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Effects of Diabetes Mellitus in Patients with Heart Failure and Chronic Kidney Disease: A Propensity-Matched Study of Multimorbidity in Chronic Heart Failure

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Abstract

Background—Chronic kidney disease (CKD) and diabetes mellitus (DM) are common comorbidities in heart failure (HF) and each is associated with poor outcomes. However, the effects of multimorbidity related to having *both* CKD and DM compared to CKD alone have not been well studied in a propensity-matched population of chronic HF patients.

Methods—Of the 7788 ambulatory chronic HF patients in the Digitalis Investigation Group trial, 3527 had CKD, of whom 1095 had DM. Based on the absence or presence of DM, patients were categorized into CKD-only and CKD-DM. Propensity scores for CKD-DM were calculated for each patient and were used to match 987 pairs of CKD-only and CKD-DM patients. Hazard ratios (HR) and 95% confidence intervals (CI) comparing CKD-DM patients with CKD-only patients were estimated using matched Cox regression models.

Results—All-cause mortality occurred in 47.0% (rate, 1783/10000 person-years) of CKD-DM patients and 39.6% (rate, 1414/10000 person-years of follow-up) of CKD-only patients (HR when CKD-DM is compared with CKD-only, 1.25; 95% CI, 1.07–1.46; p=0.006). All-cause hospitalization occurred in 75.4% (rate, 5710/10000 person-years) and 67.8% (rate, 4213/10000 person-years) of CKD-DM and CKD-only patients respectively (HR, 1.32; 95% CI, 1.15–1.52; p<0.0001). Respective HR and 95% CI for other outcomes were: cardiovascular mortality (1.27; 1.06–1.52; p=0.009), HF mortality (1.34; 1.04–1.72; p=0.025); cardiovascular hospitalization (1.29; 1.12–1.49; p=0.001) and HF hospitalization (1.37; 1.16–1.63; p<0.0001).

Conclusions—Compared with comorbidity due to CKD alone, multimorbidity with CKD and DM was associated with poor outcomes in chronic HF patients.

Keywords

heart failure; chronic kidney disease; diabetes mellitus; mortality

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1. Introduction

Multimorbidity is common in patients with heart failure (HF) [1]. Chronic kidney disease (CKD) and diabetes mellitus (DM) are common comorbidities in HF and are individually associated with poor outcomes [2,3]. However, the association of multimorbidity and outcomes in chronic HF has not been well studied. The objective of this study was to test the hypothesis that in patients with chronic HF, compared with the comorbidity due to CKD alone, multimorbidity due to *both* CKD and DM is associated with increased mortality and hospitalization.

2. Materials and Methods

2.1 Study design and patients

This is a secondary analysis of the Digitalis Investigation Group (DIG) trial, which was a randomized, double-blind placebo-controlled trial of digoxin in chronic HF conducted in the United States (186 centers) and Canada (116 centers) during 1991 to 1995. The design and the results of the DIG are well described in the literature [4–6].

2.2 Patients

All 7788 DIG participants were in normal sinus rhythm, 6800 had left ventricular ejection fraction ≤45%, and over 90% were receiving angiotensin-converting enzyme (ACE) inhibitors. Data on beta-blocker use were not collected. We focused our analysis to 3527 patients who had CKD. We categorized these patients into CKD-DM (n=1095) and CKD-only (n=2432) groups by the presence or absence of DM. CKD was defined as an estimated baseline glomerular filtration rate of <60 ml/min/1.73 m^2 body surface area [7,8]. DM was defined as a history or diagnosis of DM at baseline.

2.3 Outcomes

The primary outcomes were all-cause mortality and all-cause hospitalization during a mean follow up of 32.6 months. Secondary outcomes studied were mortality and hospitalizations due to cardiovascular causes and worsening HF. Data on vital status were 99% complete [9].

