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Renin-Angiotensin Inhibition and Outcomes in HFrEF and Advanced Kidney Disease

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All authors had access to the data and a role in writing the manuscript.

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Declaration of Competing Interest

None of the other authors report any conflicts of interest related to this manuscript.

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Abstract

Background: Renin-angiotensin system inhibitors improve outcomes in patients with heart failure with reduced ejection fraction (HFrEF). However, less is known about their effectiveness in patients with HFrEF and advanced kidney disease.

Methods: In the Medicare-linked OPTIMIZE-HF, 1582 patients with HFrEF (ejection fraction, ≤40%) had advanced kidney disease (estimated glomerular filtration rate <30 ml/min/1.73 m^2). Of these, 829 were not receiving angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) prior to admission, of whom 214 were initiated on these drugs prior to discharge. We calculated propensity scores for receipt of these drugs for each of the 829 patients and assembled a matched cohort of 388 patients, balanced on 41 baseline characteristics (mean age, 78 years; 52% women; 10% African American; 73% receiving beta blockers). Hazard ratios (HR) and 95% CIs were estimated comparing 2-years outcomes in 194 patients initiated on ACE inhibitors or ARBs to 194 patients not initiated on those drugs.

Results: The combined endpoint of heart failure readmission or all-cause mortality occurred in 79% and 84% of patients initiated and not initiated on ACE inhibitors or ARBs, respectively (HR associated with initiation, 0.79; 95% CI, 0.63–0.98). Respective HRs (95% CIs) for all-cause mortality and heart failure readmission were 0.81 (0.63–1.03) and 0.63 (0.47–0.85).

Conclusions: The findings from our study add new information to the body of cumulative evidence that suggest that renin-angiotensin system inhibitors may improve clinical outcomes in patients with HFrEF and advanced kidney disease. These hypothesis-generating findings need to be replicated in contemporary patients.

Keywords

Heart failure; renin-angiotensin system inhibitors; advanced kidney disease; mortality; hospitalization

Therapy with renin-angiotensin system (RAS) inhibitors improves clinical outcomes in patients with heart failure with reduced ejection fraction (HFrEF).[1] Because major randomized clinical trials of RAS inhibitors in HFrEF excluded those with advanced kidney disease, there is limited evidence about their efficacy and effectiveness in this population.[2] Several observational studies suggested potential clinical benefits of RAS inhibition in patients with heart failure and impaired kidney disease,[3–7] but less is known about their effectiveness in those with advanced kidney disease.[8] National heart failure guidelines recommend that RAS inhibitors be used with caution in patients with HFrEF with advanced

kidney disease,[1, 2] and these drugs remain underutilized in this high risk subset.[9, 10] In the current study, we examined the associations of angiotensin-converting enzyme (ACE) inhibitor or angiotensin-receptor blocker (ARB) use and clinical outcomes in patients with HFrEF and advanced kidney disease, defined as an estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2.

Methods

Data Source and Study Patients

We analyzed data from the Medicare-linked Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry, the details of which have been previously described.[11–13] Briefly, the OPTIMIZE-HF registry is based on an extensive web-based review of medical record of 48,612 hospitalizations due to heart failure between 2003 and 2004. Of the 25,345 unique patients discharged alive and linked to Medicare for outcomes data,[13] 10,625 had HFrEF, defined as left ventricular EF ≤40%.[14, 15] Of these, 1582 had advanced kidney disease, defined as eGFR <30 ml/min/1.73 m^2 (Figure 1, left panel).[2] We calculated eGFR using admission serum creatinine and a modified Modification of Diet in Renal Disease (MDRD) formula that excluded race.[16] For reading convenience, in the rest of the manuscript, we will use eGFR without mentioning the unit ml/min/1.73 m^2. To attenuate prevalent user bias, 753 patients receiving ACE inhibitors or ABRs prior to hospital admission were excluded to assemble inception cohorts eligible for initiation of new therapy with those drugs.[17] Of the 829 patients with advanced kidney disease (eGFR <30), 214 were initiated on ACE inhibitors or ARBs before hospital discharge (Figure 1, left panel). We then categorized the 9043 patients without advanced kidney disease to 2858 who had moderate to severely impaired kidney function (eGFR 30 to 44; Figure 1, center panel) and 6185 patients who had normal (eGFR ≥60) or mildly impaired (eGFR 45 to 59) kidney function (Figure 1, right panel).[2] We used eGFR 45 as a cutoff as values <45 have been shown to be prognostically important.[18, 19] The latter two cohorts without advanced kidney disease were used to examine the consistency of associations across the spectrum of kidney function.

Assembly of a Balanced Cohort

Using a non-parsimonious multivariable logistic regression model, we estimated propensity scores for initiation of ACE inhibitors or ARBs for each of the 829 patients with HFrEF and advanced kidney disease using 47 baseline characteristics as covariates (Figure 2).[20–23] Using matching algorithms previously described,[5, 6] we matched 194 (91% of 214) patients initiated on ACE inhibitors or ARBs with 194 not initiated on them, thus assembling a matched cohort of 388 patients (Figure 1, left panel). We assessed between-group balance for each of the 47 baseline characteristics by estimating their pre- and post-match absolute standardized differences (Figure 2, left panel). An absolute standardized difference value of 0% indicates no residual bias and bias associated with values <10% are considered inconsequential. We then replicated the above process to assemble two separate matched cohorts of 842 patients with moderate to severely impaired kidney function (Figure 1, center panel), and 1752 patients with normal or mildly impaired kidney function (Figure 1, right panel).

