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Treatment Effectiveness in Heart Failure with Comorbidity: Lung Disease and Kidney Disease

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Abstract

OBJECTIVES—Recognizing the challenges of therapeutic decision-making for heart failure (HF) patients with comorbid conditions, our study objectives were to assess: (1) the clinical effectiveness of beta-blocker therapy in patients with HF and chronic lung disease; and (2) the clinical effectiveness of ACE inhibitors/angiotensin II receptor blockers (ARBs) in patients with HF and chronic kidney disease.

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Conflicts of Interest:

The other authors report no conflicts.

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DESIGN—Retrospective cohort study.

SETTING—Large community-based cohorts of HF patients.

PARTICIPANTS—Patients with HF with reduced ejection fraction (HFrEF) or HF with preserved ejection fraction (HFpEF).

METHODS—We undertook separate new-user cohort studies to assess the effectiveness of: (1) beta-blocker therapy in HF and chronic lung disease; and (2) ACE inhibitors/angiotensin II receptor blockers (ARBs) in HF and chronic kidney disease. For the HF-chronic lung disease dyad group, we included patients who had a chronic lung disease diagnosis (ICD-9 codes 490-496, 518). For the HF-chronic kidney disease dyad group, we included patients who had an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m². The clinical outcomes of interest were death from any cause, hospitalization for HF, and hospitalization from any cause. We fitted pooled logistic marginal structural models (MSM) using inverse probability weighting, stratified by HF type.

RESULTS—Among HFrEF patients with chronic lung disease, beta-blocker therapy was protective for death (RR 0.58, 95% confidence interval (CI) 0.44–0.77) and hospitalization for HF (RR 0.78, 95% CI 0.60–1.00). Among those with HFpEF, no statistically significant associations of beta-blocker therapy use with any of the outcomes were observed. We found ACE inhibitor/ARB use to be protective for all three outcomes of interest for patients with HFrEF including death from any cause, hospitalization for HF, and hospitalization from any cause (RR 0.60, 95% CI 0.40–0.91; RR 0.43, 95% CI 0.28–0.67; and RR 0.63, 95% CI 0.45–0.89, respectively), as well as for patients with HFpEF (RR 0.52, 95% CI 0.33–0.81; RR 0.35, 95% CI 0.18–0.68; and RR 0.67, 95% CI 0.47–0.95, respectively).

CONCLUSION—Large observational studies may allow for the identification of important subgroups of the HF population that might benefit from existing treatment approaches. Our findings may also better inform the design of more definitive future observational studies and randomized trials.

Keywords

multimorbidity; heart failure; comorbidity; lung disease; kidney disease

INTRODUCTION

The presence of comorbidities in patients with heart failure (HF) can pose diagnostic and treatment challenges substantially increasing the complexity of caring for these patients.¹ As practitioners face managing not just a single condition but multiple conditions simultaneously,² caution is required in applying clinical guidelines to the care of patients with comorbidities, especially older patients, as this could result in undesirable outcomes, including adverse interactions between drugs and diseases.³ Multimorbidity greatly increases the risk of hospitalization and death among HF patients.^{4,5,6,7} Efforts to reduce these risks are particularly challenging given the limited data available to guide clinical practice.

Chronic lung disease and chronic kidney disease are frequently present in older HF patients,⁸ and these conditions are among the comorbid conditions that confer the highest excess mortality and morbidity risks.⁹ Certain HF-related treatments raise special concerns for HF patients with concomitant chronic lung disease or chronic kidney disease. For example, beta-blockers can aggravate bronchospastic symptoms in patients with reactive airway disease, and it has been recommended to use these agents cautiously in such patients.¹ Chronic kidney disease frequently complicates HF due to poor renal perfusion, pre-existing intrinsic renal disease, and as a result of the effects of medications used to treat HF. Renal function may worsen with use of ACE inhibitors in patients with HF, although the changes are generally reversible.¹⁰ While ACE inhibitors are the first choice for inhibition of the renin-angiotensin system in HF with reduced left ventricular ejection fraction, angiotensin II receptor blockers (ARBs) are considered a reasonable alternative as they have a similar adverse effect profile to ACE inhibitors.¹

In the present study, we examined a set of questions relating to the treatment of HF in the setting of two very common comorbidities. Our study objectives were to assess: (1) the clinical effectiveness of beta-blocker therapy in patients with HF and chronic lung disease; and (2) the clinical effectiveness of ACE inhibitors/ARBs in patients with HF and chronic kidney disease. In each case, we sought to separately examine the effects of these therapies in patients with HF with reduced ejection fraction (HFrEF) or HF with preserved ejection fraction (HFpEF) treated in representative community-based populations.

