA</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease or asthma</td>
<td>877 (17)</td>
<td>90 (17)</td>
<td>0.80</td>
<td>NA</td>
</tr>
<tr>
<td>Hypertension treatment</td>
<td>1692 (31)</td>
<td>202 (36)</td>
<td>0.005</td>
<td>0.98</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>32 (11)</td>
<td>37 (13)</td>
<td>&lt;0.001</td>
<td>0.01</td>
</tr>
<tr>
<td>LVEF ≤ 40%</td>
<td>4726 (85)</td>
<td>341 (71)</td>
<td>&lt;0.001</td>
<td>0.02</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73 m²</td>
<td>67 (24)</td>
<td>53 (24)</td>
<td>&lt;0.001</td>
<td>0.92</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>4.8 (1.3)</td>
<td>4.7 (1.3)</td>
<td>0.37</td>
<td>NA</td>
</tr>
<tr>
<td>ACE-I</td>
<td>4123 (72)</td>
<td>0 (0)</td>
<td>&lt;0.001</td>
<td>0.99</td>
</tr>
<tr>
<td>ARB</td>
<td>1120 (20)</td>
<td>0 (0)</td>
<td>&lt;0.001</td>
<td>0.99</td>
</tr>
<tr>
<td>ACE-I or ARB</td>
<td>5160 (90)</td>
<td>650 (82)</td>
<td>&lt;0.001</td>
<td>0.79</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>1953 (86)</td>
<td>438 (75)</td>
<td>&lt;0.001</td>
<td>0.92</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>3224 (56)</td>
<td>267 (46)</td>
<td>&lt;0.001</td>
<td>0.91</td>
</tr>
<tr>
<td>Bumetanid equivalent</td>
<td>1455 (25)</td>
<td>197 (34)</td>
<td>&lt;0.001</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td>1.4 (1.7)</td>
<td>2.1 (2.6)</td>
<td>&lt;0.001</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD or n (%). HR, heart rate; SBP, systolic blood pressure; NYHA, New York Heart Association; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CHD, coronary heart disease; HF, heart failure; eGFR, estimated glomerular filtration rate using the MDRD formula.

*a* after adjustment for PS for variable included in the PS calculation.
Survival
The median survival estimate for all patients was 75 ± 2.9 months (95% CI 69.4–80.6 months). It was 83 ± 3.5 vs. 45 ± 3.6 months, respectively, for patients treated with and for those not treated with a RASI; 82 ± 3.0 and 51 ± 3.3 months, respectively, for patients treated with and for those not treated with β-blockers at and 90 ± 3.8 vs. 63 ± 2.6 months, respectively for patients treated with and without a statin at last visit (log-rank test for all, P < 0.001).

In all patients, the combination therapy vs. no therapy (including patients treated with only a RASI or a β-blocker) was associated with a median survival of 85.0 ± 3.4 vs. 48.0 ± 2.6 months (log-rank test P-value < 0.001). Limited to the patients who met the primary indication for both RASI and β-blockers, the median survival for the combination therapy was 100.0 vs. 49.0, respectively (P < 0.001).

Multivariable Cox regression
The results from the multivariable Cox regression models are presented in Table 2. Baseline characteristics associated with a poorer survival were age, smoking, elapsed time since HF diagnosis, NYHA class, CHD as the principal cause of HF, diabetes, hypertension, and intermittent claudication. Female gender, weight (or BMI, see below), systolic blood pressure, LVEF 30–49% (compared with <30%), haemoglobin, estimated glomerular filtration rate (eGFR, MDRD method), and sodium were independently associated with a better survival. β-Blockers and statins were significantly associated with an improved survival, but bumetanide equivalent was significantly associated with a poorer survival. Aldosterone antagonist treatment was associated with an increased mortality [HR 1.29 (1.17–1.42, P < 0.001)]; however, this association was lost in the multivariate model. Renin–angiotensin system inhibitor as a combined single variable or split into its individual components of ACE-I and ARB were not associated with survival in the multivariable model. However, the ACE-I DE expressed either as a continuous variable or as a dummied variable (< or ≥ 50% of the DE) was significantly associated with survival (see Table 2 where ACE-I DE expressed as a categorical variable; expressed as a continuous variable, HR 0.81, 95% CI 0.68–0.96, P = 0.01).

