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# Causes and impact on survival of underuse of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers in heart failure

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## Abstract

Guidelines recommend angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB) for treatment of heart failure with reduced ejection fraction (HFrEF), but these medications are underprescribed in clinical practice. We reviewed the records of HF patients receiving a first visit in a tertiary outpatient clinic from January 1st 2004 to May 31st 2015, and selected those with a serum creatinine concentration (sCr) available at both the first and last visit and < 3.5 mg/dL at baseline, and a left ventricular ejection fraction (LVEF) < 50% at the first visit. Of 570 eligible patients, 92 (16.1%) never received ACEi/ARB. Compared to ACEi/ARB users, never-users were older, more often women, had higher sCr and lower systolic blood pressure, were less commonly on beta-blocker, and had more frequently anemia. Current or prior cancer also tended to be more common in ACEi/ARB never-users. ACEi/ARB users displayed an improvement in LVEF by ≥ 10% of the baseline value more often than ACEi/ARB never-users (33.7% vs. 20.7%, respectively, $P = 0.01$), whereas no difference in percent variation of sCr levels was found between the two groups (8.2% vs. 3.1%, respectively; $P = 0.13$). Over a median follow-up of 56 months (range 1–137 months), 215 (37.7%) patients died. After multiple adjustments, ACEi/ARB never-use was associated with an almost twofold increased risk of all-cause mortality (HR 1.97, 95%CI 1.39–2.80). ACEi/ARB underuse in HFrEF is a standing issue with dramatic prognostic consequences. Efforts are needed to eliminate perceived contraindications to these drugs and ensure their implementation in real-life cardiology.

**Keywords** Angiotensin-converting enzyme inhibitors · Angiotensin II receptor blockers · Heart failure with reduced ejection fraction · Underuse · Mortality

## Introduction

Activation of the renin–angiotensin aldosterone system (RAAS) is a hallmark of heart failure with reduced ejection fraction (HFrEF). Randomized clinical trials have clearly demonstrated that angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB) reduce hospitalization and mortality in patients with HFrEF [1–4]. Together with beta-blockers, these drugs represent the mainstay of HFrEF medical therapy [5]. However, epidemiological studies observed that a sizable proportion of subjects with newly diagnosed HFrEF are prescribed neither ACEi nor ARB, with concomitant kidney dysfunction and advanced age being pinpointed as the main reason for ACEi/ARB non-use [6–9]. Here, we retrospectively studied a single-center cohort of HFrEF outpatients with the aim of evaluating the frequency of ACEi/ARB non-use and

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investigating the causes and prognostic impact of this therapeutic choice.

## Methods

### Study population

The study population was identified by retrospectively reviewing the charts of all patients receiving a first visit for symptomatic HF in the tertiary outpatient clinic at the Cardiovascular Disease Unit of the IRCCS AOU San Martino—IST hospital (now IRCCS Ospedale Policlinico San Martino), Genova, Italy, from January 1st 2004 to May 31st 2015. Among these subjects, we selected those who: had at least another subsequent visit; had a serum creatinine concentration (sCr) available in the records of both the first and the last visit and < 3.5 mg/dL at baseline; had a left ventricular ejection fraction (LVEF) < 50% at the first visit; had complete information about medical therapy at both the first and the last visit, as well as about the date of death if any. Patients who were not prescribed an ACEi/ARB at both the first and last visit were considered as ACEi/ARB never-users. Improvement in LV function was defined as an increase in LVEF > 10% [10, 11], and worsening renal function (WRF) as an increase in sCr concentration by > 25% above baseline.

Smoking was ascertained by medical interview. Hypertension was defined as blood pressure ≥ 140/90 mmHg and/or use of antihypertensive medications; dyslipidemia by total cholesterol ≥ 200 mg/dL; and diabetes mellitus by history of diabetes and/or use of antidiabetic medications and/or $HbA_{1c}$ > 6.5% and/or fasting plasma glucose ≥ 126 mg/dL and/or random plasma glucose ≥ 200 mg/dL in the presence of typical symptoms of the disease [12]. Estimated glomerular filtration rate (eGFR) was calculated by means of the MDRD formula. A diagnosis of chronic obstructive pulmonary disease (COPD) was established during the first visit based on history of COPD and/or suggestive signs or symptoms and/or prior evidence of non-asthmatic airway obstruction at pulmonary function testing. Patients with previous or current malignancy were considered as affected by cancer. Anemia was defined by hemoglobin levels < 13.5 g/dL in males and < 12.5 g/dL in females [12].