METHODS

Setting

The source population included members from four participating health plans within the Cardiovascular Research Network (CVRN) from 2005 through 2008.¹¹ Sites included Kaiser Permanente Northern California, Kaiser Permanente Colorado, Kaiser Permanente Northwest, and Fallon Health. Institutional review boards at participating sites approved the study and waiver of consent was obtained due to the nature of the study.

Participants

We identified individuals with diagnosed HF based on either having been hospitalized with a primary discharge diagnosis of HF and/or having 3 ambulatory visits coded for HF with at least one visit being with a cardiologist between January 2005 and December 2008, employing *International Classification of Diseases, 9th Edition* (ICD-9) codes. Previous studies have shown a positive predictive value of >95% for admissions with a primary discharge diagnosis of HF based on these codes when compared against chart review and Framingham clinical criteria.^{12,13,14}

We ascertained information on quantitative and/or qualitative assessments of left ventricular systolic function from the results of echocardiograms, radionuclide scintigraphy, other nuclear imaging modalities, and left ventriculography test results available from site-specific databases complemented by manual chart review. We defined preserved ejection fraction as either a reported left ventricular ejection fraction $\geq$ 50% and/or based on a physician's

qualitative assessment of preserved or normal systolic function.¹⁵ Reduced ejection fraction was defined either by a reported left ventricular ejection fraction $\geq 40\%$ and/or based on a physician's qualitative assessment of moderate, moderate to severe, or severe systolic dysfunction.

We identified two HF subgroups of special interest: (1) patients who had HF and chronic lung disease and (2) patients who had HF and chronic kidney disease.

For the HF-chronic lung disease dyad group, we included patients who had a chronic lung disease diagnosis at or prior to the date relating to the inclusion of the patient in the HF study population (ICD-9 codes 490-496, 518). We excluded patients with history of organ transplant at baseline as well as those who received any beta-blocker therapy within up to 5 years prior to the index date, since we were specifically interested in the clinical effectiveness of beta-blocker therapy in patients with HF and chronic lung disease who were newly initiated on therapy. To ensure an adequate baseline period of time to characterize the patients, we excluded patients with less than 12 months of continuous health plan membership and pharmacy drug benefit before the index date.

For the HF-chronic kidney disease dyad group, we included patients who had an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m² according to laboratory results available on or before the date relating to the inclusion of the patient in the HF study population. We excluded patients with a history of organ transplant or dialysis at study entry, defined as up to 5 years before and including the index date. We also excluded patients with estimated glomerular filtration rates (eGFR) ≥ 60 ml/min/1.73m² at baseline and during follow-up using the CKD-EPI equation based on outpatient, non-emergency department serum creatinine measures,¹⁶ missing eGFR values at baseline, or missing blood hemoglobin measurements at baseline. Similar to the approach described previously for outcomes associated with beta-blockers in the dyad of HF and chronic lung disease, we excluded patients who received any ACE inhibitor or ARB therapy within up to 5 years prior to the index date to focus on the clinical effectiveness of ACE inhibitor/ARB therapy in patients with HF and chronic kidney disease who were newly initiated on therapy. To ensure an adequate baseline period of time to characterize the patients, we excluded patients with less than 12 months of continuous health plan membership and pharmacy drug benefit before the index date.