Outcomes Data

Our outcomes of interest in the study were all-cause mortality, HF readmission, and the combined endpoint of HF readmission or all-cause mortality. We limited the follow-up duration to 2 years considering the poor outcomes in patients with HFrEF and advanced kidney disease.[2] Data on outcome events and time to those events were obtained from Medicare data up to December 31, 2008.[13]

Statistical Analysis

Descriptive analyses comparing between-group baseline characteristics before and after propensity score matching were conducted using Pearson's Chi-square test and Student's t tests. Hazard ratios (HRs) and 95% confidence intervals (CIs) for 2-year outcomes associated with a discharge initiation of ACE inhibitors or ARBs were estimated in the matched cohort of 388 patients with HFrEF and advanced kidney disease using a Cox regression model. We repeated the analysis, adjusting for all baseline characteristics with a post-match absolute standardized difference value of ≥10%. For mortality outcomes, patients who survived were censored at study end and for the readmission outcomes, patients without the event of interest were censored at study end or death, whichever occurred first. We then repeated these analyses in the two other matched cohorts without advanced kidney disease. Kaplan-Meier survival plots were generated to compare the 2-year all-cause mortality across the three eGFR categories. Sensitivity analyses were conducted using Rosenbaum's approach to assess the impact of a potential unmeasured binary confounder on significant associations in the matched HFrEF and advanced kidney disease cohort.[24] All statistical tests were two-tailed with a p-value <0.05 considered significant. SPSS for Windows version 28 (IBM Corp., Armonk, NY) and SAS for Window version 8.2 (Cary, NC) were used for data analyses.

Results

Baseline Characteristics

The 388 matched patients with HFrEF and advanced kidney disease had a mean age (±SD) of 78 (±9) years, 52% were women and 10% were African American (Table 1). Before matching, patients initiated on ACE inhibitors or ARBs had a higher prevalence of women, had a lower mean ejection fraction and serum creatinine, and a higher proportion were discharged on beta-blockers (data not shown in Table 1). These and other clinically important baseline characteristics were balanced after matching (Table 1, Figure 2). Although none of the p values were <0.05, likely due to small sample size, depression had a post-match absolute standardized difference value of 19%, and five others had values between 10% and 12% (Figure 2, left panel). Descriptive data and absolute standardized difference (all <10%) for the two cohorts without advanced kidney disease are displayed in Table 1, and Figure 2, center and right panels.

Combined Endpoint

During 2 years of post-discharge follow-up, the combined endpoint of heart failure readmission or all-cause mortality occurred in 79% and 84% of the patients with HFrEF and

advanced kidney disease who were initiated and not initiated on ACE inhibitors or ARBs prior to hospital discharge, respectively (HR associated with initiation, 0.79; 95% CI, 0.63–0.98; Table 2, left panel). This association remained unchanged when adjusted for the 6 baseline characteristics with ≥10% post-match absolute standardized differences (HR, 0.79; 95% CI, 0.63–0.98; Table 2, footnote). Results of sensitivity analysis suggest that a binary unmeasured confounder that is a near-perfect predictor of 2-year combined endpoint could explain away this association if it increased the odds of ACE inhibitor or ARB initiation by 2.4% (Table 2, footnote). HR (95% CI) for the 2-year combined endpoint 0.75 (0.65–0.88) in patients with moderate to severely impaired kidney function (Table 2, center panel) and 0.98 (0.87–1.10) in those with normal to mildly impaired kidney function (Table 2, right panel). These associations were similarly observed during 30-day and 12-month follow-up (Table 2).

All-Cause Mortality

During 2 years of follow-up, all-cause mortality occurred in 61% and 69% of the patients with HFrEF and advanced kidney disease initiated and not initiated on ACE inhibitors or ARBs, respectively (HR associated with initiation, 0.81; 95% CI, 0.63–1.03; Table 2, left panel; Figure 3, left panel). Respective HRs (95% CIs) were 0.77 (0.64–0.93) in patients with moderate to severely impaired kidney function (Table 2, center panel; Figure 3, center panel) and 0.81 (0.70–0.93) in those with normal to mildly impaired kidney function (Table 2, right panel; Figure 3, right panel). Associations with 30-day and 12-month all-cause mortality are displayed in Table 2.

Heart Failure Readmission

During 2 years of follow-up, HF readmission occurred in 39% and 52% of the patients with HFrEF and advanced kidney disease initiated and not initiated on ACE inhibitors or ARBs, respectively (HR associated with initiation, 0.63; 95% CI, 0.47–0.85; Table 2, left panel). Respective HRs (95% CIs) were 0.74 (0.60–0.90) in those with moderate to severely impaired kidney function (Table 2, center panel) and 1.08 (0.93–1.25) in those with normal to mildly impaired kidney function (Table 2, right panel). Associations with 30-day and 12-month HF readmission are displayed in Table 2. RAS inhibitor use had no association with all-cause readmission.