The etiology of HFrEF was ascribed to ischemic heart disease in case of positive stress ECG or imaging, angiographic evidence of significant coronary obstruction and/or previous acute coronary syndrome, percutaneous revascularization and/or coronary artery bypass grafting.

Information regarding ongoing HFrEF therapy included use of ACEi/ARB, beta-blockers, mineralocorticoid receptor antagonists and diuretic agents and implanted devices, including those for cardiac resynchronization therapy and implantable cardioverter defibrillators.

### Statistical analysis

Statistical analyses were performed using SAS 9.3 (SAS Institute, Cary, NC, USA). Continuous variables were expressed as mean ± standard deviation, and categorical variables as percentages. Characteristics of ACEi/ARB recipients or not were compared using student T test and Chi-squared test, as appropriate. The variables that proved significantly different in univariate analyses were entered in a multivariate logistic regression model with backward selection to identify independent correlates of ACEi/ARB therapy. The risk of all-cause mortality was assessed by Kaplan–Meyer analysis and multivariate Cox regression.

## Results

### Study population

Of the patients receiving at least two visits in the outpatient clinic with the first one between January 2004 and May 2015, 711 had a baseline sCr value available. Of them, 15 were excluded because of sCr concentration above 3.5 mg/dL at baseline and 104 because of LVEF ≥ 50%. Another 22 patients were excluded because of missing follow-up information about sCr levels ($n = 16$), ACEi/ARB use ($n = 2$), or death ($n = 2$), leaving a final sample of 570 subjects. ACEi and/or ARB therapy was not prescribed at both the first and last visit in 92 (16.1%) cases. The remaining study population consisted of 329 (57.7%) patients on ACEi/ARB at both baseline and follow-up, 124 (21.8%) who were on ACEi/ARB at the first but not at the last visit, and of 25 (4.4%) who started an ACEi or ARB after the initial evaluation.

Table 1 summarizes the baseline characteristics of the overall cohort and of ACEi/ARB users compared with never-users. In the overall sample, the mean age was 69 ± 12 years and most subjects were males (74.4%). Cardiovascular risk factors were common, with the prevalence of hypertension, dyslipidemia and diabetes being 60.2%, 34.9% and 29.6%, respectively. The majority of patients had an eGFR > 60 mL/min/1.73 $m^2$, 40% had an eGFR between 30 and 59 mL/min/1.73 $m^2$ and 6.2% suffered from severe chronic kidney disease (CKD), as defined by eGFR below 30 mL/min/1.73 $m^2$.

### Characteristics associated with ACEi/ARB use and never-use

Compared to ACEi/ARB users, ACEi/ARB never-users were significantly older and more often women (Table 1).

**Table 1** Characteristics of ACEi/ARB never-users versus ACEi/ARB users at the baseline visit

| | All | ACEi/ARB never-users | ACEi/ARB users | *P* for comparison |
|---|---|---|---|---|
| No. | 570 | 92 | 478 | |
| Age (years) | 69 ± 11.5 | 72.2 ± 12.8 | 68.4 ± 11.1 | 0.004 |
| Males | 74.4% | 59.8% | 77.2% | 0.0005 |
| Hypertension | 60.2% | 52.2% | 61.7% | 0.09 |
| Smoking | 38% | 34.8% | 38.7% | 0.48 |
| Dyslipidemia | 34.9% | 34.8% | 34.9% | 0.98 |
| Diabetes | 29.6% | 31.5% | 29.3% | 0.82 |
| Creatinine (mg/dL) | 1.2 ± 0.4 | 1.4 ± 0.6 | 1.2 ± 0.4 | < 0.0001 |
| eGFR (mL/min/1.73 $m^2$) | 63.8 ± 22.2 | 54.1 ± 24.3 | 65.7 ± 21.4 | < 0.0001 |
| eGFR categories | | | | < 0.0001 |
| ≥ 60 mL/min/1.73 $m^2$ | 53.8% | 38.0% | 55.6% | |
| 45–59 mL/min/1.73 $m^2$ | 25.6% | 25.0% | 27.0% | |
| 30–44 mL/min/1.73 $m^2$ | 14.4% | 16.3% | 14.0% | |
| < 30 mL/min/1.73 $m^2$ | 6.2% | 20.7% | 3.4% | |
| COPD | 14% | 16.3% | 13.6% | 0.49 |
| Anemia | 9.1% | 15.2% | 8% | 0.03 |
| Cancer | 9.3% | 14.1% | 8.4% | 0.08 |
| SBP (mm/Hg) | 128.1 ± 19 | 123.2 ± 18.8 | 129 ± 18.9 | 0.008 |
| NYHA class III–IV | 48.9% | 51.1% | 48.5% | 0.65 |
| LVEF (%) | 32.4 ± 8.5 | 30.9 ± 8.7 | 32.6 ± 8.4 | 0.13 |
| LVEF < 40% | 76.8% | 75.3% | 84.8% | 0.05 |
| Atrial fibrillation | 17.9% | 18.5% | 17.8% | 0.87 |
| Ischemic heart disease | 44.6% | 37% | 46% | 0.11 |
| Beta-blocker | 82.1% | 72.8% | 89.9% | 0.01 |
| MRA | 45.3% | 50% | 44.4% | 0.32 |
| Diuretic | 78.4% | 79.4% | 78.2% | 0.81 |
| ICD | 19% | 14.1% | 19.8% | 0.20 |
| CRT | 8.3% | 12% | 7.5% | 0.16 |