2.4 Calculation of propensity scores

To assemble a cohort in which CKD-only and CKD-DM patients would be well-balanced on all measured baseline covariates, we calculated propensity scores for CKD-DM for each of the 3527 patients using a non-parsimonious multivariable logistic regression model [10,11]. The propensity score for CKD-DM is the conditional probability of a patient having CKD-DM given that patient's measured covariates. In the model for propensity score, CKD-DM was the dependent variables and all baseline patient characteristics displayed in Figure 1 were used as covariates. We then used propensity scores to match 987 pairs of CKD-only and CKD-DM patients [2,12].

2.5. Assessment of bias reduction: absolute standardized differences

We assessed post-match covariate balance between the two groups by estimating absolute standardized differences and presented those results as Love plots [12]. Absolute standardized differences of <10% are taken to indicate inconsequential bias ([12–14].

2.6. Statistical analysis

For descriptive analyses, we used Pearson Chi square and Wilcoxon rank-sum tests for the prematch, and McNemar's test and paired sample t-test for the post-match comparisons, as appropriate. Kaplan-Meier and matched Cox regression analyses were used to estimate

associations of CKD-DM with various outcomes. We confirmed the assumption of proportional hazards by a visual examination of the log (minus log) curves. Homogeneity of the association between CKD-DM and all-cause mortality was further investigated in various subgroups of patients.

Although excellent balance was achieved in our post-match cohort in all measured covariates between the two groups, it is possible that there was bias due to imbalances in unmeasured covariates. Therefore, we conducted a formal sensitivity analysis to quantify the degree of a hidden bias that would need to be present to invalidate our main conclusions. All statistical tests were done using SPSS-15 for Windows [15].

3. Results

3.1 Patient Characteristics

Baseline characteristics for both groups before and after matching are displayed in Table 1 and Figure 1. Values of absolute standardized differences for all covariates were <5% after matching, suggesting substantial bias reduction (Figure 1).

3.2 CKD-DM and mortality

Overall, 855 (43.3%) patients died from all causes. All-cause mortality occurred in 47.0% (rate, 1783/10000 person-years) of CKD-DM patients, and 39.6% (rate, 1414/10000 person-years) of patients with CKD (matched hazard ratio {HR} when CKD-DM was compared with CKD-only, 1.25; 95% confidence interval {CI}, 1.07–1.46; p=0.006; Figure 2a and Table 2). In the absence of a hidden bias, a sign-score test for matched data with censoring provides strong evidence (p=0.005) that CKD-only patients outlived those with CKD-DM. A hidden covariate that is near-perfect predictor of mortality would need to increase the odds of having CKD-DM by 7.08% to potentially explain away this association. The association between CKD-DM and all-cause mortality was homogenous across different subgroups (Figure 3). Associations of CKD-DM with cardiovascular and HF mortality are displayed in Table 2.

3.4 CKD-DM and hospitalization

Overall 1413 (71.6%) patients were hospitalized for all causes. All-cause hospitalization occurred in 75.4% (rate, 5710/10000 person-years) and 67.8% (rate, 4213/10000 person-years) of CKD-DM and CKD-only patients, respectively (matched HR when CKD-DM was compared with CKD-only, 1.32; 95% CI, 1.15–1.52; p<0.0001; Figure 2b and Table 2). A sign-score test for matched data with censoring provides strong evidence (p<0.0001) that CKD-only patients had fewer hospitalizations than those with CKD-DM. A hidden covariate would need to increase the odds of hospitalization by 16.00% to potentially explain away this association. Associations of CKD-DM with cardiovascular and HF hospitalization are displayed in Table 2.

4. Discussion

4.1 Key study findings

In the current analysis, we demonstrate that in patients with chronic HF, the risk of adverse outcomes associated with CKD is further increased by the presence of additional comorbidity due to DM. These findings are important as HF is common among older adults who also suffer from multimorbidity. To the best of our knowledge, this is the first report of a propensity-matched study of associations of multimorbidity associated with DM with outcomes in chronic HF patients with CKD.

