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Comparison of Medication Practices in Patients with Heart Failure and Preserved vs those with Reduced Ejection Fraction (from the Cardiovascular Research Network)

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Abstract

Limited data exist describing differences in the medical management of patients with heart failure with preserved ejection fraction (HF-PEF) from those with heart failure with reduced ejection fraction (HF-REF) in more generalizable population-based cohorts. We studied individuals with incident HF diagnosed between 2005 and 2008 from 4 sites participating in the Cardiovascular Research Network. These persons, their medication profile, and left ventricular systolic function status were identified based on hospital discharge and ambulatory visit diagnoses, pharmacy dispensing information, and imaging reports found in health plan electronic databases and through chart review. The study population consisted of 6,210 patients with newly diagnosed HF-PEF and 3,914 patients with newly diagnosed HF-REF. The mean age of our study population was 73 years, 48% were women, and 74% were Caucasian. Patients with HF-REF were less likely to have been treated with various cardiac and HF related medications prior to their index HF event, but were significantly more likely to have been treated with new cardiac medications and HF therapies after the diagnosis of HF, than patients with HF-PEF. After controlling for several potentially

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confounding factors, patients with HF-PEF were significantly less likely to have been treated with multiple cardiac drug regimens (adjusted odds ratio (OR) = 0.69; 95% CI 0.59, 0.81) and multiple HF related therapies (OR = 0.40; 95% 0.38,0.42) than patients with HF-REF. The present results from a large, population-based sample suggest considerable variation in the prior and new use of different cardiac medication classes of drugs in patients with HF-PEF vs. HF-REF.

Keywords

heart failure; management practices; drug therapy; population research

INTRODUCTION

Although heart failure is recognized as a contemporary epidemic in the U.S., the epidemiology and management of patients with heart failure and preserved left ventricular ejection fraction (HF-PEF) is less well known and described (1–7). While a number of therapies presently exist to improve the symptoms associated with chronic heart failure with reduced ejection fraction (HF-REF) and its long-term prognosis, there are no specific guidelines for the treatment of patients with HF-PEF (8). The contemporary management of these patients is also relatively unknown. Using data from the Cardiovascular Research Network (9, 10), we examined differences in the medical management of patients with incident HF-REF as compared to those with newly diagnosed HF-PEF.

METHODS

The source population for this study included adult members from 4 participating health plans within the National Heart, Lung, and Blood Institute sponsored Cardiovascular Research Network (CVRN) (9, 10). Study sites included Kaiser Permanente Northern California, Kaiser Permanente Colorado, Kaiser Permanente Northwest, and the Fallon Community Health Plan. These sites were identified on the basis of providing care to a socioeconomically diverse population across varying clinical practice settings and geographic locations. Institutional review boards at participating sites approved the study.

The CVRN Virtual Data Warehouse (VDW) at each study site served as the primary data source for the present investigation. The CVRN VDW is a distributed standardized data resource comprised of electronic datasets at each CVRN site (9). The VDW is populated with demographic, pharmacy, outpatient and inpatient laboratory test results, and health care utilization data for individuals in CVRN health plans.

The study sample consisted of adults aged ≥21 years with heart failure (HF) who were enrolled in participating health plans between January, 2005 and December, 2008. The diagnosis of HF was 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 being with a cardiologist. The following *International Classification of Diseases, 9th edition (ICD-9)* codes were used to identify patients with HF (398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.0, 428.1, 428.20, 428.21, 428.22, 428.23, 428.30, 428.31, 428.32, 428.33, 428.40, 428.41, 428.42, 428.43, and 428.9). We have previously shown that the vast majority (>95%) of patients with a primary discharge diagnosis of HF based on these codes were confirmed as having clinical HF by chart review using Framingham clinical criteria (11–13).

Information on quantitative and/or qualitative assessments of left ventricular systolic function was abstracted from the results of echocardiograms, nuclear imaging studies, and

left ventriculography from health plan databases, which was complemented by the manual review of electronic health records. We defined preserved ejection fraction as either a left ventricular ejection fraction ≥50% and/or a physician's qualitative determination of normal or preserved ejection fraction (12); reduced ejection fraction was defined as a left ventricular ejection fraction ≤40% and/or a physician's qualitative determination of moderately or severely reduced ejection fraction. Patients (n=1,870) with borderline ejection fraction findings (>40% – <50%) were excluded from the study sample because we wanted to focus this paper on patients with preserved versus reduced ejection fraction findings. We restricted our study sample to patients with an incident episode of HF based on a 5 year look-back period. We determined whether the patient had been previously diagnosed with HF prior to their index date of HF from ambulatory and hospitalization data sources.