*ACEi* angiotensin-converting enzyme inhibitors, *ARB* angiotensin II receptor blockers, *COPD* chronic obstructive pulmonary disease, *CRT* cardiac resynchronization therapy, *eGFR* estimated glomerular filtration rate, *ICD* implantable cardioverter defibrillator, *LVEF* left ventricular ejection fraction, *MRA* mineralocorticoid receptor antagonists, *NYHA* New York Heart Association, *SBP* systolic blood pressure

Cardiovascular risk factors were similarly distributed in the two groups, but with a trend for a less frequent history of hypertension in those never taking ACEi/ARB. sCr concentrations were significantly higher, and eGFR was significantly lower, in ACEi/ARB never-users than ACEi/ARB users (Table 1). Consistently, an eGFR value below 60 mL/min/1.73 $m^2$ was significantly more common in subjects not given ACEi/ARB as compared with those receiving these medications (62% vs. 44.4%, respectively; $P = 0.002$). Furthermore, significantly more ACEi/ARB never-users than users had severe CKD. Anemia was significantly more often present in patients who were not prescribed ACEi/ARB, as was more common a history of cancer, although not to a significant extent (Table 1).

Regarding clinical presentation, ACEi/ARB never-users had significantly lower blood pressure values and showed a trend for a higher frequency of LVEF > 40% as compared with subjects on ACEi/ARB (Table 1). Almost 90% of patients on ACEi/ARB were on a beta-blocker at the first evaluation, whereas the prevalence of beta-blocker therapy in the ACEi/ARB never-user group was significantly lower (72.8%). No significant differences were found in the other therapies analyzed. In multivariate logistic regression, female gender, higher sCr or reduced eGFR, lower blood pressure, and lack of treatment with beta-blocker were independent correlates of ACEi/ARB omission (Table 2 and Supplemental Table 1).

## Prognostic impact of ACEi/ARB never-use

Over a median follow-up of 56 months (range 1–137 months), 215 (37.7%) patients died by any cause, with a trend for a higher mortality in those not taking ACEi/ARB than in those given these medications (46.7% vs. 36%, $P = 0.05$). Kaplan–Meier analysis confirmed that patients not prescribed ACEi/ARB were more likely to die over the

**Table 2** Correlates of ACEi/ARB omission in the study population

| | Full | | | Reduced | | |
|---|---|---|---|---|---|---|
| | *β* | 95%CI | *P* | *β* | 95%CI | *P* |
| Age | 1.02 | 0.99–1.04 | 0.17 | | | |
| Male gender | 0.33 | 0.19–0.55 | < 0.0001 | 0.31 | 0.19–0.52 | < 0.0001 |
| Creatinine | 3.47 | 1.94–6.20 | < 0.0001 | 3.51 | 2.14–5.77 | < 0.0001 |
| Anemia | 0.88 | 0.39–1.95 | 0.75 | | | |
| Cancer | 1.72 | 0.84–3.51 | 0.14 | | | |
| Hypertension | 0.70 | 0.40–1.21 | 0.21 | | | |
| SBP | 0.98 | 0.97–1.00 | 0.02 | 0.98 | 0.96–0.99 | 0.0007 |
| LVEF < 40% | 0.69 | 0.36–1.31 | 0.25 | | | |
| Beta-blocker | 0.55 | 0.31–0.97 | 0.04 | 0.52 | 0.30–0.92 | 0.02 |

*eGFR* estimated glomerular filtration rate, *LVEF* left ventricular ejection fraction, *SBP* systolic blood pressure

course of our extended follow-up (Fig. 1). In univariate analysis, ACEi/ARB never-use was associated with an almost twofold increased risk of death (HR 1.93, 95%CI 1.38–2.71). After multiple adjustment, the association between omission of ACEi/ARB and all-cause mortality persisted (Table 3).