4.2 Mechanistic insights to study findings

All patients in our study had chronic HF and CKD and thus had a high baseline risk for poor outcomes [2]. The additional risk associated with the presence of DM may be a direct intrinsic effect of DM, a confounding effect by one or more measured covariates, and/or a confounding effect by one or more unmeasured covariates. DM is associated with activation of neurohormonal systems and the direct metabolic effects of DM and hyperglycemia are well known [16,17]. Patients with DM are at increased risk of developing diabetic cardiomyopathy and diabetic nephropathy, which may indicate poor control or long duration of DM. Therefore, DM in the presence of CKD may be a marker of advanced DM and concomitant vascular disease from oxidative stress, inflammation, and advanced glycation endproducts [18]. The association between multimorbidity and poor outcomes may also be explained by the disease burden. With each additional comorbidity, the overall disease burden is increased, which in turn may increase the risk of disease-disease and disease-treatment interaction, and poor outcomes.

The findings of our study are unlikely to be explained by differences in baseline characteristics, as our matched cohort was well-balanced at baseline on all measured covariates. Results of our sensitivity analysis suggest that our findings may be relatively insensitive to a hidden bias. However, sensitivity analysis cannot determine if such a hidden bias exists or not. More importantly, for an imaginary hidden bias to explain away our findings it should be a near-perfect predictor of mortality and hospitalization, and also should not be strongly correlated with any of the covariates used in our propensity score model.

4.3 Comparison with prior studies

In patients with acute myocardial infarction, the rate of all-cause mortality has been shown to be significantly higher in those with CKD and DM than those with CKD only (40% versus 27%; $p < 0.001$) [19]. However, to the best of our knowledge this is the first report of a propensity-matched study of the association between multimorbidity involving DM and CKD in patients with chronic HF.

4.4 Study limitations

Several limitations of this study need to be acknowledged. Patients in the DIG trial were relatively young, predominantly white and mostly men, with normal sinus rhythm from the pre-beta-blocker era of HF therapy, which may limit generalizability. We also had no data on duration, severity and treatment of DM at baseline or during follow up. Patients without DM at baseline may have developed DM during follow up. This phenomenon, called regression dilution, may have underestimated the true associations observed in our study [20].

4.5 Conclusions

In conclusion, in this propensity-matched study of chronic HF patients with CKD, in which patients with and without DM were well-balanced on all measured baseline characteristics, the presence of DM was associated with significant increases in mortality and hospitalization. These findings highlight the importance of multimorbidity associated with DM and CKD on outcomes relative comorbidity due to CKD in patients with chronic HF. Future studies need to prospectively test preventive and therapeutic interventions to prevent multimorbidity and to reduce multimorbidity-associated poor outcomes in chronic HF.