We ascertained information on coexisting illnesses based on medical diagnoses or receipt of selected procedures using relevant ICD-9 codes, laboratory test results, or filled outpatient prescriptions from health plan hospitalization discharge, ambulatory visit, laboratory, and pharmacy databases (13). We collected baseline and follow-up data on diagnoses of selected comorbidities and interventional procedures based on relevant ICD-9 and/or CPT procedure codes. We also ascertained available ambulatory results for blood pressure, serum lipid levels, estimated glomerular filtration rate, and serum hemoglobin levels on or before the index date of diagnosis of preserved or reduced systolic function (14).

Prescription data were used to identify prior (up to 120 days prior to, but not including, the index date of diagnosis of HF and remaining active within 30 days of index date) and post-diagnosis (up to 90 days after the index date of diagnosis) use of cardiac and HF medications. The cardiac medications examined included anticoagulants, antiplatelet agents, calcium channel blockers, thiazide diuretics, statins, and other lipid lowering drugs. The HF related medications included angiotensin converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs), aldosterone antagonists, beta blockers, digoxin, loop diuretics, and nitrates and hydralazine. We further subdivided the HF therapies into those that have been shown to affect prognosis (ACE inhibitors/ARB's, aldosterone antagonists, beta blockers, nitrates and hydralazine) and those used to treat symptoms (digoxin, loop diuretics).

We characterized this cohort of patients with HF-REF and HF-PEF with regards to several socio-demographic, medical history, and clinical characteristics. We modeled differences, through the use of logistic regression modeling, in the new receipt of each of our different medication categories (cardiac medication only, HF medication only, HF prognosis related therapy, HF symptom related therapy) between newly diagnosed patients with preserved versus reduced systolic function while simultaneously controlling for age, sex, race/ethnicity, history of cardiovascular disease, receipt of coronary reperfusion/revascularization procedures, dyslipidemia, hypertension, diabetes, hospitalized bleeding episodes, diagnosed dementia or depression, chronic liver or lung disease, systemic cancer, estimated GFR, systolic blood pressure, hemoglobin, serum lipid values, and study site.

RESULTS

Among 10,124 patients with newly diagnosed HF between 2005 to 2008 at the 4 study sites, 6,210 patients (61.3%) had HF-PEF and 3,914 patients had HF-REF. The mean age of our study population was approximately 73 years, 48% were women, and three quarters were Caucasian. The mean (± SD) ejection fraction findings in patients with HF-PEF and HF-REF were 57.2% (± 19.7%) and 29.1% (± 9.6%), respectively.

Patients with incident HF-PEF were significantly older, and included a greater proportion of women, whites, patients with a history of coronary heart disease, cerebrovascular disease, atrial fibrillation, peripheral arterial disease, prior bleeding episodes, and other selected comorbidities than patients with HF-REF (Table 1). These patients had lower baseline eGFR and serum hemoglobin levels, higher systolic but lower diastolic levels of blood pressure, higher HDL-cholesterol levels, and lower serum LDL-cholesterol levels.

Patients with newly diagnosed HF-PEF were significantly more likely to have been previously treated with ACE inhibitors/ARB's, anticoagulants, beta-blockers, calcium channel blockers, digoxin, diuretics, nitrates and hydralazine, and statins than patients with HF-REF. Patients with HF-REF were significantly, but only slightly, more likely to have been previously treated with aldosterone antagonists (Table 2).

In terms of our 4 major cardiac and HF treatment categories, patients with HF-PEF were significantly more likely than patients with HF-REF to have been treated with all cardiac-related drugs examined (76.3% vs 59.4%), HF-related drugs (82.3% vs 64.7%), HF medications that have been shown to improve prognosis (76.4% vs 57.5%), and medications that have been shown to manage HF-related symptoms (38.0% vs 28.5%) before the initial HF diagnosis (all p's <0.001).

At the time of their HF diagnosis, and up to the 90 days thereafter, a significantly greater proportion of patients with newly diagnosed HF-REF were treated with each of the cardiac- and HF-related medications examined in comparison to those with newly diagnosed HF-PEF (Table 3). Patients with HF-REF were significantly more likely than those with HF-PEF to have been newly treated with selected cardiac (58.8% vs 50.3%) and HF-related medications (92.8% vs 81.8%) (p<0.001); these differences were also noted when we examined the prescribing of HF medications shown to improve patient's prognosis (89.3% vs 65.1%, p<0.001) whereas HF drugs used to provide symptomatic relief were similarly prescribed to our primary comparison groups (75.4% vs 73.6%).