Study design: exposures, follow-up, and outcomes

For each corresponding dyad, we ascertained use of beta-blocker or ACE inhibitor/ARB therapy from filled outpatient prescriptions from pharmacy database. We employed a "new user" design to eliminate prevalent user bias, by restricting the analysis to persons under observation at the start of treatment.¹⁷ We characterized time-varying exposure to therapy using previously validated methods based on estimated days supply information per dispensed prescription and refill patterns found in health plan pharmacy databases.¹⁸ Briefly, for any two consecutive prescriptions, we examined the time between the projected end date of the first prescription and the date of the next filled prescription. Since dose adjustment is not uncommon, we allowed a "grace period" of 30 days between prescriptions. If the time between the projected end date of the first prescription and the fill date of the next

prescription was 30 days, we considered that individual to be continuously receiving the therapy of interest. If the refill interval was >30 days, we considered the individual off therapy starting the day after the projected end date of the first prescription until the date of next filled prescription, if any. If a refill occurred earlier than the predicted end of days' supply, then any overlap in days' supply was not added to the end of the next prescription.

Follow-up occurred from the index date through December 31, 2008 for a maximum of 4 years. Median follow-up was 1.6 years (interquartile range [IQR], 0.6–2.8) within the HF-chronic lung disease dyad group, and 1.1 years (IQR, 0.3–2.2) within the HF-chronic kidney disease dyad group. The clinical outcomes of interest were death from any cause, hospitalization for HF, and hospitalization from any cause. Subjects were censored if they disenrolled from the health plan, received an organ transplant, initiated chronic dialysis, or reached the end of study follow-up. Deaths were identified from hospital and billing claims databases, administrative health plan databases, state death certificate registries, and Social Security Administration files as available at each site. These approaches have yielded >97% vital status information in prior studies.^{12,13}

Covariates

We ascertained information on coexisting illnesses based on diagnoses or procedures using relevant ICD-9 codes, laboratory results, or filled outpatient prescriptions from health plan hospitalization discharge, ambulatory visit, laboratory, and pharmacy databases, as well as site-specific cancer registries.¹⁹ We defined prevalent HF as having any hospitalization or ambulatory HF diagnosis during a look-back period of up to 5 years prior to the date of the diagnosis that led to inclusion in the study cohort.

We ascertained available ambulatory results for baseline and time-updated systolic and diastolic blood pressure, serum LDL and HDL cholesterol measurements, eGFR, dipstick proteinuria, and blood hemoglobin level. We also collected baseline and time-updated information on receipt of other selected medications including aldosterone antagonists, calcium channel blockers, digoxin, loop diuretics, thiazide diuretics, nitrates, statins, other lipid lowering drugs, anticoagulants, and antiplatelet agents.

Statistical analysis

Analyses were conducted using SAS, version 9.3 (Cary, N.C.). We compared the baseline characteristics for patients who did or did not initiate the therapies of interest, using ANOVA or the relevant non-parametric test for continuous variables and chi-square tests for categorical variables.

For each dyad and associated therapy of interest, we fitted pooled logistic marginal structural models (MSM)²⁰ stratified by HF_rEF or HF_pEF at baseline. We first constructed our analytic dataset based on a directed acyclic graph (DAG) of exposure and outcome relationships based on the published literature. Each patient's follow-up time was then divided into 30-day intervals starting on their index date. Exposures, outcomes, and covariates were then organized into proper time order within and across these time intervals. Next, we calculated inverse probability weights (IPW) to adjust for potential baseline and time-dependent confounders.²¹ We separately calculated exposure and censoring IPWs, then

multiplied them to determine the final summary IPW for each patient. We constructed three models to characterize exposure to the therapy of interest to facilitate generation of weights: probability of exposure at start of follow-up, probability of exposure given previously not exposed in the prior period, and probability of exposure given previously being exposed in the prior period. One censoring model was used to capture censoring due to disenrollment from the health plan or end of administrative study follow-up. After evaluation of the distribution, the final summary IPW was truncated at 2% and 98% for model stability. Our modeling approach was an “as-treated” MSM analysis evaluating the effect of exposure to the therapy of interest on outcomes, with incorporation of IPWs to account for baseline and time-dependent confounders, as well as splines set to 1%, 25%, 50%, 75%, and 99% of overall cohort follow-up time to adjust for the potential effect of time.

RESULTS

Among the 2414 patients with a history of chronic lung disease and no prior beta-blocker use at study entry, there were 986 with HFrEF and 1428 with HFpEF. Details of cohort assembly are provided in Supplementary Figure S1.