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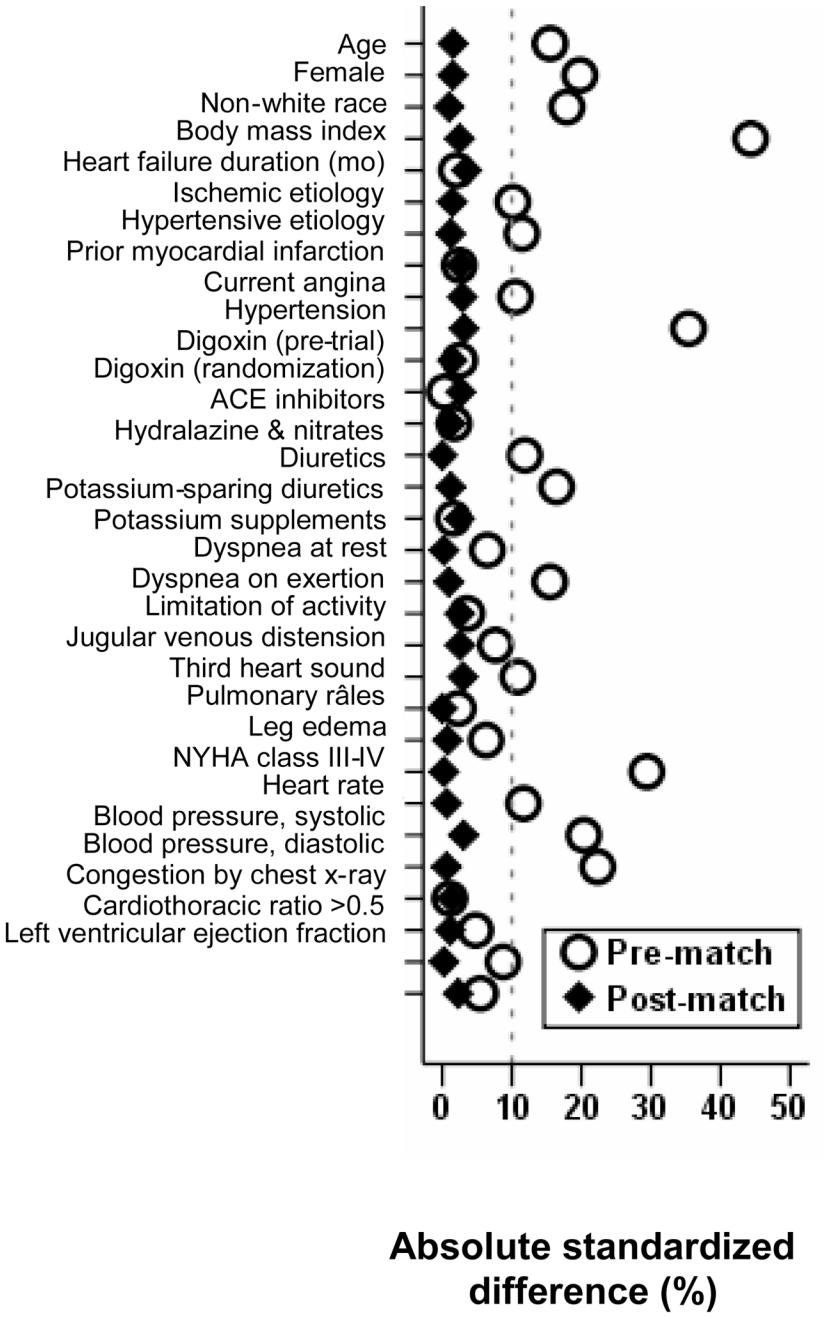

Figure 1.
Love plot displaying absolute standardized differences for covariates between chronic heart failure patients with comorbidity due to chronic kidney disease alone and those with multimorbidity due to both chronic kidney disease and diabetes mellitus, before and after propensity score matching (ACE=angiotensin-converting enzyme; NYHA=New York Heart Association)