After controlling for a variety of demographic, medical history, and clinical characteristics, patients with newly diagnosed HF-PEF were significantly less likely to have been prescribed selected cardiac medications (adjusted odds ratio [OR]=0.77; 95% CI 0.66, 0.91), HF-related medications (adjusted OR = 0.42; 95% CI 0.34, 0.52), HF therapies shown to improve patient's prognosis (adjusted OR = 0.26; 95% CI 0.24, 0.29), and HF therapies used to treat patient's HF-related symptoms (adjusted OR = 0.82; 95% CI 0.77, 0.88) than patients with HF-REF after their index diagnosis.

Of the various cardiac medications examined prior to the patient's index HF diagnosis, 16.4% were not treated with any of these medications, 37.4% of all patients were treated with any 1 therapy, 29.4% were treated with any 2, and 16.8% were treated with any 3 or more of these medications. Multiple cardiac medication use (≥2) was more common in patients with HF-PEF versus HF-REF (Table 4). Among new cardiac medication users, there were little to no differences in the use of multiple cardiac medications in patients with HF-PEF versus HF-REF (Table 4).

In examining differences in the receipt of HF-related medications prior to the patient's index date of HF diagnosis, 3.8% of all patients with HF were not treated with any of these therapies, 36.8% were treated with any 1 medication, 38.7% with any 2, and 20.7% were treated with any 3 or more of these modalities; none of these medications, with the exception of single medication use, were used more frequently in patients with HF-REF compared with HF-PEF (Table 4). On the other hand, prescriptions for new multiple (≥3) medications used for HF were more commonly documented in patients with HF-REF (Table 4).

In terms of combination therapies, 16.1% of all patients with HF were treated with ACE inhibitors/ARBs and beta blockers, 8.9% were treated with diuretics and digoxin, 20.9% were treated with ACE inhibitors/ARBs and diuretics, whereas 12.3% were treated with ACE inhibitors/ARBs, beta blockers, and diuretics.

Patients with HF-REF were significantly more likely to have been treated with these combination medications as reflected by differences in the receipt of ACE inhibitors/ARBs and beta blockers (30.3% vs 7.1%), diuretics and digoxin (14.0% vs 5.7%), diuretics and ACE inhibitors/ARBs (31.4% vs 14.3%), and ACE inhibitors/ARBs, beta blockers, and diuretics (23.2% vs 5.4%) (all comparisons p<.001).

In examining the use of both multiple (≥2) cardiac-related and multiple HF-related therapies (versus one or none of these medications), patients with HF-PEF were significantly less likely to have been treated with multiple cardiac-related regimens (adjusted OR 0.69; 95% CI 0.59, 0.81) and multiple HF related therapies (adjusted OR 0.40; 95% CI 0.38, 0.42) than patients with HF-REF after controlling for age, sex, race/ethnicity, prior comorbidities, and a number of physiologic variables .

DISCUSSION

The results of this large observational study demonstrate that among patients with newly diagnosed HF, those with HF-REF are significantly more likely than those with HF-PEF to be treated with both single and multiple cardiac- and HF-related medications, as well as HF therapies that have been shown to reduce patient mortality and their acute symptoms.

Increasing interest is being paid to HF and its 2 major subtypes. Indeed, a limited number of epidemiologic studies during recent years suggest that the prevalence of HF-PEF is increasing over time relative to that of HF-REF in the U.S. (15–17).

Although there are extensive published guidelines for the treatment of HF, the evidence-base supporting treatment recommendations for HF with reduced left ventricular ejection fraction greatly surpasses that for HF with preserved left ventricular ejection fraction (18, 19). This is due largely to the lack of randomized trials in patients with HF-PEF, the variable definitions of HF-PEF used in prior studies, as well as an underappreciation of the high prevalence of, and poor outcomes associated with, HF-PEF. For example, the most recent American College of Cardiology/American Heart Association guidelines state that “most patients with HF should be routinely managed with an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB) and a beta blocker” (19). However, these are class I (level of evidence A) recommendations for patients with HF with reduced left ventricular ejection fraction and class IIb (level of evidence C) recommendations for patients with HF with preserved left ventricular ejection fraction.

Physicians may have been less likely to have prescribed various medications recommended for the management of HF-REF in patients with HF-PEF. Recent studies, however, suggest that the outcomes in patients with a clinical diagnosis of HF are not widely disparate across the spectrum of EF findings (15, 20), reinforcing the importance of studying the use and impact of HF related therapies in patients with HF-PEF. Moreover, there is a general lack of evidence on which to base decisions on the management of older patients with HF who have a complex array of accompanying conditions and might beat higher risk for drug-related adverse events (e.g., renal failure with ACE-inhibitors).