Patients with HFrEF and use of beta-blocker therapy were considerably younger than those with no use during follow-up (mean age 69.0 versus 77.7; $p<0.001$) (Table 1). They were less likely to have previous percutaneous coronary intervention, atrial fibrillation or flutter, ventricular tachycardia or fibrillation, mitral and/or aortic valvular disease, a pacemaker, hospitalized bleeds, dementia, and falls. HFrEF patients with beta-blocker use also had higher eGFR, hemoglobin, and systolic and diastolic blood pressure levels (Supplementary Table S1). In contrast, HFrEF beta-blocker users were less likely to use loop diuretics, nitrates, antiplatelet agents, and/or anticoagulants (Supplementary Table S2). In an MSM analysis among HFrEF patients with chronic lung disease that accounted for potential baseline and time-dependent confounders, beta-blocker therapy was protective for death from any cause (HR 0.58 [95% CI:0.44–0.77]) and hospitalization for HF (HR 0.78 [95% CI:0.60–1.00]), but there was no statistically significant association observed with hospitalization from any cause (Figure 1).

Patients with HFpEF and use of beta-blocker therapy were significantly younger than those with no use (mean age 73.2 versus 75.6; $p<0.001$) (Table 1). They were less likely to have prior acute myocardial infarction, ischemic stroke or transient ischemic attack, atrial fibrillation or flutter, mitral and/or aortic valvular disease, and hospitalized bleeds. HFpEF patients with beta-blocker use were more likely to have a diagnosis of dyslipidemia, receive statin therapy and have higher systolic and diastolic blood pressure and lower HDL levels (Supplementary Table S1), but were less likely to use aldosterone receptor antagonists, digoxin, loop diuretics, and anticoagulants (Supplementary Table S2). In contrast to results seen in HFrEF patients, among eligible patients with HFpEF and chronic lung disease, there were no statistically significant associations of beta-blocker therapy use with any of the outcomes of interest in MSM analyses (Figure 1).

Among the 1,492 patients with chronic kidney disease and no prior ACE inhibitors/angiotensin II receptor blockers use, 482 had HFrEF and 1,010 patients had HFpEF (Supplementary Figure S2).

Patients with HFrEF and use of ACE inhibitor/ARB therapy were less likely than non-users to have a prior acute myocardial infarction, percutaneous coronary intervention, ischemic stroke or transient ischemic attack, ventricular tachycardia or fibrillation, implantable cardioverter defibrillator, or liver disease (Table 2). Patients with ACE inhibitor/ARB use had higher eGFR levels and were less likely to have dipstick proteinuria (Supplementary Table S3). They were also less likely to use aldosterone receptor antagonists, calcium channel blockers, loop diuretics, and nitrates (Supplementary Table S4). In MSM models among eligible HFrEF patients with concomitant chronic kidney disease that adjusted for baseline and time-dependent confounders, ACE inhibitor/ARB therapy was protective for death from any cause (HR 0.60 [95%CI: 0.40–0.91]), hospitalization for HF (HR 0.43 [95%CI: 0.28–0.67]), and hospitalization from any cause (HR 0.63 [95%CI: 0.45–0.89]) (Figure 2).

Patients with HFpEF and use of ACE inhibitor/ARB therapy were less likely to be female and to have a history of atrial fibrillation or flutter, ventricular tachycardia or fibrillation, hospitalized bleeds, and cancer than non-users (Table 2). Patients with ACE inhibitor/ARB use had higher eGFR and diastolic blood pressure, lower LDL cholesterol levels, and were less likely to have dipstick proteinuria (Supplementary Table S3). They were also less likely to use calcium channel blockers, and nitrates, and more likely to use thiazide diuretic therapy (Supplementary Table S4). Similar to results seen in HFrEF patients, MSM model results revealed a favorable impact of ACE inhibitor/ACE therapy on all three outcomes among eligible patients with HFpEF and chronic kidney disease (RR 0.52 [95% CI 0.33–0.81]; RR 0.35 [95% CI 0.18–0.68]; and RR 0.67 [95% CI 0.47–0.95], respectively) (Figure 2).