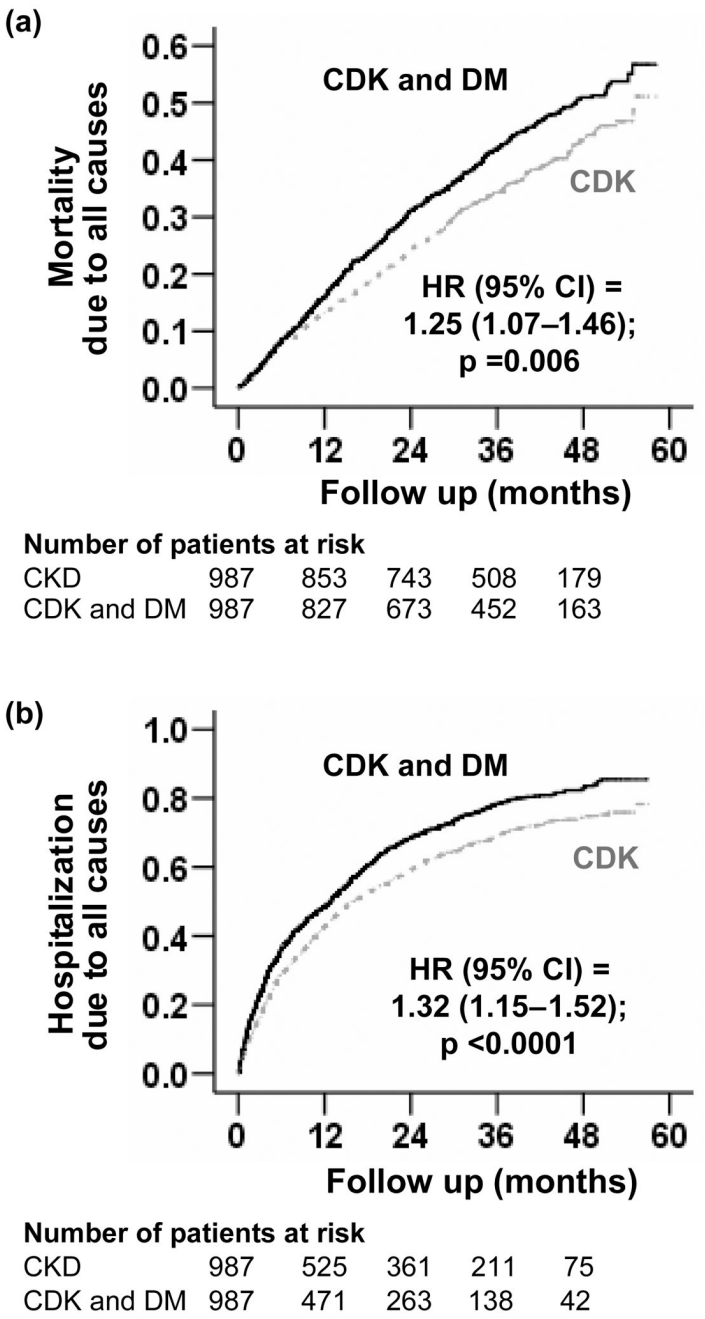

Figure 2.
Kaplan-Meier plots for (a) all-cause mortality, and (b) all-cause hospitalization (CI=confidence interval; CKD=chronic kidney disease; DM=diabetes mellitus; HR=hazard ratio)