Sub-analysis
Statins and cholesterol
A total of 4598 patients had total cholesterol measured at entry (4.74 ± 1.27 mmol/L). Mean total cholesterol was, respectively, 4.31 ± 1.11 vs. 5.26 ± 1.26 mmol/L in patients treated with and those not treated with a statin at entry (P < 0.001). In those patients, the median survival estimate was, respectively, 90.0 ± 4.4 vs. 64 ± 3.1 months (log-rank test P < 0.001). Statins were associated with survival in the univariable Cox regression (HR 0.77, 95% CI 0.70–0.86, P < 0.001). On a bivariate analysis with cholesterol, both statin use and cholesterol were associated with a better survival. HR for statin treatment was 0.70, 95% CI 0.63–0.78, P < 0.001 and for total cholesterol 0.87, 95% CI 0.83–0.91, P < 0.001. There was no interaction between statin and total cholesterol (P for the interaction term = 0.23). Finally, by adding total cholesterol to the same multivariable model given in Table 2, thereby excluding patients without a total cholesterol value at entry, statin remained associated with a better survival but total cholesterol did not (statin, HR 0.72, 95% CI 0.63–0.82, P < 0.001; total cholesterol HR 0.97, 95% CI 0.92–1.02, P = 0.22; P for interaction term, 0.50).

Propensity score analysis
The P-values for difference in means and proportions between treatment groups after adjustment for the PS are shown in Table 1. They demonstrate that the groups with and without treatment are considerably better balanced in terms of measured baseline characteristics after compared with before adjustment for the PS.

Renin–angiotensin system inhibition
The variables used to calculate the PS for exposure to RASI at last visit were: age, gender, living alone, rhythm at first visit, weight, LVEF, NYHA class, elapsed time since HF diagnosis, diabetes, stroke, intermittent claudication, hypertension treatment, past coronary revascularization, haemoglobin, eGFR (MDRD method), sodium, potassium, aspirin, β-blockers, statins, aldosterone blockers, calcium-channel blockers, and bumetanide equivalent. In the univariable Cox regression analysis, RASI was associated with better survival HR 0.61, 95% CI 0.55–0.70, P < 0.001. Adjusted for PS, the association remained significant, HR 0.85, CI 0.72–0.997, P = 0.046. However, after further adjustment for the LVEF (n = 3634), the association did not

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**Table 2** Cox regression analysis of risk factors for all-cause mortality in outpatients with heart failure after final adjustment of renin–angiotensin system inhibitor, β-blockers, and statins

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariable analysis</th>
<th></th>
<th>Multivariable analysis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio</td>
<td>95% CI</td>
<td>P-value</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>ACE-I dose ≥50% of target</td>
<td>0.65</td>
<td>0.59</td>
<td>0.71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ARB</td>
<td>0.87</td>
<td>0.78</td>
<td>0.98</td>
<td>0.02</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>0.67</td>
<td>0.59</td>
<td>0.74</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Statin</td>
<td>0.76</td>
<td>0.69</td>
<td>0.83</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The model has been adjusted for age, sex, present smoking, weight, months since heart failure diagnosis, systolic blood pressure, New York Heart Association functional class, coronary heart disease as the main reason for heart failure, diabetes mellitus, stroke, intermittent claudication, treatment for hypertension, haemoglobin, renal function, serum sodium, and daily dose of diuretic.

RASI, renin–angiotensin system inhibitors; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.
remain significant, HR 0.84, 95% CI 0.705–1.004, P = 0.055. However, among the patients fulfilling the guidelines indication definition criteria, RASI treatment exposure remained associated with survival after adjustment for the PS. In the multivariate Cox regression analysis, ARB treatment was not significantly associated with a lower all-cause mortality.

