Published in final edited form as:

Am J Cardiol. 2009 January 1; 103(1): 88–92. doi:10.1016/j.amjcard.2008.08.035.

Multimorbidity due to Diabetes Mellitus and Chronic Kidney Disease and Outcomes in Chronic Heart Failure

O. James Ekundayo, MBChB, DrPH^a, Maureen Muchimba, MPH^a, Inmaculada B. Aban, PhD^a, Christine Ritchie, MD, MSPH^a, Ruth C. Campbell, MD^a, and Ali Ahmed, MD, MPH^{a,b,*}

^a University of Alabama at Birmingham, Birmingham, AL

^b VA Medical Center, Birmingham, AL

Abstract

Diabetes mellitus (DM) and chronic kidney disease (CKD) are common in patients with chronic heart failure (HF) and are associated with poor outcomes. However, the impact of multimorbidity due to DM and CKD on outcomes, relative to comorbidity due to DM alone, has not been well studied in these patients. Of the 7788 patients with chronic HF in the Digitalis Investigation Group trial, 2218 had DM. We categorized these patients into those with DM alone (DM-only; n=1123) and those with both DM and CKD (DM-CKD; n=1095). Propensity scores for DM-CKD, calculated for each of the 2218 patients, were used to match 699 pairs of DM-only and DM-CKD patients. Matched Cox regression models were used to estimate associations between DM-CKD and outcomes. All-cause mortality occurred in 44% (rate, 1648/10000 person-years) of DM-CKD patients and 39% (rate, 1349/10000 person-years of follow-up) of DM-only patients (hazard ratio when DM-CKD was compared with DM-only, 1.34; 95% confidence interval {CI}, 1.11–1.62; p=0.003). All-cause hospitalization occurred in 76% (rate, 5799/10000 person-years) and 73% (rate, 4909/10000 person-years) of DM-CKD and DM-only patients respectively (hazard ratio, 1.16; 95% CI, 0.99–1.36; p=0.064). Respective hazard ratios (95% CI) for other outcomes were: cardiovascular mortality (1.33; 1.07–1.66; p=0.010), HF mortality (1.41; 1.02–1.96; p=0.040), cardiovascular hospitalization (1.17; 0.99–1.39; p=0.064) and HF hospitalization (1.26; 1.03–1.55; p=0.026). In conclusion, compared to comorbidity due to DM alone, the presence of multimorbidity due to DM and CKD was associated with increased mortality and morbidity in patients with chronic HF.

Keywords

heart failure; multimorbidity; diabetes; chronic kidney disease; outcomes

Diabetes mellitus (DM) and chronic kidney disease (CKD) are common comorbidities in HF and are known to be associated with poor outcomes.^{1–4} However, the effect of multimorbidity with DM and CKD (versus DM alone) on outcomes in chronic HF has not been well studied. We used a public-use copy of the Digitalis Investigation Group (DIG) trial dataset, obtained from the National Heart, Lung, and Blood Institute, to study the effect of DM and CKD in a propensity-matched population of patients with chronic HF and DM.

*Corresponding author: Ali Ahmed, MD, MPH, University of Alabama at Birmingham, 1530 3rd Ave South, CH-19, Ste-219, Birmingham AL 35294-2041; Telephone: 1-205-934-9632; Fax: 1-205-975-7099; Email: aahmed@uab.edu.

Conflict of Interest Disclosures: None

Methods

The DIG was a multicenter randomized clinical trial of digoxin in patients with chronic HF in normal sinus rhythm and receiving ACE inhibitors conducted in the United States and Canada.^{5,6} Of the 7788 DIG participants, 2218 (26%) had a history of DM, of whom 1095 (49%) had CKD.² Data on DM were collected at baseline from medical history and CKD was defined as an estimated glomerular filtration rate of <60 ml/min/1.73 m² body surface area.^{4,7,8} Based on the presence of CKD, we categorized these 2218 patients into DM-only (n=1123) and DM-CKD (n=1095) groups. Our primary outcomes were mortality and hospitalization due to all causes, and secondary outcomes were those due to cardiovascular causes and HF. Data on vital status were known for 99% of DIG participants.⁹