Physician management of patients with HF-PEF is based on empiric findings and it is assumed, though untested, that medications used to manage patients with HF-REF would be similarly applied and be equally beneficial to patients with HF-PEF. Indeed, several

therapies beneficial to patients with HF-REF either have failed to improve long-term outcomes in patients with HF-PEF or have yet to be systematically examined in randomized clinical trials in these patients (8, 21–24). On the other hand, the recent findings from a large observational Swedish HF registry suggest benefit for the use of renin-angiotensin system antagonists in patients with HF-PEF (25). These findings reinforce the need for carefully designed and conducted contemporary observational studies and randomized trials of individual and combination medical therapies in patients with HF-PEF, especially since the presently available treatments for HF-REF may not be indicated for patients with HF-PEF.

In the present study, there were marked differences in the receipt of pre- and post-HF diagnosis therapies between patients with HF-PEF and HF-REF. Consistent with the results of the AHA Get With the Guidelines-HF Study, more than 40,000 patients with preserved HF in this investigation were less likely to have been treated with effective HF medications than the more than 55,000 patients hospitalized with HF-REF (17). Interestingly, between 2005 and 2010, there was a decline in the prescription of ACE inhibitors/ARB's at the time of hospital discharge, and a concomitant increase in the use of beta blockers, across the 3 left ventricular EF groups (≤40%, 41%–49%, ≥50%) examined in the Get With the Guidelines project (17).

The strengths of the present study include a large socioeconomically diverse cohort of patients with newly diagnosed HF recruited from varying clinical practice settings as well as the use of standardized methods for linking health care related information along with documenting the presence of preserved vs. reduced left ventricular systolic function. In terms of study limitations, the insured populations included in our participating health plans may not be completely representative of the general population of U.S. adults with HF. Despite this potential limitation, as well as our inability to directly assess medication adherence, the inclusion of 4 geographically diverse health plans representing a large, diverse community-based sample, suggest that findings from our study are likely to be generalizable to patients with HF-PEF and HF-REF in real world practice settings.

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Table 1

Baseline Characteristics of Patients According to Type of Newly Diagnosed Heart Failure

Variable	Ejection Fraction		p-value
	Preserved (n = 6,210)	Reduced (n = 3,914)	
Age (mean (SD), years)	74.7 (12.1)	69.1 (14.0)	<.001
Women	3,543 (57.1 %)	1,277 (32.6 %)	<0.001
Race			
White	4,759 (76.6%)	2,742 (70.1%)	<.001
African American	428 (6.9%)	387 (9.9%)	
Medical History, n (%)			
Acute myocardial Infraction/Unstable angina	599 (9.6%)	362 (9.2%)	0.51
Coronary artery bypass surgery and/or percutaneous coronary intervention	610 (9.8%)	368 (9.4%)	0.49
Ischemic stroke or transient ischemic attack	438 (7.1%)	187 (4.8%)	<0.001
Atrial fibrillation or flutter	2,195 (35.3%)	918 (23.5%)	<0.001
Mitral and/or aortic valvular disease	1,315 (21.2%)	408 (10.4%)	<0.001
Peripheral arterial disease	398 (6.4%)	191 (4.9%)	<0.001
Implantable cardioverter defribrillator	22 (0.4%)	71 (1.8%)	<0.001
Pacemaker	282 (4.5%)	150 (3.8%)	0.09
Dyslipidemia	3,833 (61.7%)	2,151 (55.0%)	<0.001
Hypertension	5,114 (82.4%)	2,478 (63.3%)	<.001
Diabetes mellitus	1,217 (19.6%)	701 (17.9%)	0.03
Hospitalized bleeding episodes	306 (4.9 %)	114 (2.9%)	<0.001
Dementia	480 (7.7%)	195 (5.0%)	<0.001
Depression	1,141 (18.4%)	524 (13.4%)	<0.001
Chronic lung disease	2,369 (38.1%)	1,150 (29.4%)	<0.001
Chronic liver disease	242 (3.9%)	129 (3.3%)	0.12
Systemic cancer	493 (7.9%)	249 (6.4%)	0.003
Estimated GFR Mean (SD) mL/min/1.73 m^2	61.1 (24.7%)	66.4 (23.8%)	<.001
Hemoglobin Mean (SD) (gm/dl)	12.5 (2.0%)	13.5 (1.9%)	<.001
Systolic blood pressure (mmHg) Mean (SD)	138.6 (24.3%)	132.8 (21.9%)	<.001
Diastolic blood pressure (mmHg) Mean (SD)	76.8 (13.6%)	80.3 (14.3%)	<.001
HDL (g/dL) Mean (SD)	49.0 (15.5%)	47.2 (14.6%)	<.001
LDL (g/dL) Mean (SD)	97.4 (33.9%)	102.1 (35.5%)	<.001