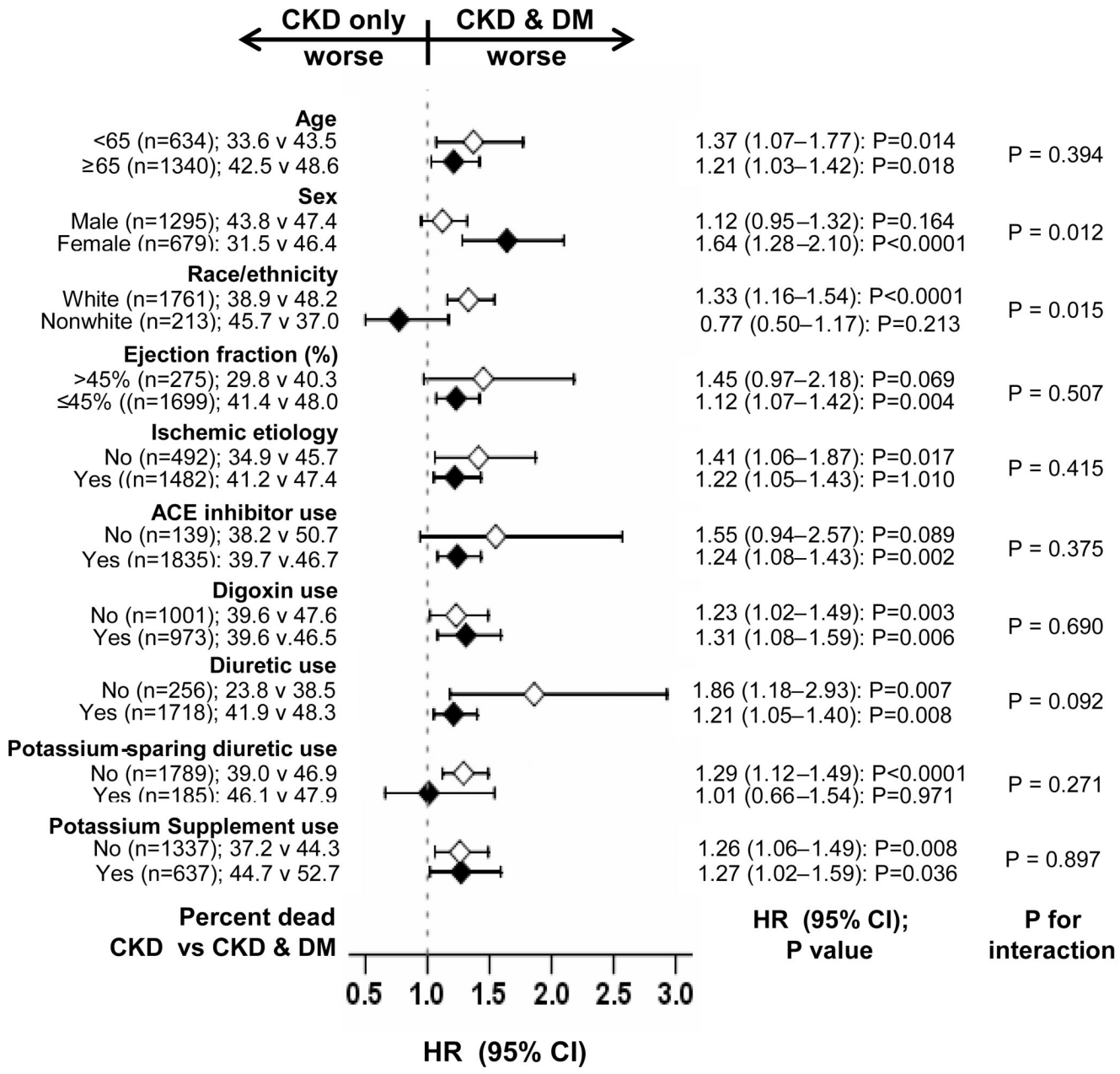

Figure 3.

Association of multimorbidity due to chronic kidney disease (CKD) and diabetes mellitus (DM) with all-cause mortality in subgroups of propensity-matched chronic heart failure patients (ACE=angiotensin-converting enzyme; CI=confidence interval; HR=hazard ratio)

Table 1

Baseline patient characteristics, before and after propensity score matching

N (%) or mean (±SD)	Before matching			After matching		
	CKD (N = 2432)	CKD & DM (N=1095)	P	CKD (N = 987)	CKD & DM (N = 987)	P
Age (years)	69 (±9)	67 (±8)	<0.0001	68 (±10)	68 (±8)	0.733
Female	688 (28%)	411 (36%)	<0.0001	336 (34%)	343 (35%)	0.776
Non-white	175 (7%)	137 (13%)	<0.0001	105 (11%)	108 (11%)	0.884
Body mass index, kg/m^2	26 (±5)	29 (±6)	<0.0001	28 (±5)	28 (±5)	0.532
Duration of HF (months)	30 (±36)	31 (±38)	0.580	30 (±37)	31 (±38)	0.443
Primary cause of HF						
Ischemic	1735 (71%)	830 (76%)		738 (75%)	744 (75%)	
Hypertensive	226 (9%)	141 (13%)		129 (13%)	125 (13%)	
Idiopathic	318 (13%)	96 (9%)	<0.0001	93 (9%)	90 (9%)	0.667
Others	153 (6%)	28 (3%)		27 (3%)	28 (3%)	
Prior myocardial infarction	1591 (65%)	729 (67%)	0.503	651 (66%)	663 (67%)	0.605
Current angina	661 (27%)	350 (32%)	0.004	291 (30%)	304 (31%)	0.554
Hypertension	1101 (45%)	686 (63%)	<0.0001	602 (61%)	587 (60%)	0.487
Medications						
Pre-trial digoxin use	1025 (42%)	475 (43%)	0.493	417 (42%)	424 (43%)	0.791
Trial use of digoxin	1205 (50%)	541 (49%)	0.938	480 (49%)	493 (50%)	0.574
ACE inhibitors	2248 (92%)	1017 (93%)	0.643	919 (93%)	916 (93%)	0.862
Hydralazine & nitrates	33 (1%)	34 (3%)	<0.0001	26 (3%)	26 (3%)	1.000
Diuretics	1989 (82%)	960 (88%)	<0.0001	861 (87%)	857 (87%)	0.838
PS diuretics	220 (9%)	104 (10%)	0.667	89 (9%)	96 (10%)	0.639
Potassium supplement	731 (30%)	362 (33%)	0.074	318 (32%)	319 (32%)	1.000
Symptoms and signs of HF						
Dyspnea at rest	504 (21%)	299 (27%)	<0.0001	261 (26%)	257 (26%)	0.877
Dyspnea on exertion	1872 (77%)	859 (78%)	0.333	785 (80%)	775 (79%)	0.621
Limitation of activity	1867 (77%)	875 (80%)	0.038	793 (80%)	783 (79%)	0.616
Jugular venous distension	331 (14%)	192 (18%)	0.002	163 (17%)	174 (18%)	0.548
Third heart sound	600 (25%)	281 (26%)	0.529	257 (26%)	257 (26%)	1.000