## Impact of ACEi/ARB never-use on left ventricular ejection fraction

Median time between the first and the last visit was 21 months (range 1–137 months), during which LVEF increased by 14.3 ± 35.4% in the overall population. When the ACEi/ARB never-users and users were compared, no significant difference in the mean change in LVEF was observed (10.4 ± 24.6% vs. 14.9 ± 36.8%, respectively; $P = 0.35$). However, LVEF improvement by ≥ 10% of the baseline value was significantly less frequent in the group not receiving ACEi/ARB than in the one on these drugs (20.7% vs. 33.7%, respectively, $P = 0.01$), and a trend persisted after accounting for age, gender and baseline LVEF ($P = 0.08$).

## Impact of ACEi/ARB never-use on renal function

The percent change in sCr concentration between the first and last visit was 7.4 ± 29.8%. No significant difference in percent variation of sCr levels was found among ACEi/ARB never-users and ACEi/ARB users (3.1 ± 30.4 vs. 8.2 ± 29.6, respectively; $P = 0.13$), nor was significantly different the number of subjects who experienced WRF (12% ACEi/ARB never-users vs. 17.2% ACEi/ARB users, $P = 0.22$). Remarkably, WRF did not show an independent association with mortality, and there was no significant interaction between WRF and ACEi/ARB use (data not shown), indicating that

**Fig. 1** .

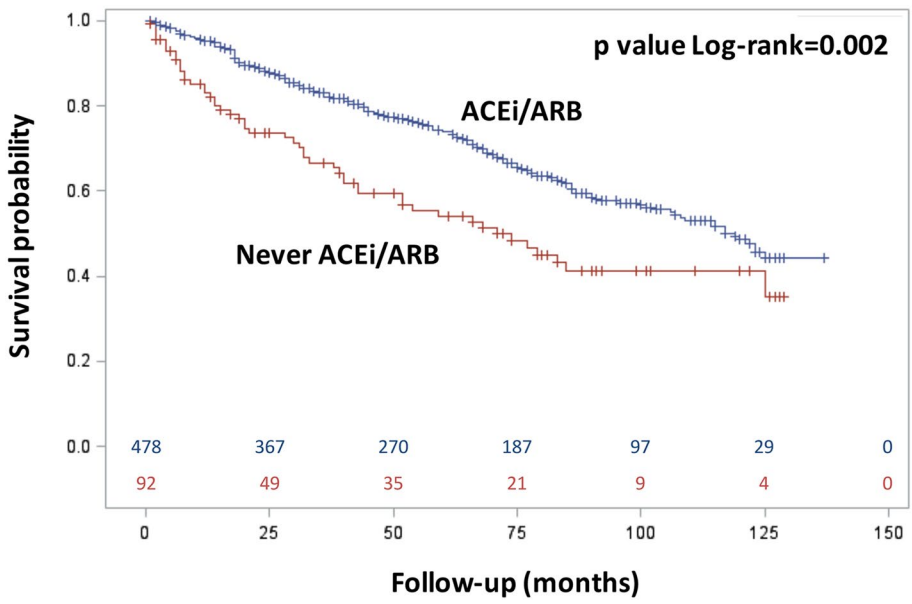

**Table 3** Hazard ratios (HR) for all-cause mortality in the study population

| | Full | | | Reduced | | |
|---|---|---|---|---|---|---|
| | HR | 95%CI | *P* | HR | 95%CI | *P* |
| ACEi/ARB never-use | 1.80 | 1.23–2.61 | 0.002 | 1.97 | 1.39–2.80 | 0.0002 |
| Age | 1.04 | 1.02–1.05 | < 0.0001 | 1.04 | 1.02–1.05 | < 0.0001 |
| Male gender | 1.57 | 1.08–2.72 | 0.02 | 1.64 | 1.16–2.33 | 0.006 |
| Diabetes | 1.42 | 1.05–1.92 | 0.03 | 1.39 | 1.04–1.87 | 0.03 |
| COPD | 1.25 | 0.85–1.83 | 0.26 | | | |
| Anemia | 2.10 | 1.31–3.35 | 0.002 | 2.32 | 1.55–3.48 | < 0.0001 |
| Cancer | 1.67 | 1.08–2.57 | 0.02 | 1.65 | 1.08–2.53 | 0.02 |
| Creatinine | 1.17 | 0.80–1.71 | 0.41 | | | |
| SBP | 1.00 | 0.99–1.01 | 0.99 | | | |
| NYHA III–IV | 1.01 | 0.75–1.36 | 0.96 | | | |
| Atrial fibrillation | 1.04 | 0.72–1.50 | 0.85 | | | |
| Ischemic heart disease | 1.36 | 0.96–1.92 | 0.08 | | | |
| LVEF > 40% | 0.91 | 0.64–1.30 | 0.59 | | | |
| Beta-blocker | 0.72 | 0.51–1.02 | 0.07 | 0.63 | 0.46–0.87 | 0.005 |
| Diuretic | 1.60 | 1.03–2.49 | 0.04 | 1.98 | 1.32–2.96 | 0.001 |
| Digoxin | 1.32 | 0.93–1.87 | 0.12 | | | |
| Statin | 0.69 | 0.49–0.97 | 0.03 | | | |
| MRA | 1.17 | 0.86–1.59 | 0.32 | | | |
| PM/ICD | 1.45 | 1.07–1.95 | 0.02 | 1.56 | 1.17–2.09 | 0.003 |