Discussion

The findings from our study demonstrate that in hospitalized older patients with HFrEF and advanced kidney disease not receiving therapy with ACE inhibitors or ARBs before hospital admission, the initiation of these drugs prior to hospital discharge was associated with a significantly lower risk of the composite endpoint of heart failure readmission or all-cause mortality that became apparent during the first 30 days of follow-up and continued for up to 2 years. Although the associated lower risk of mortality did not reach statistical significance, likely due to inadequate statistical power, the associated risk of heart failure readmission was significantly lower. To the best of our knowledge, this is the first study to use propensity score-matching and a new-user design to provide evidence of associated improved clinical

outcomes including hospitalization in patients with HFrEF and advanced kidney disease initiated on RAS inhibitors.

Because patients with moderate to severely impaired kidney function were excluded from randomized controlled trials of ACE inhibitors and ARBs in HFrEF, the evidence of their efficacy in these patients has been considered weak, especially for those with advanced kidney disease.[2] In the Studies of Left Ventricular Dysfunction (SOLVD) Treatment trial, the first major randomized trial of a RAS inhibitor in patients with chronic HFrEF, those with a serum creatinine of >2 mg/dL were excluded (41% had eGFR <60, and 11% had eGFR <45).[25, 26] This would exclude typical heart failure patients such as a 65-year-old female patient with a serum creatinine of 2.1 mg/dL (eGFR, 26). However, the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) Alternative and Added trials enrolled patients with HFrEF with serum creatinine up to 3.0 mg/dL,[27–29] which would include a 65-year-old male patient with a serum creatinine of 2.9 mg/dL (eGFR, 23). The inclusion of patients with more advanced kidney disease in CHARM and other later trials, and findings from subgroup analysis of the SOLVD trial,[26] and other observational studies,[3–6] suggest a potential clinical benefit of RAS inhibition in patients with HFrEF with impaired kidney function. However, patients with eGFR <30 continue to be excluded from the randomized trials of RAS inhibitors in HFrEF,[30] and RAS inhibitors continue to be underutilized in patients with HFrEF with eGFR <30.[9, 10]

Despite a perceived concern of renal harm from RAS inhibitors, these drugs have been shown to improve renal outcomes in patients with renal insufficiency.[31–33] Although RAS inhibitors are more likely to increase serum creatinine and/or potassium in patients with heart failure than without,[34] these increases are often minimal and considered natural extensions of their hemodynamic and neurohormonal effects.[26, 35] In the SOLVD trial, among patients randomized to enalapril, the rise of serum creatinine during the first 12 months was greater in those with eGFR ≥60 than <60 (by 0.09 vs. 0.04 mg/dL, respectively; p=0.003).[26] When compared with the 12-month rise in serum creatinine in the placebo group, the rise in the enalapril group were by 0.04 and 0.06 mg/dL for those with eGFR ≥60 and <60, respectively.[26] Although similar data is not available in patients with advanced kidney disease, the consistency of the RAS inhibitor-associated lower mortality across the spectrum of kidney function in our study suggests that baseline kidney function or a potential worsening of kidney function during therapy did not confound the association in those with advanced kidney disease.

Although we had no data on baseline serum potassium, the between-group imbalance in baseline serum potassium would be expected to be minimum considering that major predictors of hyperkalemia, such as eGFR, prevalence of diabetes mellitus and use of loop diuretics and mineralocorticoid receptor antagonists, were balanced in our study. In the SOLVD trial, among patients randomized to enalapril, the rise of serum potassium during the first 12 months was similar in those with eGFR ≥60 and <60 (by 0.18 vs. 0.20 mEq/L, respectively; p=0.632).[26] When compared with the 12-month rise in serum potassium in the placebo group, the rise in the enalapril group were by 0.22 and 0.26 mEq/L for those with eGFR ≥60 and <60, respectively.[26]

In patients with eGFR <30, we observed that the RAS inhibition-associated risk reduction for 2-year HF readmission (37%) was greater than it was for death (19%), which is consistent with the findings from the SOLVD trial.[25] However, unlike in the SOLVD trial, there was no association with heart failure readmission in patients with eGFR ≥45 despite their kidney function being similar to that of SOLVD participants.[25, 26] While this is intriguing, the effect of RAS inhibitors has been known to be more pronounced in those with impaired kidney function.[7, 36] In the Heart Outcomes and Prevention Evaluation (HOPE) trial that excluded patients with heart failure, ramipril, an ACE inhibitor, significantly reduced the risks of death and heart failure hospitalization in 980 patients with renal insufficiency, but not in 8307 patients without.[36] One potential explanation is the lower baseline risk (in the non-RAS inhibitor group) in patients with better kidney function (eGFR >30). For example, these patients had a 30-day heart failure readmission rate of 10%, while it was 19% for those with eGFR <30, likely attributable in part to congestion and fluid retention that occur with advanced kidney disease.[37] Diuretic effects are known to be more pronounced in patients with greater congestion.[39–41] It is possible that the RAS inhibitor-associated reduction in heart failure hospitalization observed in our study was in part mediated by the natriuretic properties of these drugs.[38]