DISCUSSION

Among community-based patients with HFrEF and chronic lung disease, we found that beta-blocker therapy was associated with a reduced risk for death from any cause and hospitalization, but there were no statistically significant associations of beta-blocker therapy use with any of the outcomes of interest in those with HFpEF and chronic lung disease. Among patients with HFpEF or HFrEF complicated by chronic kidney disease, ACE inhibitor/ARB use was independently associated with reduced risks for death from any cause, hospitalization for HF, and hospitalization for any cause.

The findings of two recent meta-analyses are intriguing in relation to our results. Bavishi and colleagues undertook a meta-analysis to evaluate the efficacy of beta-blockers on mortality and morbidity in patients with HFpEF.²² Observational studies included in this meta-analysis suggested a favorable association between receipt of beta-blockers and all-cause mortality, but not for HF-related hospitalization. No subgroup analyses were performed relevant to patients with specific comorbidities and potential time-dependent confounding was not addressed. A recent meta-analysis of randomized controlled trials assessing the

efficacy of inhibition of the renin-angiotensin aldosterone system (RAAS) in HF suggested that the relative beneficial effects decreased with increasing mean left ventricular ejection fraction for outcomes including mortality and HF hospitalization.²³ However, although no benefit of RAAS inhibition on all-cause mortality was observed above a mean ejection fraction of 50%, a significant benefit on HF-related hospitalization was observed (RR 0.88 [95% CI:0.80 to 0.97]). Again, no subgroup analyses were performed relevant to patients with specific comorbidities.

Our study has several strengths and limitations. Insured populations receiving care in the health care delivery systems relevant to our study may not be fully representative of all HF populations. This limitation is counterbalanced by the breadth of geographic and demographic diversity, as well as the community-based nature of health care delivery, suggesting that findings of our investigations are likely to be highly generalizable to patients with HF in “real-world” practice settings in relation to the treatments they receive and the effectiveness of these treatments. In addition, individual diagnoses of HF were not adjudicated through medical record abstraction and expert review. However, prior studies in our population have shown a high positive predictive value for the approach we used to identify patients with HF.^{12,13} We also used both quantitative and qualitative assessments of left ventricular systolic function to characterize patients as having HFrEF versus HFpEF. While chronic kidney disease diagnoses were based on the estimated glomerular filtration rate, diagnoses of chronic lung disease were based on diagnosis codes and were not validated.

Small sample sizes in subgroups of interest adversely impacted the precision of our estimates of effect. We also did not study HF patients with an EF of 41–49 percent, who were relatively few in number. These patients, who fall into a “borderline”, “intermediate”, or “mid-range” group, may comprise a separate group with regard to characteristics, pathophysiology, and treatment.²⁴

Our new-user study design addressed the problem of prevalent user bias that plagues many observational studies of treatment effectiveness in the “real world,” when information about baseline medication use is lacking.¹⁷ However, an inherent limitation of observational studies is the potential for residual confounding and selection bias. Of particular concern is “healthy user bias,” which we attempted to mitigate through our analytic approach. However, residual confounding may still exist, because users of beta-blockers or ACE inhibitor or ARB therapy had a lower comorbidity burden than non-users. Strategies to address healthy user bias include having an active control,²⁵ which was not possible in these studies. We combined this design approach with marginal structural modeling and inverse probability weighting to address potential time-dependent confounding, overcoming the limitations of several commonly used methods such as propensity score matching and Cox regression.²⁶

Trials of treatments for HF have excluded the types of patients most commonly presenting with this condition, particularly older adults and those with high burdens of comorbidity,^{27,28,29} posing an ongoing challenge for clinical decision-making in these growing numbers of high risk HF patients.^{3,5,8,30} In addition, the current non-evidence-

based approach to the care of patients with HFpEF remains extremely frustrating.³¹ The imperative to address this situation has never been greater, as the majority of older patients who present with a new diagnosis of HF have HFpEF.³² With the aging of the US population, it is likely that the numbers of patients affected by this form of HF will increase dramatically over the coming decades, with many if not most, burdened by additional chronic conditions. The findings of our efforts suggest that large observational studies may allow for the identification of important subgroups of the HF population that might benefit from existing treatment approaches and inform the design of more definitive future randomized controlled trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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IMPACT STATEMENT

1. We certify that this work is novel or confirmatory of recent novel clinical research. 2. The potential impact of this research on clinical care or health policy includes the following: informing the design of more definitive future observational studies and randomized trials relevant to the treatment of heart failure patients with multiple chronic conditions.