To ensure that DM-only and DM-CKD patients would be well-balanced on all measured baseline characteristics, we used a propensity-matched design.^{10–13} First, we estimated propensity scores for DM-CKD for each of the 2218 patients using a non-parsimonious, multivariate logistic regression model. In that model, DM-CKD was used as the dependent variable and all measured baseline covariates displayed in Figure 1 were used as covariates.^{2,4,14} We then used the propensity scores to match 699 DM-CKD patients with 699 DM-only patients. Post-match covariate balance was objectively assessed by estimating absolute standardized differences and presented as a Love plot, developed by Thomas E. Love, PhD.^{15,16} We used Kaplan-Meier and matched Cox regression analyses to examine the association of DM-CKD with outcomes, and assessed the homogeneity of this association in various subgroups of patients. Finally, to examine if there was a synergism between DM and CKD in chronic HF, we analyzed the pre-match data, to estimate unadjusted hazard ratios for all-cause mortality separately for DM, CKD, and DM-CKD, compared with those without DM or CKD. We then assessed additive synergism by comparing the individual effects of DM and CKD with the observed combined effect of DM-CKD. All statistical tests were done using SPSS-15 for Windows.¹⁷

Results

Baseline characteristics for both groups before and after matching are displayed in Table 1. Values of absolute standardized differences for all covariates were $<10\%$ (most $<5\%$) after matching, suggesting substantial bias reduction (Figure 1). Of the 1398 patients included in the propensity-matched analysis 582 (42%) patients died from all causes and 1040 (74%) patients were hospitalized for all causes.

All-cause mortality occurred in 44% (rate, 1648/10000 person-years) and 39% (rate, 1349/10000 person-years) of DM-CKD and DM-only patients respectively (matched hazard ratio {HR} when DM-CKD was compared with DM-only, 1.34; 95% confidence interval {CI}, 1.11–1.62; $p=0.003$; Figure 2a and Table 2). The association was homogenous across different subgroups (Figure 3). In the absence of a hidden confounder, a sign-score test for matched data with censoring provides strong evidence ($p=0.0027$) that DM-CKD was associated with increased mortality. An unmeasured covariate which is a near-perfect predictor of mortality would need to increase the odds of having both DM and CKD by 10.55% to explain away this association. Associations of DM-CKD with cardiovascular and HF mortality are displayed in Table 2.

Analysis of pre-match data did not reveal any additive synergistic interaction between DM and CKD. The unadjusted hazard ratios for all-cause mortality for patients with neither DM nor CKD, DM only, CKD only and both DM and CKD were respectively 1.00, 1.47, 1.63 and 2.12. Based on these unadjusted hazard ratios, the expected ($1 + 0.47 + 0.63 = 2.10$) and the observed (2.12) effects of DM-CKD were similar.

All-cause hospitalization occurred in 76% (rate, 5799/10000 person-years) of DM-CKD patients, and 73% (rate, 4909/10000 person-years) of DM-only patients (HR when DM-CKD was compared with DM-only, 1.16; 95% CI, 0.99–1.36; $p=0.064$; Figure 2b and Table 2). Associations of DM-CKD with cardiovascular and worsening HF hospitalization are displayed in Table 2.

Discussion

Findings from this study demonstrate that among patients with chronic HF, compared with comorbidity due to DM alone, multimorbidity due to DM and CKD was associated with worse prognosis. These findings are important as most HF patients are older adults who suffer from multimorbidity, and DM and CKD are common comorbidities in these patients. To the best of our knowledge, this is the first propensity-matched study to demonstrate additional prognostic effect of baseline multimorbidity due to DM and CKD compared with comorbidity due to DM alone in patients with chronic HF.

There are several potential explanations for our findings: a direct effect of CKD, a confounding effect by one or more of the measured covariates, or a confounding effect by one or more of the unmeasured covariates. The adverse effect of CKD in the population in general, and in HF patients in particular, is well-established.^{4,18} CKD is associated with activation of the renin-angiotensin-aldosterone system, which is also activated in DM and HF.^{19,20} Even though it is not clearly understood how these three conditions with similar neurohormonal activation interact with each other. Our data suggest that the presence of CKD as an additional comorbidity further increases the risk of death and hospitalization in those with HF and DM. However, findings from our study also suggest that these two comorbidities may exert their negative prognostic effect individually and there may not be any additional synergism between them. The poor prognosis of DM-CKD patients are unlikely to be explained by imbalances in measured baseline covariates as they were all well-balanced in our matched cohort. Results of our sensitivity analysis suggest that our finding of association between DM-CKD and all-cause mortality was relatively insensitive to an unmeasured covariate.