**β-Blockers**
The variables used for the β-blockers PS model were: age, gender, smoking, living alone, sinus rhythm, atrial fibrillation, height, weight, LVEF, NYHA class, elapsed time since HF diagnosis, number of hospitalizations in the previous 6 months, CHD, diabetes, stroke, chronic obstructive pulmonary disease, hypertension treatment, past revascularization, haemoglobin, eGFR, sodium, aspirin, ACE-I, ARB and statin, butenamide equivalent. In the univariable Cox regression analysis, β-blocker treatment was associated with a better survival, HR 0.69, 95% CI 0.62–0.77, P < 0.001. Adjusted for the PS, it remained significant, HR 0.84, 95% CI 0.72–0.98, P = 0.03. Among the patients fulfilling the guidelines indication definition criteria, β-blocker treatment exposure remained significantly associated with survival after adjustment for the PS and LVEF (P = 0.02).

**Statins**
The variables used for the PS model of exposure to statins were: age, gender, smoking, living alone, heart rate, sinus rhythm, atrial fibrillation, height, weight, systolic blood pressure, LVEF, NYHA, number of hospitalizations in the previous 6 months, CHD, diabetes, stroke, claudication, hypertension treatment, past revascularization, haemoglobin, sodium, potassium, total cholesterol and aspirin, ACE-I, ARB, β-blocker, and warfarin. In the univariable Cox regression analysis, treatment with a statin was associated with a better survival, HR 0.78, 95% CI 0.71–0.85, P < 0.001. Adjusted for the PS, this association remained significant, HR 0.84, 95% CI 0.72–0.98, P = 0.03. Among the patients fulfilling the guidelines indication definition criteria, β-blocker treatment exposure remained significantly associated with survival after adjustment for the PS and LVEF (P = 0.02).

**Discussion**
In this real-life registry study, adherence to ESC guidelines in patients with HF was associated with an improved outcome. Both multivariable and PS analyses showed survival benefits with β-blockers, and adequate doses of ACE-I in this contemporary HF cohort. Patients exposed to the higher dose equivalents of ACE-I had a better survival compared with low-dose ACE-I treatment. The high level of treatment with β-blockers contrasted with that in the pre-β-blocker era randomized controlled trials (RCTs) of ACE-I in HF. In the usual clinical setting, the ACE-I doses prescribed are often lower than those that were used in the RCTs that have established their utility. In placebo-controlled RCTs, ACE-I were shown to reduce mortality in patients with asymptomatic left ventricular dysfunction, in patients with NYHA class II–III and IV HF. The ARB candesartan reduced cardiovascular mortality and hospital admissions for CHF in patients with symptomatic HF and intolerance to ACE-I. Although the study was not designed for it, lower all-cause mortality was shown with candesartan in the covariate-adjusted analysis. The NETWORK study did not show any difference in outcome in three groups randomized toenalapril 2.5, 5, or 10 mg twice daily. Nanas et al. found no significant differences in survival, nor clinical and haemodynamic variables between patients receiving standard or high doses of enalapril. In the ATLAS study, patients in the high-dose (32.5–35 mg daily) lisinopril group had a non-significant (P = 0.13) 8% lower risk of death and 24% fewer hospitalizations for HF (P = 0.002) than patients in the low-dose group (2.5–5.0 mg daily). In our study, we have found that the ACE-I DE expressed as a continuous variable was associated with a better survival and that patients with ≥50% of the maximal recommended target dose had a significantly better survival. However, the ability to achieve higher doses may only identify patients who are at lower risk.

A significant and independent association between β-blockers and improved survival was found in our study. However, in contrast with the ACE-I observations, no equivalent dose relation was found. However, in the previous MOCHA study subjects with mild-to-moderate HF from systolic dysfunction, carvedilol produced dose-related improvements in LV function and dose-related reductions in mortality and hospitalization rate. In our study, there was a significant but weak correlation between the β-blocker DE and heart rate (−0.06, respectively, P < 0.001). Individual differences in response to β-blockers may explain this weak relation.