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Figure 1. Effect of beta-blockers on risks of death from any cause, hospitalization for heart failure, and hospitalization from any cause among adults with heart failure and chronic lung disease, stratified by left ventricular ejection fraction.

Figure 2.
Effect of ACE inhibitor/angiotensin II receptor blocker therapy on risks of death from any cause, hospitalization for heart failure, and hospitalization from any cause among adults with heart failure and chronic kidney disease, stratified by left ventricular ejection fraction.

Table 1
Baseline characteristics of patients with HF and lung disease, stratified by HFrEF or HFpEF status and use of beta-blocker therapy.

	Reduced EF N=986		β -blocker N=757		No β -blocker N=229		p-values	Preserved EF N=1428		β -blocker N=705		No β -blocker N=723		p-values
Age, yr, mean (SD)	71.0	13.4	69	13.3	77.7	11.1	<0.001	74.4	12.1	73.2	11.9	75.6	12.3	<0.001
Age categories	n	%	n	%	n	%	<0.001	n	%	n	%	n	%	<0.001
Age <45	44	4.5	41	5.4	3	1.3		24	1.7	13	1.8	11	1.5	
Age 45–54	91	9.2	84	11.1	7	3.1		76	5.3	43	6.1	33	4.6	
Age 55–64	171	17.3	150	19.8	21	9.2		214	15	112	15.9	102	14.1	
Age 65–74	239	24.2	198	26.2	41	17.9		342	23.9	200	28.4	142	19.6	
Age 75–84	314	31.8	210	27.7	104	45.4		488	34.2	227	32.2	261	36.1	
Age 85	127	12.9	74	9.8	53	23.1		284	19.9	110	15.6	174	24.1	
Female gender	406	41.2	320	42.3	86	37.6	0.2	861	60.3	423	60	438	60.6	0.82
Race							0.11							0.02
White	736	74.6	559	73.8	177	77.3		1112	77.9	553	78.4	559	77.3	
Black/African Am.	87	8.8	75	9.9	12	5.2		104	7.3	55	7.8	49	6.8	
Asian	48	4.9	39	5.2	9	3.9		50	3.5	29	4.1	21	2.9	
Native Hawaiian	5	0.5	5	0.7	0	0		2	0.1	2	0.3	0	0	
Other	2	0.2	2	0.3	0	0		4	0.3	4	0.6	0	0	
Missing/Unknown	108	11.0	77	10.2	31	13.5		156	10.9	62	8.8	94	13	
Medical History														
Prevalent HF	424	43.0	285	37.6	139	60.7	<0.001	785	55	345	48.9	440	60.9	<0.001
AMI	34	3.4	22	2.9	12	5.2	0.09	44	3.1	14	2	30	4.1	0.02
Unstable angina	8	0.8	6	0.8	2	0.9	0.91	31	2.2	14	2	17	2.4	0.64
CABG	9	0.9	7	0.9	2	0.9	0.94	23	1.6	12	1.7	11	1.5	0.79
PCI	29	2.9	17	2.2	12	5.2	0.02	39	2.7	20	2.8	19	2.6	0.81
Stroke/TIA	41	4.2	27	3.6	14	6.1	0.09	88	6.2	34	4.8	54	7.5	0.04
Other thromboembolic event	5	0.5	3	0.4	2	0.9	0.37	13	0.9	6	0.9	7	1	0.82
AF or flutter	248	25.2	171	22.6	77	33.6	0.001	536	37.5	242	34.3	294	40.7	0.01
V tach or V fib	28	2.8	17	2.2	11	4.8	0.04	16	1.1	4	0.6	12	1.7	0.05