Prior studies of RAS inhibitors in HFrEF with advanced kidney disease are mostly limited to subgroup analyses of RCTs and registries.[2] In one study, in a propensity score-matched cohort of HFrEF with advanced kidney disease, RAS inhibitor use was associated with a lower risk of death.[8] Our study is distinguished by our use of a new user design to avoid prevalent user bias and the examination of non-death outcomes.[17, 42] Furthermore, we examined the association of RAS inhibitors with outcomes in two separately assembled propensity score-matched balanced cohorts of patients with eGFR 30–44 and ≥45, which allowed us to examine consistency of the observed associations across the kidney function spectrum within the same OPTIMIZE-HF population. The findings from the current study provide evidence to support the use of RAS inhibitors in HFrEF with advanced kidney disease. However, the risk of RAS inhibitor-associated hyperkalemia is higher in these patients and serum potassium needs to be monitored. Emerging evidence suggests that newer potassium binders are effective in reducing the risk of hyperkalemia in patients with kidney disease treated with RAS inhibitors.[43, 44] Future studies need to examine the effectiveness of these drugs in improving clinical outcomes.[45]

Although it would be ideal to test and confirm the hypothesis-generating findings of our study in adequately powered randomized trials, it is unlikely to occur due to ethical and financial constraints. It may be unethical to recruit symptomatic patients with heart failure and advanced kidney disease into long-term randomized placebo-controlled trials considering the collective evidence of the efficacy of RAS inhibitor in heart failure from multiple trials, and evidence of effectiveness from subsequent observational studies, including in patients with heart failure with advanced kidney disease.[7] Findings of the current study, taken together with the collective randomized and observational evidence, now suggest that the clinical benefits of RAS inhibitors may be extended to this high-risk subset of the HFrEF population with advanced kidney disease. Future studies need to replicate these findings in contemporary HFrEF populations with advanced kidney disease receiving mineralocorticoid receptor antagonists.[46]

Limitations

As in any observational study, bias due to unmeasured confounders is possible. We had no data on the dosages of RAS inhibitors used. Although dose of RAS inhibitor is less relevant in patients with HFrEF,[47, 48] below-target doses have been shown to be more effective in HFrEF with CKD.[26] We had no data on incident end-stage kidney disease. Lack of data on serum potassium levels at baseline or during follow-up is another limitation. Finally, results of our study based on fee-for-service Medicare beneficiaries may limit generalizability to other populations.

Conclusions

Among hospitalized older patients with HFrEF and advanced kidney disease, the initiation of therapy with ACE inhibitors or ARBs was associated with significantly improved clinical outcomes, which is similar to those observed in patients without advanced kidney disease. These findings add new information to the body of cumulative evidence that suggest that the clinical benefit of RAS inhibition in HFrEF may be extended to those with advanced kidney disease. These hypothesis-generating findings need to be replicated in larger and more contemporary cohorts of HFrEF and advanced kidney disease.

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Clinical Significance

Less is known whether renin-angiotensin system inhibitors would improve clinical outcomes in patients with heart failure with reduced ejection fraction with advanced kidney disease.

Findings from our study suggest that initiation of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers before hospital discharge is associated with improved clinical outcomes in HFrEF patients with advanced kidney disease.

Clinical benefits are notable across the spectrum of renal impairment.