In the ESC HF guidelines, aldosterone antagonist treatment is recommended if HF patients treated with β-blockers and ACE inhibitors still are in NYHA class II–IV. Thus not all HF patients are recommended to be on MRA treatment. We found no statistically significant relation between aldosterone antagonist treatment and survival after adjustment for confounders. The increased mortality in the aldosterone antagonist treated group in the univariate analysis was most likely because of adherence to the ESC HF guidelines. Thus, only the patients with the highest cardiovascular risk were given this type of drug.

Contrary to previous observational studies, two recent RCTs have shown that rosuvastatin 10 mg did not affect the main outcome in patients with HF. Bias selection in the observation studies have been pointed at as the most probable reason to explain this discrepancy. Statins could be ineffective in patients with HF because disease progression is not dominated by the progression of atheroma. Our study is in concordance with the previous observation studies, even with methodological attempt at correcting for confounders. Differences in patient selection between studies must be pointed out. In the CORONA trial, patients were eligible if the investigators thought they did not need treatment with a cholesterol-lowering drug. In that trial, rosuvastatin did reduce the rate of atherothrombotic events. Our study did not evaluate the value of initiating statins in HF patients, and patients treated with statins at baseline were characterized by a high burden of vascular diseases. Also, the duration of statin treatment before entry into the registry was not known and the association with improved survival could be the long-term result of risk modification in patients with established vascular disease. Low total cholesterol levels have been shown to be associated with an increase in mortality in chronic HF and could reflect poor nutritional status or a high level of systemic inflammation, however, reducing cholesterol with statins did not have a detrimental effect on patients with HF.

**Limitations**
The primary limitation of this study is its observational nature. Strong associations do not prove cause-effect links and could be the sole
result of confounders. Extreme caution has to be taken in interpreting the results that do differ from those of previous RCTs. We have made every effort possible to correct for the effects of confounders recorded in this registry. The NHFR provides a large set of baseline covariates that have been corrected for in a large and inclusive multivariable Cox regression model. The utilization of PS methods as an alternative way of limiting the influence of confounder effects in the assessed association should strengthen our results. Particular attention was paid in assessing the effectiveness of bias reducing with PS. Missing values is another weakness of this study.

No prospective registry can be free of selection bias. Another important limitation is that we dealt with all-cause mortality as a single hard outcome. The proportion of the deaths that might have been non-related to cardiovascular mortality is unknown. This should, however, have limited our ability to detect strong associations. No other hard HF outcomes, like heart transplant and hospitalizations, were available, which is an obvious limitation to the information provided by this study. No information on non-pharmacological treatments was also collected. A substantial number of patients in the study probably met the criteria for both ICD and resynchronization therapy and their impact on survival and their interaction with other risk factors could not be ascertained. Angiotensin II receptor blocker doses were unavailable. Recently, Konstam et al. have demonstrated that losartan 150 mg daily reduced the combined endpoint of death or admission for HF compared with 50 mg daily in patients intolerant to ACE-I.

**Conclusion**

In this contemporary HF cohort, HF guideline-indicated drugs prescription levels were high and were even higher when considering specific definitions for indication. Adherence to ESC guidelines in patients with HF was associated with an improved outcome. Both multivariable and PS analyses showed an increased survival in patients exposed to β-blockers, ACE-I doses ≥50% of the maximal recommended target and statins. This study stresses the importance of guideline adherence. Moreover, aiming at the recommended target doses of ACE-I may have a crucial role in survival improvement, but in the multivariable Cox regression analysis ARB treatment was not significantly associated with a lower all-cause mortality. If otherwise indicated, statins should probably be continued in patients diagnosed with new HF.

**Conflict of interests:** none declared.

**References**