*ACEi* angiotensin-converting enzyme inhibitors, *ARB* angiotensin II receptor blockers, *COPD* chronic obstructive pulmonary disease, *ICD* implantable cardioverter defibrillator, *LVEF* left ventricular ejection fraction, *MRA* mineralocorticoid receptor antagonists, *NYHA* New York Heart Association, *PM* pacemaker, *SBP* systolic blood pressure

WRF did not have an impact on the outcome in both ACEi/ARB users and never-users.

## Discussion

In this retrospective study, we found that a substantial proportion of HFrEF outpatients were not prescribed ACEi/ARB and that omission of these drugs was associated with an increased risk of death. These findings are in agreement with previous work reporting underuse of ACEi/ARB in real-life HFrEF patients, with a prevalence as high as 24% [7] and negative prognostic impact [6–9], in spite of long-standing evidence and class I recommendation in guidelines [1–5]. Thus, actions are still needed to improve the prescription rate of RAAS-targeting drugs in HFrEF.

In our cohort, ACEi/ARB never-use was associated with worse renal function at baseline. Again, this observation is in line with earlier studies, which pinpointed kidney dysfunction as a major reason for ACEi/ARB omission in HFrEF [6–9], and most likely reflects the fear of clinicians to start ACEi/ARB therapy in the presence of even mild CKD, because of the concern of an acute fall in eGFR and the development of hyperkaliemia. This behavior captures a conflict between guidelines, based on pathophysiological reasoning and epidemiological data, and real-world practice, often prompted by personal perception and single-case experience. In fact, the worsening of renal function following ACEi/ARB initiation is assumed to result from intrarenal hemodynamic changes secondary to RAAS blockade and not from structural renal damage. Consistently, a recent meta-analysis of HFrEF clinical trials demonstrated that the initial decrease in eGFR associated with ACEi/ARB use portends a greater reduction in all-cause mortality compared with no modification in renal function after ACEi/ARB administration [13]. Moreover, the benefit associated with ACEi/ARB treatment in patients with eGFR < 60 mL/min/1.73 $m^2$ is comparable to the one observed in individuals with preserved renal function [14]. On the other hand, the practicing physician may give emphasis to ACEi/ARB-related fluctuations in sCr and deem them more relevant than they actually are: referring to the present study, the trend to increased sCr in ACEi/ARB recipients, although not statistically significant, may have accounted for the reluctance to prescribe RAAS inhibitors to other patients.

Scarce evidence is available regarding ACEi/ARB effectiveness in HFrEF patients with severe CKD, which were not adequately represented in or excluded from clinical trials [1–4]. As a consequence, current HF guidelines recommend caution in this setting, and ACEi/ARB should be halved in

dosage or withdrawn if sCr increases more than 50% above baseline, or eGFR decreases below 25 mL/min/1.73 $m^2$ despite adjustment of concomitant medications [5]. However, observational studies reported that the mortality benefit conferred by ACEi/ARB in HFrEF also applies to subjects with severe CKD, with the exception of those on dialytic treatment [9, 15, 16].

Older age and anemia were other correlates of ACEi/ARB never-use in our population, suggesting that a high burden of comorbidities may also cause ACEi/ARB underuse in HFrEF, possibly because of the tendency to withhold prescription of these drugs in individuals that are likely to poorly tolerate them. Nonetheless, it was shown that comorbidities have a negative impact on morbidity and mortality in HF [17], but they do not interfere with the beneficial effects of ACEi [18].

The reasoning that ACEi/ARB treatment may be not tolerable may also explain why ACEi/ARB never-use tended to be more frequent in the case of a history of cancer. Emerging evidence indicates that the incidence of cancer is higher in HF patients compared to individuals without HF [19, 20], and the co-occurrence of the two conditions is associated with a poorer prognosis compared with that of patients with either HF or cancer, possibly reflecting the fact that one disease hinders the management of the other one. Indeed, medical therapy for HFrEF may be simplified or discontinued when a malignancy develops, especially if the tumor and/or antineoplastic therapy lead to fatigue, hypotension and deterioration of renal function [21]. This issue is topical and must be addressed in the next future [21].