There were only 20 extra hospitalizations due to all causes compared with 38 extra deaths in the DM-CKD group compared with the DM-only group (Table 2). This preferential effect of DM-CKD on mortality relative to hospitalization may have been due to sudden cardiac death in those with DM-CKD which may have prevented those patients from being hospitalized. The effect of CKD on mortality was observed in a wide spectrum of chronic HF patients with DM. The significant interaction between race and CKD in these patients is likely a chance finding given the small number of nonwhite patients in our study. A relatively stronger association of CKD with mortality in DIG participants with normal left ventricular ejection fraction has been previously reported.⁴

Our study has several limitations. Patients in the DIG trial were younger white men in normal sinus rhythm from the pre-beta-blocker era of HF therapy which may limit the generalizability of these findings to contemporary HF patients. Also, it is possible that patients without CKD at baseline developed CKD during follow up, which could have underestimated the association observed in our study. As in all observational study, we cannot rule out bias due to imbalance in an unmeasured covariate. Our sensitivity analysis indicates that our findings are modestly insensitive to an unmeasured binary covariate that is a near-perfect predictor of mortality. However, sensitivity analysis cannot determine if such a hidden cofounder exists or not. It is important to remember that an unmeasured covariate does not automatically become an unmeasured confounder. To be a confounder, a covariate that is a near-perfect predictor of mortality, is also required to be associated with both DM and CKD, and must not be strongly correlated with any of the covariates used to calculate propensity scores. Despite these

limitations, the findings from this first report of a propensity-matched study of multimorbidity highlight the additional burden of CKD in chronic HF patients with DM and underscore the importance of prevention and treatment of comorbidities in chronic HF.

Acknowledgements

“The Digitalis Investigation Group (DIG) study was conducted and supported by the NHLBI in collaboration with the DIG Investigators. This Manuscript was prepared using a limited access dataset obtained by the NHLBI and does not necessarily reflect the opinions or views of the DIG Study or the NHLBI.”

Funding/Support: Dr. Ahmed is supported by the National Institutes of Health through grants from the National Heart, Lung, and Blood Institute (5-R01-HL085561-02 and P50-HL077100), and a generous gift from Ms. Jean B. Morris of Birmingham, Alabama

References

1. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. *Am J Cardiol* 1974;34:29–34. [PubMed: 4835750]
2. Ahmed A, Aban IB, Vaccarino V, Lloyd-Jones DM, Goff DC Jr, Zhao J, Love TE, Ritchie C, Ovalle F, Gambassi G, Dell'Italia LJ. A propensity-matched study of the effect of diabetes on the natural history of heart failure: variations by sex and age. *Heart* 2007;93:1584–1590. [PubMed: 17488764]
3. Smilde TD, Hillege HL, Voors AA, Dunselman PH, Van Veldhuisen DJ. Prognostic importance of renal function in patients with early heart failure and mild left ventricular dysfunction. *Am J Cardiol* 2004;94:240–243. [PubMed: 15246913]
4. Ahmed A, Rich MW, Sanders PW, Perry GJ, Bakris GL, Zile MR, Love TE, Aban IB, Shlipak MG. Chronic kidney disease associated mortality in diastolic versus systolic heart failure: a propensity matched study. *Am J Cardiol* 2007;99:393–398. [PubMed: 17261405]
5. The Digitalis Investigation Group. Rationale, design, implementation, and baseline characteristics of patients in the DIG trial: a large, simple, long-term trial to evaluate the effect of digitalis on mortality in heart failure. *Control Clin Trials* 1996;17:77–97. [PubMed: 8721804]
6. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997;336:525–533. [PubMed: 9036306]
7. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999;130:461–470. [PubMed: 10075613]
8. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002;39:S1–266. [PubMed: 11904577]
9. Collins JF, Howell CL, Horney RA. Determination of vital status at the end of the DIG trial. *Control Clin Trials* 2003;24:726–730. [PubMed: 14662278]
10. Rosenbaum PR, Rubin DB. The central role of propensity score in observational studies for causal effects. *Biometrika* 1983;70:41–55.
11. Rosenbaum PR, Rubin DB. Reducing bias in observational studies using subclassification on the propensity score. *J Am Stat Asso* 1984;79:516–524.
12. Rubin DB. Estimating causal effects from large data sets using propensity scores. *Ann Intern Med* 1997;127:757–763. [PubMed: 9382394]
13. Rubin DB. Using propensity score to help design observational studies: Application to the tobacco litigation. *Health Services and Outcomes Research Methodology* 2001;2:169–188.
14. Ahmed A, Husain A, Love TE, Gambassi G, Dell'Italia LJ, Francis GS, Gheorghiadu M, Allman RM, Meleth S, Bourge RC. Heart failure, chronic diuretic use, and increase in mortality and hospitalization: an observational study using propensity score methods. *Eur Heart J* 2006;27:1431–1439. [PubMed: 16709595]
15. D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med* 1998;17:2265–2281. [PubMed: 9802183]