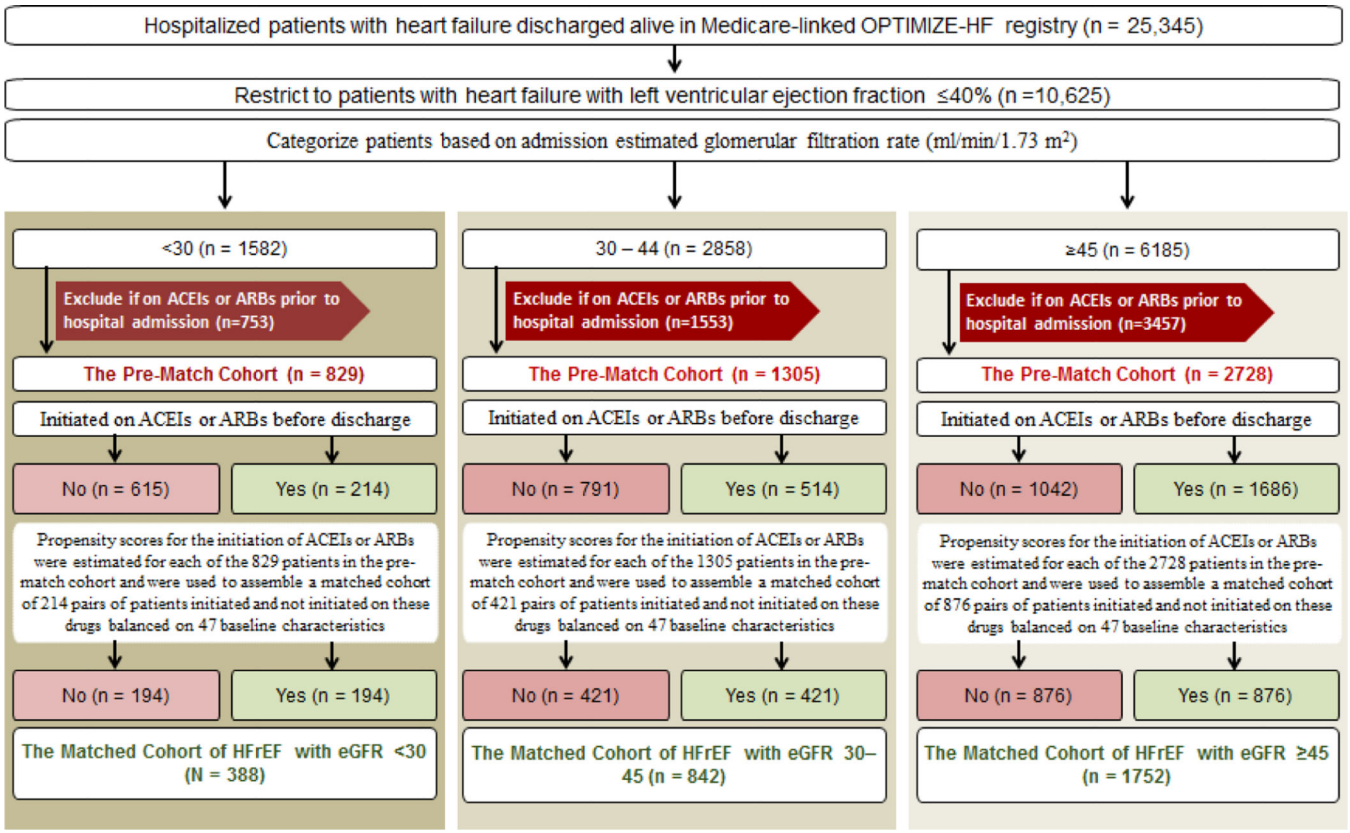

Figure 1.

Flow chart displaying the assembly of a propensity score-matched cohort of patients with HFrEF (≤40%) and advanced kidney disease (eGFR <30) who were not receiving ACE inhibitors or ARBs (left panel). Corresponding data on those with moderate to severely impaired kidney function (eGFR 30–45) and normal to mildly impaired kidney function (eGFR ≥45) are presented in the middle and right panels, respectively. The propensity score model for all three cohorts are based on 47 baseline characteristics, displayed in Figure 2. ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; EF = ejection fraction; HF = heart failure; HFrEF = heart failure and reduced ejection fraction; eGFR = estimated glomerular filtration rate (ml/min/1.73 m^2); OPTIMIZE-HF = Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure

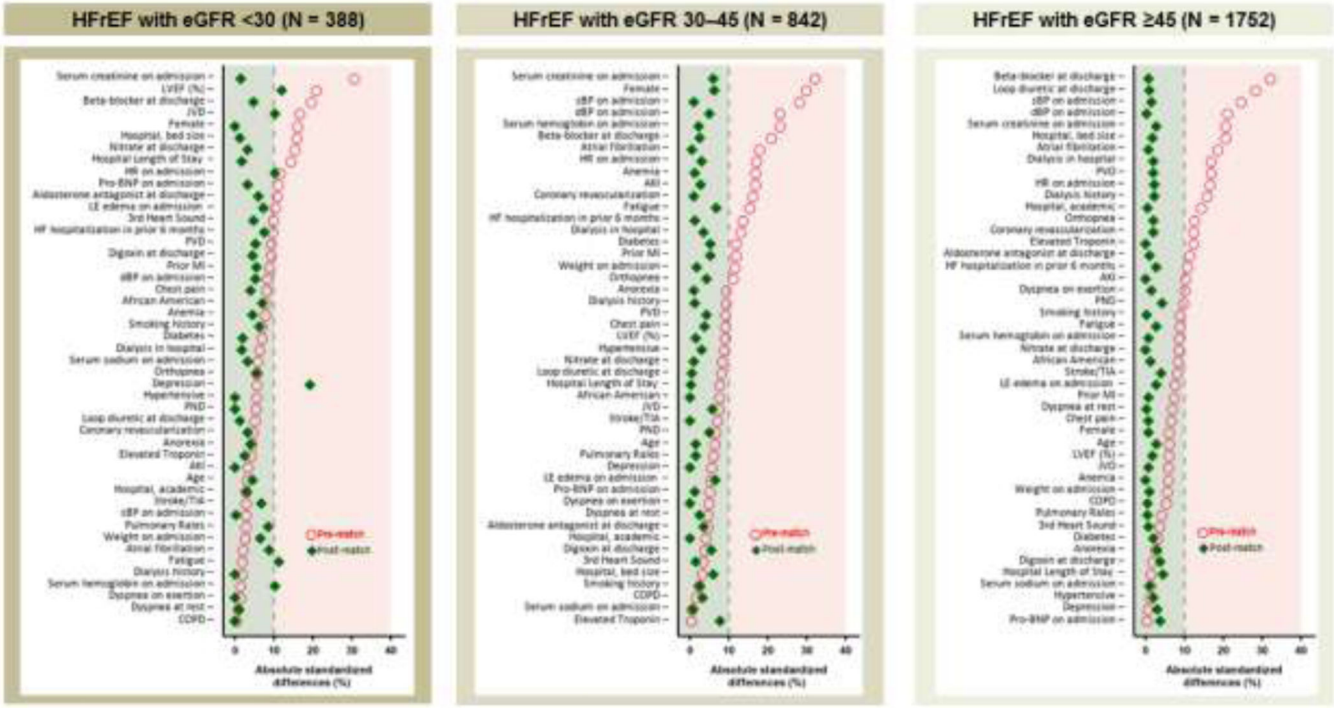

Figure 2.