	Reduced EF N=986		β -blocker N=757		No β -blocker N=229		p-values	Preserved EF N=1428		β -blocker N=705		No β -blocker N=723		p-values
Mitral and/or AV disease	166	16.8	110	14.5	56	24.5	<0.001	353	24.7	153	21.7	200	27.7	0.009
PAD	60	6.1	40	5.3	20	8.7	0.06	104	7.3	48	6.8	56	7.7	0.5
Rheumatic heart	16	1.6	9	1.2	7	3.1	0.05	63	4.4	24	3.4	39	5.4	0.07
ICD	33	3.3	23	3	10	4.4	0.3274	5	0.4	3	0.4	2	0.3	0.63
Pacemaker	45	4.6	27	3.6	18	7.9	0.006	67	4.7	31	4.4	36	5	0.6
Dyslipidemia	523	53.0	402	53.1	121	52.8	0.94	790	55.3	412	58.4	378	52.3	0.02
Hypertension	599	60.8	460	60.8	139	60.7	0.99	1043	73	514	72.9	529	73.2	0.91
Diabetes mellitus	236	23.9	173	22.9	63	27.5	0.15	340	23.8	162	23	178	24.6	0.47
Hospitalized bleeds	40	4.1	22	2.9	18	7.9	0.001	101	7.1	31	4.4	70	9.7	<0.001
Dx dementia	58	5.9	33	4.4	25	10.9	<0.001	118	8.3	54	7.7	64	8.9	0.41
Dx depression	170	17.2	130	17.2	40	17.5	0.92	325	22.8	161	22.8	164	22.7	0.94
Liver disease	43	4.4	33	4.4	10	4.4	0.99	77	5.4	39	5.5	38	5.3	0.82
Fall	18	1.8	10	1.3	8	3.5	0.03	65	4.6	25	3.5	40	5.5	0.07
Systemic cancer	76	7.7	58	7.7	18	7.9	0.92	131	9.2	63	8.9	68	9.4	0.76

Native Hawaiian includes Other Pacific Islanders

HF = Heart failure; AMI = Acute myocardial infarction; CABG= Coronary artery bypass graft surgery; PCI= Percutaneous coronary intervention; TIA = Transient ischemic attack; AF = Atrial fibrillation;
 V tach/V fib = Ventricular tachycardia/Ventricular fibrillation; AV = Aortic valve; PAD = Peripheral arterial disease; ICD = Implantable cardioverter defibrillator; Dx = Diagnosed

Baseline characteristics of patients with HF and CKD stratified by HFpEF or HFrEF status and use of ACE inhibitors/Angiotensin II receptor blockers (ACEi/ARB)

Table 2

	Reduced EF N=482		ACEi/ARB N=282		No ACEi/ARB N=200		p-values	Preserved EF N=1010		ACEi/ARB N=362		No ACEi/ARB N=648		p-values
Age, yr, mean (SD)	81.8	9.5	81.2	8.9	82.7	10.1	0.08	83.0	8.7	82.3	8.8	83.3	8.7	0.09
Age categories	n	%	n	%	n	%	0.02	n	%	n	%	n	%	0.17
Age <45	1	0.2	0	0.0	1	0.5		2	0.2	0	0.0	2	0.3	
Age 45–54	7	1.5	4	1.4	3	1.5		12	1.2	7	1.9	5	0.8	
Age 55–64	20	4.1	11	3.9	9	4.5		26	2.6	8	2.2	18	2.8	
Age 65–74	68	14.1	44	15.6	24	12.0		104	10.3	42	11.6	62	9.6	
Age 75–84	194	40.2	128	45.4	66	33.0		439	43.5	166	45.9	273	42.1	
Age 85	192	39.8	95	33.7	97	48.5		427	42.3	139	38.4	288	44.4	
Female gender	156	32.4	93	33.0	63	31.5	0.73	564	55.8	183	50.6	381	58.8	0.01
Race							0.38							0.27
White	406	84.2	242	85.8	164	82.0		857	84.9	312	86.2	545	84.1	
Black/African Am.	15	3.1	10	3.5	5	2.5		33	3.3	9	2.5	24	3.7	
Asian	27	5.6	12	4.3	15	7.5		34	3.4	14	3.9	20	3.1	
Native Hawaiian	1	0.2	1	0.4	0	0.0		7	0.7	4	1.1	3	0.5	
Other	0	0.0	0	0.0	0	0.0		3	0.3	2	0.6	1	0.2	
Missing/Unknown	33	6.8	17	6.0	16	8.0		76	7.5	21	5.8	55	8.5	
Medical History														
Prevalent HF	201	41.7	85	30.1	116	58.0	<0.001	505	50.0	137	37.8	368	56.8	<0.001
AMI	49	10.2	21	7.4	28	14.0	0.02	69	6.8	19	5.2	50	7.7	0.14
Unstable angina	12	2.5	7	2.5	5	2.5	0.99	37	3.7	13	3.6	24	3.7	0.93
CABG	13	2.7	6	2.1	7	3.5	0.36	29	2.9	14	3.9	15	2.3	0.16
PCI	33	6.8	12	4.3	21	10.5	0.008	45	4.5	11	3.0	34	5.2	0.1
Stroke/TIA	33	6.8	13	4.6	20	10.0	0.02	92	9.1	32	8.8	60	9.3	0.82
Other thromboembolic	1	0.2	0	0.0	1	0.5	0.23	9	0.9	3	0.8	6	0.9	0.87
AF or flutter	169	35.1	94	33.3	75	37.5	0.34	477	47.2	150	41.4	327	50.5	0.006