Low systolic blood pressure is correlated with poor outcomes in HFrEF [22], and because clinicians are concerned of aggravating hypotension, disease-modifying medications may be withheld in hypotensive patients [23]. Accordingly, we found that low systolic blood pressure was significantly associated with ACEi/ARB never-use. Symptomatic hypotension was reported as a side effect in 6–8% in patients enrolled in ACEi/ARB clinical trials, and its prevalence in real-life HF patients is estimated in the range of 5–10% [22]. Importantly, hypotension is also a common limiting factor for use and up-titration of the angiotensin receptor neprilysin inhibitor, sacubitril/valsartan, since its impact on blood pressure is even higher than the one of ACEi/ARB [24]. Similar to patients with severe CKD, those with low systolic blood pressure were often not adequately represented in key HFrEF clinical trials, but the mortality benefit associated with ACEi/ARB and sacubitril/valsartan [25] is not blunted in this group of patients. Therefore, careful up-titration of these drugs should be attempted to assess their tolerability, even in the presence of low systolic blood pressure at baseline. It is worth noting that, despite the larger effect on blood pressure, sacubitril/valsartan was associated with a slower rate of eGFR decline compared with ACEi [26]. In the light of this more favorable effect on renal function, preferring sacubitril/valsartan may represent a strategy to overcome ACEi/ARB underuse in HFrEF.

Whereas hypotension and WRF were seemingly perceived as contraindications to ACEi/ARB therapy, the fact that a similar proportion of ACEi/ARB users and never-users were treated with MRA suggests that the risk of hyperkaliemia did not deter clinicians from prescribing potassium-sparing diuretics in our study. Similar to ACEi/ARB, MRA are underused in HFrEF, and their underuse is not inversely correlated to potassium levels, but rather it decreases with impaired renal function [27].

Finally, we relate the association of ACEi/ARB never-use with female gender and lack of treatment with beta-blocker to non-ischemic etiology of HFrEF, in that cardiologists are more aggressive in prescribing neurohormonal inhibitors to patients with ischemic heart disease, who are more often male.

Although our study was not designed to assess the trajectory of LVEF in treated HFrEF, ACEi/ARB underuse negatively impacted on the frequency of reverse LV remodeling at follow-up, this finding further highlights the detrimental consequences of ACEi/ARB omission in HFrEF.

We acknowledge that our study is limited by its retrospective design and single-center origin of the sample examined. Furthermore, our analysis included patients with the form of HF that is defined as HF with mid-range LVEF (HFmrEF) by the latest guidelines of the European Society of Cardiology, i.e. with LVEF between 41 and 50% [5]. Although this type of HF may have distinctive features, it shares important similarities with HF with LVEF < 40%, such as, in particular, the fact that inhibition of the RAAS is the cornerstone of medical treatment [28]. Notably, in a sensitivity analysis limited to patients with LVEF < 40% the results were substantially unchanged (data not shown).

Our considerations on the effects of ACEi/ARB treatment on renal function are limited in that they are based exclusively on evaluation of sCr levels at first and last visit. Finally, we did not take into account dosages of ACEi/ARB, since this information was inconsistently available in the medical records reviewed for the study.

## Conclusions

We confirm that prescription of ACEi/ARB is suboptimal in HFrEF, and that this therapeutic omission takes the toll of an almost twofold increase in mortality. ACEi/ARB underuse may be due to several reasons, among which, in particular, the concerns regarding the impact of these medications on renal function, systolic blood pressure and quality of life, especially in frail patients and/or with concomitant CKD. Thus, a gap persists between ideal evidence-based

and real-life use of ACEi/ARB in HFrEF, despite a negative prognostic impact having been consistently reported for more than two decades [7, 23, 29]. Interventions are urgently needed to ensure effective implementation of optimal HFrEF medical therapy in clinical practice.

## Compliance with ethical standards

**Conflict of interest** The authors have no conflict of interest to disclose.

**Statements on human and animal rights** The study protocol was approved by the local Ethics Committee and conforms to the ethical guidelines of the 1974 Declaration of Helsinki.