Love plots displaying absolute standardized differences of 47 baseline characteristics in patients initiated and not initiated on ACE inhibitors or ARBs before discharge in patients with HFrEF (≤40%) and advanced kidney disease (eGFR <30), before and after propensity score matching (left panel). Corresponding data on those with moderate to severely impaired kidney function (eGFR 30–45) and normal to mildly impaired kidney function (eGFR ≥45) are presented in the middle and right panels, respectively. Absolute standardized differences values <10% suggest inconsequential confounding and a 0% values suggest no residual confounding. ACE = angiotensin-converting enzyme; AKI = acute kidney injury; ARB = angiotensin receptor blocker; BNP = B-Type natriuretic peptide; COPD = chronic obstructive pulmonary disease; dBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate (ml/min/1.73 m^2); HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HR = heart rate; JVP = jugular venous pressure; LE = lower extremity; LVEF = left ventricular ejection fraction; sBP = systolic blood pressure; PND = paroxysmal nocturnal dyspnea; PVD = peripheral vascular disease; TIA = transient ischemic attack.

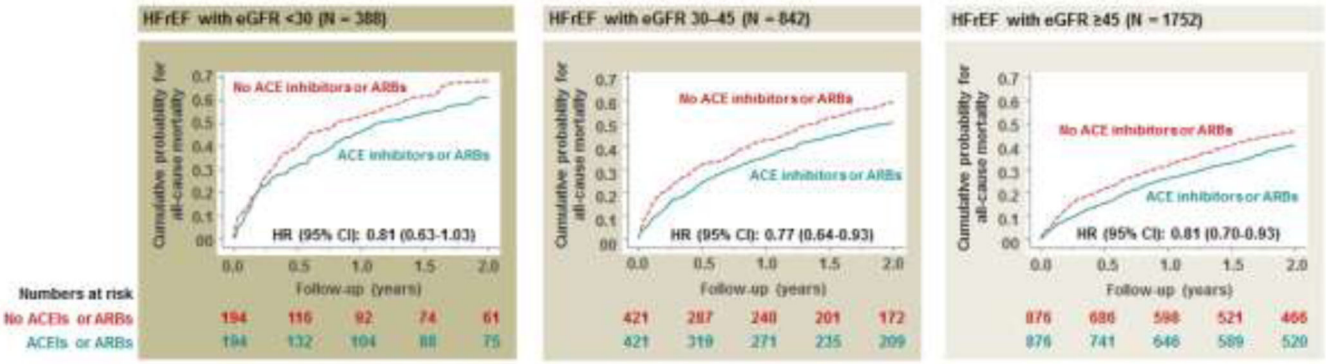

Figure 3.

Kaplan Meier plots displaying all-cause mortality among patients initiated and not initiated on ACE inhibitors or ARBs before discharge in a propensity score-matched cohort of patients with HFrEF and advanced kidney disease (eGFR <30; left panel), who were not receiving these drugs before hospital admission. Corresponding data on those with moderate to severely impaired kidney function (eGFR 30–45) and normal to mildly impaired kidney function (eGFR ≥45) are presented in the middle and right panels, respectively. ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate, presented as ml/min/1.73 m^2; HFrEF = heart failure with reduced ejection fraction (≤40%).

Table 1.

Baseline characteristics by discharge initiation of ACEI or ARB in a propensity score-matched cohort of patients with HFrEF and advanced kidney disease (eGFR <30; left panel). Corresponding data on those with moderate to severely impaired kidney function (eGFR 30–45) and normal to mildly impaired kidney function (eGFR ≥45) are presented in the middle and right panels, respectively.