Table 2

Prior Medication Use* According to Type of Newly Diagnosed Heart Failure

Variable	Ejection Fraction		p-value
	Preserved (n = 6,210)	Reduced (n = 3,914)	
Medication			
ACE inhibitors/Angiostensin II receptor blockers (ARB)	3,080 (49.6%)	1,681 (42.9%)	<0.001
Aldosterone receptor agonist	93 (1.5%)	99 (2.5%)	<0.001
Anticoagulants	1,198 (19.3%)	513 (13.1%)	<0.001
Antiplatelets	484 (7.8%)	287 (7.3%)	0.42
Beta-blocker	3,877 (62.4%)	1,539 (39.5%)	<0.001
Calcium channel blocker	2,099 (33.8%)	599 (15.3%)	<0.001
Digoxin	498 (8.1%)	250 (6.4%)	<0.005
Diuretics (loop)	2,085 (33.6%)	973 (24.9%)	<0.001
Diuretics (thiazide)	1,728 (27.8%)	678 (17.3%)	<0.001
Nitrates	723 (11.6%)	408 (10.4%)	0.06
Nitrates and hydralazine	71 (1.1%)	14 (0.4%)	<.001
Statin	2,980 (48.0%)	1,572 (40.2%)	<0.001

* on medication up to 120 days prior to, but not including, the index date of HF diagnosis and remaining active within 30 days of index date of diagnosis.

Table 3

Incident Medication Use* According to Type of Newly Diagnosed Heart Failure

Medication	Ejection Fraction		p-value
	Preserved (n = 6,210)	Reduced (n = 3,914)	
ACE inhibitors/Angiostensin II receptor blocker	1,343 (42.9)	1,732 (77.6)	<0.001
Aldosterone receptor agonist	315 (5.2)	828 (21.7)	<0.001
Anticoagulants	1,139 (48.8)	1,886 (79.4)	<.05
Antiplatelets	516 (9.0)	830 (22.7)	<0.001
Beta-blocker	2,965 (71.9)	2,090 (71.1)	<0.001
Calcium channel blocker	326 (7.3)	199 (6.2)	<.001
Digoxin	809 (14.7)	759 (21.7)	<0.001
Diuretics (loop)	242 (3.9)	218 (5.6)	0.45
Diuretics (thiazide)	767 (23.8)	966 (41.3)	<.05
Nitrates	183 (3.2)	196 (5.4)	<0.001
Nitrates and hydralazine	796 (15.9)	601 (17.7)	<.001
Statin	565 (13.7)	201 (6.1)	<0.001

* on selected medication at time of HF diagnosis and up to 90 days thereafter

Table 4

Use of Selected Cardiac and Heart Failure Medications Prior to and After the Diagnosis of Heart Failure

	Prior Cardiac Medication Use		New Cardiac Medication Use	
Number of Medications	**Preserved EF (n=5,470)**	**Reduced EF (n=2,978)**	**Preserved EF (n=740)**	**Reduced EF (n=936)**
0	731 (13.4%)	655 (22.0%)	N/A	N/A
1	1,919 (35.1%)	1,240 (41.6%)	497 (67.2%)	627 (67.0%)
2	1,733 (31.7%)	749 (25.2%)	201 (27.2%)	260 (27.8%)
≥3	893 (16.3%)	27 0 (9.1%)	40 (5.4%)	45 (4.8%)
≥4	194 (3.6%)	64 (2.1%)	2 (0.3%)	4 (0.4%)
	Prior Heart Failure Medication Use		New Heart Failure Medication Use	
	Preserved EF (n=5,310)	Reduced EF (n=2,633)	Preserved EF (n=900)	Reduced EF (n=1,281)
0	200 (3.8%)	99 (3.8%)	0	0
1	1,829 (34.4%)	1,094 (41.5%)	212 (23.6%)	60 (4.7%)
2	2,119 (39.9%)	959 (36.4%)	292 (32.4%)	217 (16.9%)
≥3	1,016 (19.1%)	390 (14.8%)	300 (33.3%)	536 (41.9%)
≥4	146 (2.8%)	91 (3.5%)	96 (10.7%)	468 (36.5%)