**Informed consent** Informed consent was obtained from all participants in the study.

## References


1. CONSENSUS Trial Study Group (1987) Effects of enalapril on mortality in severe congestive heart failure. Results of the cooperative north scandinavian enalapril survival study (CONSENSUS). N Engl J Med 316(23):1429–1435. https://doi.org/10.1056/nejm198706043162301
2. Investigators SOLVD, Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN (1991) Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 325(5):293–302. https://doi.org/10.1056/NEJM199108013250501
3. Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B, Ostergren J, Pfeffer MA, Swedberg K, CHARM Investigators and Committees (2003) Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-alternative trial. Lancet 362(9386):772–776. https://doi.org/10.1016/S0140-6736(03)14284-5
4. McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, Olofsson B, Yusuf S, Pfeffer MA, CHARM Investigators and Committees (2003) Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-added trial. Lancet 362(9386):767–771. https://doi.org/10.1016/S0140-6736(03)14283-3
5. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, ESC Scientific Document Group (2016) 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 37(27):2129–2200. https://doi.org/10.1093/eurheartj/ehw128
6. Butler J, Arbogast PG, Daugherty J, Jain MK, Ray WA, Griffin MR (2004) Outpatient utilization of angiotensin-converting enzyme inhibitors among heart failure patients after hospital discharge. J Am Coll Cardiol 43(11):2036–2043. https://doi.org/10.1016/j.jacc.2004.01.041
7. Masoudi FA, Rathore SS, Wang Y, Havranek EP, Curtis JP, Foody JM, Krumholz HM (2004) National patterns of use and effectiveness of angiotensin-converting enzyme inhibitors in older patients with heart failure and left ventricular systolic dysfunction. Circulation 110(6):724–731. https://doi.org/10.1161/01.CIR.0000138934.28340.ED
8. Setoguchi S, Levin R, Winkelmayer WC (2008) Long-term trends of angiotensin-converting enzyme inhibitor and angiotensin-receptor blocker use after heart failure hospitalization in community-dwelling seniors. Int J Cardiol 125(2):172–177. https://doi.org/10.1016/j.ijcard.2007.10.009
9. Edner M, Benson L, Dahlstrom U, Lund LH (2015) Association between renin–angiotensin system antagonist use and mortality in heart failure with severe renal insufficiency: a prospective propensity score-matched cohort study. Eur Heart J 36(34):2318–2326. https://doi.org/10.1093/eurheartj/ehv268
10. Tayal U, Prasad SK (2017) Myocardial remodelling and recovery in dilated cardiomyopathy. JRSM Cardiovasc Dis 6:2048004017734476. https://doi.org/10.1177/2048004017734476
11. Huttin O, Coiro S, Selton-Suty C, Juilliere Y, Donal E, Magne J, Sadoul N, Zannad F, Rossignol P, Girerd N (2016) Prediction of left ventricular remodeling after a myocardial infarction: role of myocardial deformation—a systematic review and meta-analysis. PLoS ONE 11(12):e0168349. https://doi.org/10.1371/journal.pone.0168349
12. Gigli L, Ameri P, Secco G, De Blasi G, Miceli R, Lorenzoni A, Torre F, Chiarella F, Brunelli C, Canepa M (2016) Clinical characteristics and prognostic impact of atrial fibrillation in patients with chronic heart failure. World J Cardiol 8(11):647–656. https://doi.org/10.4330/wjc.v8.i11.647
13. Clark H, Krum H, Hopper I (2014) Worsening renal function during renin–angiotensin–aldosterone system inhibitor initiation and long-term outcomes in patients with left ventricular systolic dysfunction. Eur J Heart Fail 16(1):41–48. https://doi.org/10.1002/ejhf.13
14. McAlister FA, Ezekowitz J, Tonelli M, Armstrong PW (2004) Renal insufficiency and heart failure: prognostic and therapeutic implications from a prospective cohort study. Circulation 109(8):1004–1009. https://doi.org/10.1161/01.CIR.0000116764.53225.A9
15. Berger AK, Duval S, Manske C, Vazquez G, Barber C, Miller L, Luepker RV (2007) Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients with congestive heart failure and chronic kidney disease. Am Heart J 153(6):1064–1073. https://doi.org/10.1016/j.ahj.2007.03.017
16. Pandey A, Golwala H, DeVore AD, Lu D, Madden G, Bhatt DL, Schulte PJ, Heidenreich PA, Yancy CW, Hernandez AF, Fonarow GC (2016) Trends in the use of guideline-directed therapies among dialysis patients hospitalized with systolic heart failure: findings from the american heart association get with the guidelines-heart failure program. JACC Heart Fail 4(8):649–661. https://doi.org/10.1016/j.jchf.2016.03.002
17. Braunstein JB, Anderson GF, Gerstenblith G, Weller W, Niefeld M, Herbert R, Wu AW (2003) Noncardiac comorbidity increases preventable hospitalizations and mortality among Medicare beneficiaries with chronic heart failure. J Am Coll Cardiol 42(7):1226–1233
18. Böhm M, Pogue J, Kindermann I, Poss J, Koon T, Yusuf S (2014) Effect of comorbidities on outcomes and angiotensin converting enzyme inhibitor effects in patients with predominantly left ventricular dysfunction and heart failure. Eur J Heart Fail 16(3):325–333. https://doi.org/10.1002/ejhf.23
19. Hasin T, Gerber Y, McNallan SM, Weston SA, Kushwaha SS, Nelson TJ, Cerhan JR, Roger VL (2013) Patients with heart