	eGFR <30 (N = 388)		**eGFR 30 – 45 (N = 842)**		**eGFR ≥45 (N = 1752)**	
	ACEI or ARB initiated		**ACEI or ARB initiated**		**ACEI or ARB initiated**	
	No (n=194)	**Yes (n=194)**	**No (n=421)**	**Yes (n=421)**	**No (n=876)**	**Yes (n=876)**
Age (years)	78 (±9)	78 (±10)	79 (±9)	79 (±10)	75 (±12)	75 (±11)
Female	101 (52%)	101 (52%)	208 (49%)	195 (46%)	342 (39%)	345 (39%)
African American	21 (11%)	17 (9%)	38 (9%)	38 (9%)	124 (14%)	128 (15%)
Ejection fraction (%)	27 (±8)	26 (±8)	27 (±8)	27 (±8)	28 (±8)	27 (±9)
Past medical history						
Smoking history	26 (13%)	22 (11%)	39 (9%)	42 (10%)	144 (16%)	145 (17%)
HF hospitalization in prior 6 months	47 (24%)	41 (21%)	76 (18%)	78 (19%)	114 (13%)	122 (14%)
Hypertension	132 (68%)	132 (68%)	265 (63%)	271 (64%)	522 (60%)	513 (59%)
Myocardial infarction	68 (35%)	63 (32%)	120 (29%)	130 (31%)	231 (26%)	234 (27%)
Coronary revascularization	74 (38%)	77 (40%)	162 (38%)	160 (38%)	293 (33%)	285 (33%)
Diabetes mellitus	90 (46%)	88 (45%)	164 (39%)	175 (42%)	292 (33%)	300 (34%)
Stroke / TIA	36 (19%)	31 (16%)	75 (18%)	75 (18%)	130 (15%)	143 (16%)
Peripheral arterial disease	37 (19%)	33 (17%)	82 (19%)	75 (18%)	129 (15%)	123 (14%)
Atrial fibrillation	58 (30%)	66 (34%)	131 (31%)	132 (31%)	288 (33%)	285 (33%)
Acute kidney injury	10 (5%)	10 (5%)	13 (3%)	11 (3%)	17 (2%)	17 (2%)
Dialysis history	8 (4%)	8 (4%)	14 (3%)	13 (3%)	20 (2%)	23 (3%)
COPD	49 (25%)	49 (25%)	106 (25%)	112 (27%)	236 (27%)	238 (27%)
Anemia	57 (29%)	53 (27%)	78 (19%)	76 (18%)	105 (12%)	105 (12%)
Depression	34 (18%)	21 (11%)	38 (9%)	38 (9%)	92 (11%)	84 (10%)
Admission symptoms and signs						
Dyspnea on exertion	111 (57%)	111 (57%)	267 (63%)	267 (63%)	537 (61%)	531 (61%)
Orthopnea	61 (31%)	56 (29%)	103 (24%)	111 (26%)	232 (26%)	224 (26%)
Paroxysmal nocturnal dyspnea	29 (15%)	29 (15%)	53 (13%)	60 (14%)	140 (16%)	127 (14%)
Dyspnea at rest	92 (47%)	91 (47%)	176 (42%)	181 (43%)	373 (43%)	374 (43%)
Chest pain	33 (17%)	36 (19%)	80 (19%)	74 (18%)	193 (22%)	190 (22%)
Fatigue	39 (20%)	48 (25%)	88 (21%)	100 (24%)	211 (24%)	201 (23%)
Anorexia	13 (7%)	15 (8%)	25 (6%)	26 (6%)	44 (5%)	50 (6%)
Jugular venous pressure elevated	53 (27%)	62 (32%)	126 (30%)	137 (33%)	257 (29%)	254 (29%)
Third heart Sound	23 (12%)	26 (13%)	42 (10%)	44 (10%)	87 (10%)	89 (10%)
Pulmonary rales	115 (59%)	123 (63%)	280 (67%)	277 (66%)	554 (63%)	556 (63%)
Lower extremity edema	111 (57%)	118 (61%)	256 (61%)	269 (64%)	512 (58%)	524 (60%)
Admission vital signs						

	eGFR <30 (N = 388)		eGFR 30 – 45 (N = 842)		eGFR ≥45 (N = 1752)	
	ACEI or ARB initiated		ACEI or ARB initiated		ACEI or ARB initiated	
	No (n=194)	Yes (n=194)	No (n=421)	Yes (n=421)	No (n=876)	Yes (n=876)
Weight (kg)	75 (±18)	76 (±18)	76 (±19)	76 (±21)	77 (±20)	78 (±21)
Heart rate (bpm)	83 (±17)	85 (±20)	87 (±22)	86 (±20)	90 (±22)	90 (±21)
Systolic blood pressure (mmHg)	132 (±27)	132 (±27)	137 (±29)	137 (±27)	136 (±28)	136 (±26)
Diastolic blood pressure (mmHg)	73 (±14)	72 (±16)	74 (±15)	75 (±15)	77 (±16)	77 (±15)
Admission laboratory findings						
Hemoglobin (g/dL)	11.5 (±2.0)	11.8 (±2.1)	12.2 (±2.0)	12.1 (±2.0)	12.7 (±2.1)	12.6 (±2.3)
Serum creatinine (mg/dL)	2.5 (±0.5)	2.5 (±0.6)	1.7 (±0.3)	1.7 (±0.3)	1.1 (±0.3)	1.1 (±0.3)
Serum sodium (mEq/L)	136 (±13)	136 (±14)	136 (±14)	136 (±13)	136 (±12)	136 (±12)
Serum pro-BNP (pg/ml)	1951 (±2049)	1896 (±1359)	1637 (±1155)	1624 (±1133)	1358 (±1085)	1319 (±945)
Serum troponin, elevated	42 (22%)	44 (23%)	111 (26%)	97 (23%)	158 (18%)	158 (18%)
Dialysis in hospital	16 (8%)	17 (9%)	21 (5%)	18 (4%)	28 (3%)	31 (4%)
Discharge medications						
Beta-blocker at discharge	140 (72%)	144 (74%)	291 (69%)	296 (70%)	553 (63%)	556 (63%)
Aldosterone antagonist at discharge	13 (7%)	16 (8%)	57 (14%)	62 (15%)	132 (15%)	135 (15%)
Loop diuretic at discharge	154 (79%)	153 (79%)	343 (81%)	342 (81%)	659 (75%)	663 (76%)
Digoxin at discharge	54 (28%)	58 (30%)	134 (32%)	145 (34%)	327 (37%)	343 (39%)
Nitrate at discharge	60 (31%)	63 (32%)	139 (33%)	137 (33%)	205 (23%)	205 (23%)
Hospital length of stay (days)	7.3 (±8.9)	7.5 (±5.2)	6.5 (±5.9)	6.5 (±6.3)	5.6 (±5.3)	5.8 (±4.6)
Hospital, bed size	422 (±260)	425 (±237)	419 (±255)	434 (±268)	386 (±209)	390 (±217)
Hospital, academic	85 (44%)	88 (45%)	201 (48%)	201 (48%)	379 (43%)	381 (43%)

Values are mean ±SD or n (%). ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BNP = B-Type natriuretic peptide; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate, presented as ml/min/1.73 m^2; HF = heart failure; HFrEF = heart failure with reduced ejection fraction (≤40%); TIA = transient ischemic attack

Table 2.