N (%) or mean (±SD)	Before matching			After matching		
	CKD (N = 2432)	CKD & DM (N=1095)	P	CKD (N = 987)	CKD & DM (N = 987)	P
Pulmonary râles	433 (18%)	222 (20%)	0.081	200 (20%)	203 (21%)	0.909
Lower extremity edema	461 (19%)	346 (32%)	<0.0001	293 (30%)	292 (30%)	1.000
NYHA functional class, %						
Class I	298 (12%)	127 (12%)		130 (13%)	118 (12%)	
Class II	1283 (53%)	523 (48%)		461 (47%)	476 (48%)	
Class III	789 (32%)	405 (37%)	0.008	365 (37%)	360 (37%)	0.984
Class IV	62 (3%)	40 (4%)		31 (3%)	33 (3%)	
Heart rate (/minute),	77 (±13)	80 (±12)	<0.0001	80 (±13)	79 (±12)	0.488
Blood pressure (mm Hg)						
Systolic	127 (±21)	132 (±22)	<0.0001	131 (±22)	131 (±21)	0.894
Diastolic	75 (±11)	74 (±11)	0.769	74 (±12)	74 (±11)	0.757
Chest radiograph findings						
Pulmonary congestion	364 (15%)	183 (17%)	0.185	161 (16%)	165 (17%)	0.856
Cardiothoracic ratio >0.5	1497 (62%)	720 (66%)	0.017	641 (65%)	640 (65%)	1.000
Ejection fraction	32 (±13)	33 (±12)	0.139	33 (±13)	32 (±12)	0.620

ACE=angiotensin-converting enzyme; CKD=chronic kidney disease; DM=diabetes mellitus; HF=heart failure; NYHA=New York Heart Association; PS=potassium sparing; SD=standard deviation

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Table 2

Association of multimorbidity due to both by chronic kidney disease (CKD) and diabetes mellitus (DM) relative to CKD alone, with mortality and hospitalization

Outcomes	CKD (N = 987)	CKD & DM (N = 987)	Absolute Rate Difference (per 10,000 Person-Years)†	Matched Hazard Ratio (95% Confidence Interval)	P Value
	Rate per 10,000 Person-Years (Events / Total Follow-Up Years)				
Mortality					
All-cause	1414 (391 / 2766)	1783 (464 / 2603)	+ 369	1.25 (1.07–1.46)	0.006
Cardiovascular	1121 (310 / 2766)	1402 (365 / 2603)	+ 281	1.27 (1.06–1.52)	0.009
Heart failure	524 (145 / 2766)	707 (184 / 2603)	+ 183	1.34 (1.04–1.72)	0.025
Hospitalization*					
All-cause	4213 (669 / 1588)	5710 (744 / 1303)	+ 1497	1.32 (1.15–1.52)	<0.0001
Cardiovascular	2764 (521 / 1885)	3851 (615 / 1597)	+ 1087	1.29 (1.12–1.49)	0.001
Heart failure	1409 (325 / 2306)	2082 (421 / 2022)	+ 673	1.37 (1.16–1.63)	<0.0001

*Data shown include the first hospitalization of each patient due to each cause.

†Absolute differences were calculated by subtracting the percentage of patients dead or hospitalized in the CKD group from the rates of death and hospitalization in the CKD and DM group (before values were rounded)