failure have an increased risk of incident cancer. J Am Coll Cardiol 62(10):881–886. https://doi.org/10.1016/j.jacc.2013.04.088
20. Banke A, Schou M, Videbaek L, Moller JE, Torp-Pedersen C, Gustafsson F, Dahl JS, Kober L, Hildebrandt PR, Gislason GH (2016) Incidence of cancer in patients with chronic heart failure: a long-term follow-up study. Eur J Heart Fail 18(3):260–266. https://doi.org/10.1002/ejhf.472
21. Ameri P, Canepa M, Anker MS, Belenkov Y, Bergler-Klein J, Cohen-Solal A, Farmakis D, Lopez-Fernandez T, Lainscak M, Pudil R, Ruschitska F, Seferovic P, Filippatos G, Coats A, Suter T, Von Haehling S, Ciardiello F, de Boer RA, Lyon AR, Tocchetti CG, Heart Failure Association Cardio-Oncology Study Group of the European Society of Cardiology (2018) Cancer diagnosis in patients with heart failure: epidemiology, clinical implications and gaps in knowledge. Eur J Heart Fail 20(5):879–887. https://doi.org/10.1002/ejhf.1165
22. Ather S, Chan W, Chillar A, Aguilar D, Pritchett AM, Ramasubbu K, Wehrens XH, Deswal A, Bozkurt B (2011) Association of systolic blood pressure with mortality in patients with heart failure with reduced ejection fraction: a complex relationship. Am Heart J 161(3):567–573. https://doi.org/10.1016/j.ahj.2010.12.009
23. Ahmed A, Centor RM, Weaver MT, Perry GJ (2005) A propensity score analysis of the impact of angiotensin-converting enzyme inhibitors on long-term survival of older adults with heart failure and perceived contraindications. Am Heart J 149(4):737–743. https://doi.org/10.1016/j.ahj.2004.06.030
24. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, Investigators P-H, Committees (2014) Angiotensin–neprilysin inhibition versus enalapril in heart failure. N Engl J Med 371(11):993–1004. https://doi.org/10.1056/NEJMoa1409077
25. Böhm M, Young R, Jhund PS, Solomon SD, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Swedberg K, Zile MR, Packer M, McMurray JJV (2017) Systolic blood pressure, cardiovascular outcomes and efficacy and safety of sacubitril/valsartan (LCZ696) in patients with chronic heart failure and reduced ejection fraction: results from PARADIGM-HF. Eur Heart J 38(15):1132–1143. https://doi.org/10.1093/eurheartj/ehw570
26. Damman K, Gori M, Claggett B, Jhund PS, Senni M, Lefkowitz MP, Prescott MF, Shi VC, Rouleau JL, Swedberg K, Zile MR, Packer M, Desai AS, Solomon SD, McMurray JJV (2018) Renal effects and associated outcomes during angiotensin–neprilysin inhibition in heart failure. JACC Heart Fail 6(6):489–498. https://doi.org/10.1016/j.jchf.2018.02.004
27. Savarese G, Carrero JJ, Pitt B, Anker SD, Rosano GMC, Dahlstrom U, Lund LH (2018) Factors associated with underuse of mineralocorticoid receptor antagonists in heart failure with reduced ejection fraction: an analysis of 11 215 patients from the Swedish Heart Failure Registry. Eur J Heart Fail. https://doi.org/10.1002/ejhf.1182
28. Tsuji K, Sakata Y, Nochioka K, Miura M, Yamauchi T, Onose T, Abe R, Oikawa T, Kasahara S, Sato M, Shiroto T, Takahashi J, Miyata S, Shimokawa H, CHART-2 Investigators (2017) Characterization of heart failure patients with mid-range left ventricular ejection fraction-a report from the CHART-2 study. Eur J Heart Fail 19(10):1258–1269. https://doi.org/10.1002/ejhf.807
29. Bart BA, Gattis WA, Diem SJ, O'Connor CM (1997) Reasons for underuse of angiotensin-converting enzyme inhibitors in patients with heart failure and left ventricular dysfunction. Am J Cardiol 79(8):1118–1120