Outcomes by discharge initiation of ACEI or ARB in a propensity score-matched cohort of patients with HFrEF and advanced kidney disease (eGFR <30; left panel). Corresponding data on those with moderate to severely impaired kidney function (eGFR 30–45) and normal to mildly impaired kidney function (eGFR ≥45) are presented in the middle and right panels, respectively.

	eGFR <30 ml/min/1.73 m2 (N = 388)			**eGFR 30 – 44 ml/min/1.73 m^2 (N = 842)**			**eGFR ≥45 ml/min/1.73 m^2 (N = 1752)**		
	ACEIs or ARBs initiated		**Hazard ratio (95% CI)**	**ACEIs or ARBs initiated**		**Hazard ratio (95% CI)**	**ACEIs or ARBs initiated**		**Hazard ratio (95% CI)**
	No (n=194)	**Yes (n=194)**		**No (n=421)**	**Yes (n=421)**		**No (n=876)**	**Yes (n=876)**	
HF readmission or all-cause mortality									
30 days	57 (29%)	35 (18%)	0.56 (0.37–0.85)	85 (20%)	62 (15%)	0.72 (0.52–0.99)	129 (15%)	103 (12%)	0.78 (0.60–1.01)
1 year	139 (72%)	127 (66%)	0.78 (0.61–0.98)	284 (68%)	248 (59%)	0.77 (0.65–0.91)	451 (52%)	435 (50%)	0.92 (0.81–1.05)
2 years	163 (84%)	154 (79%)	0.79 (0.63–0.98) *,§	336 (80%)	295 (70%)	0.75 (0.65–0.88)	568 (65%)	580 (66%)	0.98 (0.87–1.10)
All-cause mortality									
30 days	23 (12%)	16 (8%)	0.67 (0.36–1.27)	48 (11%)	25 (6%)	0.51 (0.31–0.83)	45 (5%)	34 (4%)	0.75 (0.48–1.17)
1 year	102 (53%)	90 (46%)	0.82 (0.62–1.08)	181 (43%)	150 (36%)	0.77 (0.62–0.95)	278 (32%)	230 (26%)	0.78 (0.66–0.93)
2 years	133 (69%)	119 (61%)	0.81 (0.63–1.03) ≠,§	249 (59%)	212 (50%)	0.77 (0.64–0.93)	410 (47%)	356 (41%)	0.81 (0.70–0.93)
HF readmission									
30 days	36 (19%)	20 (10%)	0.51 (0.29–0.87)	42 (10%)	40 (10%)	0.93 (0.61–1.44)	88 (10%)	71 (8%)	0.78 (0.57–1.07)
1 year	83 (43%)	67 (35%)	0.68 (0.50–0.94)	179 (43%)	151 (36%)	0.74 (0.60–0.92)	277 (32%)	300 (34%)	1.04 (0.88–1.22)
2 years	100 (52%)	76 (39%)	0.63 (0.47–0.85) †,§	206 (49%)	177 (42%)	0.74 (0.60–0.90)	340 (39%)	382 (44%)	1.08 (0.93–1.25)

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BNP = B-Type natriuretic peptide; COPD = chronic obstructive pulmonary disease; eGFR = and estimated glomerular filtration rate, presented as ml/min/1.73 m^2; HF = heart failure; HFrEF = heart failure with reduced ejection fraction (≤40%)

Results of the formal sensitivity analyses for the 2-year associations in the matched cohort with HFrEF with eGFR <30 are presented below (performed only for associations that were significant):

[*] For the combined endpoint of 2-year HF readmission or death, in 96% (187/194) of the matched pairs, we were able to determine which patients within a pair clearly had longer time to HF readmission or death during 2 years of follow-up, and in 58% (108/187) of those pairs, these patients belonged to the group initiated on ACEIs or ARBs before discharge (sign-score test P=0.034). A hidden confounder that is a near-perfect predictor of this combined endpoint could explain away this association if it could increase the odds of ACEI or ARB initiation by 2.38%.

[†] For 2-year HF readmission, in 53% (103/194) of the matched pairs, we were able to determine which patients within a pair clearly had longer time to HF readmission during 2 years of follow-up, and in 61% (63/103) of those pairs, these patients belonged to the group initiated on ACEIs or ARBs before discharge (sign-score test P=0.023). A hidden confounder that is a near-perfect predictor of this combined endpoint could explain away this association if it could increase the odds of ACEI or ARB initiation by 6.24%.

[‡] For 2-year all-cause mortality, in 87% (168/194) of the matched pairs, we were able to determine which patients within a pair clearly had longer survival during 2 years of follow-up, and in 57% (96/168) of those pairs, these patients belonged to the group initiated on ACEIs or ARBs before discharge (sign-score test P=0.064). However, since this association was not significant, there was no formal sensitivity analysis for this outcome.

[§] The 2-year associations remained unchanged when adjusted for the 6 baseline characteristics with ≥10% post-match absolute standardized differences (fatigue, depression, pulse, jugular venous pressure elevation, hemoglobin, and ejection fraction) with HRs (95% CIs) of 0.79 (0.63–0.98), 0.80 (0.62–1.02) and 0.65 (0.48–0.88), respectively for the combined endpoint, death and HF readmission.