	Reduced EF N=482		ACEi/ARB N=282		No ACEi/ARB N=200		p-values	Preserved EF N=1010		ACEi/ARB N=362		No ACEi/ARB N=648		p-values
	13	2.7	4	1.4	9	4.5		13	1.3	1	0.3	12	1.9	
V tach or V fib														0.03
Mitral and/or AV disease	74	15.4	39	13.8	35	17.5	0.27	247	24.5	84	23.2	163	25.2	0.49
PAD	40	8.3	20	7.1	20	10.0	0.25	99	9.8	28	7.7	71	11.0	0.1
Rheumatic heart	22	4.6	11	3.9	11	5.5	0.41	35	3.5	13	3.6	22	3.4	0.87
ICD	13	2.7	4	1.4	9	4.5	0.04	4	0.4	0	0.0	4	0.6	0.13
Pacemaker	43	8.9	22	7.8	21	10.5	0.31	65	6.4	21	5.8	44	6.8	0.54
Dyslipidemia	251	52.1	142	50.4	109	54.5	0.37	536	53.1	195	53.9	341	52.6	0.7
Hypertension	303	62.9	167	59.2	136	68.0	0.05	800	79.2	284	78.5	516	79.6	0.66
Diabetes mellitus	85	17.6	43	15.2	42	21.0	0.1	186	18.4	62	17.1	124	19.1	0.43
Hospitalized bleeds	26	5.4	11	3.9	15	7.5	0.08	85	8.4	20	5.5	65	10.0	0.01
Dx dementia	49	10.2	25	8.9	24	12.0	0.26	130	12.9	37	10.2	93	14.4	0.06
Dx depression	58	12.0	35	12.4	23	11.5	0.76	170	16.8	68	18.8	102	15.7	0.22
Lung disease	154	32.0	81	28.7	73	36.5	0.07	438	43.4	144	39.8	294	45.4	0.09
Liver disease	18	3.7	6	2.1	12	6.0	0.03	31	3.1	9	2.5	22	3.4	0.42
Fall	18	3.7	10	3.5	8	4.0	0.8	53	5.2	15	4.1	38	5.9	0.24
Systemic cancer	42	8.7	23	8.2	19	9.5	0.61	92	9.1	23	6.4	69	10.6	0.02

Native Hawaiian includes Other Pacific Islanders

HF = Heart failure; AMI = Acute myocardial infarction; CABG= Coronary artery bypass graft surgery; PCI= Percutaneous coronary intervention; TIA = Transient ischemic attack; AF = Atrial fibrillation;

V tach/V fib = Ventricular tachycardia/Ventricular fibrillation; AV = Aortic valve; PAD = Peripheral arterial disease; ICD = Implantable cardioverter defibrillator; Dx = Diagnosed