16. Normand ST, Landrum MB, Guadagnoli E, Ayanian JZ, Ryan TJ, Cleary PD, McNeil BJ. Validating recommendations for coronary angiography following acute myocardial infarction in the elderly: a matched analysis using propensity scores. *J Clin Epidemiol* 2001;54:387–398. [PubMed: 11297888]
17. SPSS. SPSS for Windows, Rel. 15. Chicago, IL: SPSS Inc., Chicago, IL; 2008.
18. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;351:1296–1305. [PubMed: 15385656]
19. Remuzzi G, Perico N, Macia M, Ruggenti P. The role of renin-angiotensin-aldosterone system in the progression of chronic kidney disease. *Kidney Int Suppl* 2005:S57–65. [PubMed: 16336578]
20. Lim HS, MacFadyen RJ, Lip GY. Diabetes mellitus, the renin-angiotensin-aldosterone system, and the heart. *Arch Intern Med* 2004;164:1737–1748. [PubMed: 15364666]

Figure 1.

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

Figure 2a

Figure 2b

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 both diabetes mellitus (DM) and chronic kidney disease (CKD) 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

Variable	Before Propensity Score Matching			After Propensity Score Matching		
	DM (n = 1123)	DM and CKD (n = 1095)	P value	DM (n = 699)	DM and CKD (n = 699)	P value
Age (years)	61 (±9)	67 (±8)	<0.0001	65 (±8)	65 (±8)	0.836
Female	239 (21%)	411 (38%)	<0.0001	193 (28%)	185 (27%)	0.657
Non-white	252 (22%)	137 (13%)	<0.0001	120 (17%)	111 (16%)	0.554
Body mass index (kg/m ²)	29 (±6)	29 (±6)	0.005	29 (±6)	29 (±6)	0.431
Duration of heart failure (months)	29 (±36)	31 (±38)	0.182	32 (±40)	30 (±35)	0.313
Primary cause of heart failure						
Ischemic	808 (72%)	830 (76%)	0.001	527 (75%)	513 (73%)	0.709
Hypertensive	129 (12%)	141 (13%)		81 (12%)	85 (12%)	
Idiopathic	124 (11%)	96 (9%)		68 (10%)	77 (11%)	
Others	62 (6%)	28 (3%)		23 (3%)	24 (3%)	
Prior myocardial infarction	719 (64%)	729 (67%)	0.207	467 (67%)	451 (65%)	0.383
Current angina pectoris	319 (28%)	350 (32%)	0.068	208 (30%)	204 (29%)	0.862
Hypertension	629 (56%)	686 (63%)	0.001	406 (58%)	406 (58%)	1.000
Medications						
Pre-trial digoxin use	484 (43%)	475 (43%)	0.894	289 (41%)	274 (39%)	0.450
Trial use of digoxin	555 (49%)	541 (49%)	0.994	348 (50%)	347 (50%)	1.000
ACE inhibitors	1071 (95%)	1017 (93%)	0.012	661 (95%)	661 (95%)	1.000
Diuretics	910 (81%)	960 (88%)	<0.0001	598 (86%)	595 (85%)	0.878
PS diuretics	67 (6%)	104 (10%)	0.002	56 (8%)	50 (7%)	0.617
Potassium suppl.	314 (28%)	362 (33%)	0.009	212 (30%)	207 (30%)	0.816
Symptoms/signs of heart failure						
Dyspnea at rest	288 (26%)	299 (27%)	0.376	199 (29%)	171 (25%)	0.095
Dyspnea on exertion	846 (75%)	859 (78%)	0.082	551 (79%)	544 (78%)	0.694
Limitation of activity	879 (78%)	875 (80%)	0.344	560 (80%)	555 (79%)	0.784
JVD	156 (14%)	192 (18%)	0.018	118 (17%)	108 (16%)	0.518
Third heart sound	260 (23%)	281 (26%)	0.169	162 (23%)	159 (23%)	0.900
Pulmonary rales	206 (18%)	222 (20%)	0.249	140 (20%)	132 (19%)	0.640

Variable	Before Propensity Score Matching			After Propensity Score Matching		
	DM (n = 1123)	DM and CKD (n = 1095)	P value	DM (n = 699)	DM and CKD (n = 699)	P value
Leg edema	299 (27%)	346 (32%)	0.010	221 (32%)	210 (30%)	0.567
NYHA class						
Class I	136 (12%)	127 (12%)	0.001	85 (12%)	76 (11%)	0.465
Class II	615 (55%)	523 (48%)		348 (50%)	377 (54%)	
Class III	351 (31%)	405 (37%)		252 (36%)	228 (33%)	
Class IV	21 (2%)	40 (4%)		14 (2%)	18 (3%)	
Heart rate (beat/minute)	82 (±12)	80 (±12)	<0.0001	81 (±12)	81 (±12)	0.838
Blood pressure (mm Hg)						
Systolic	129 (±20)	132 (±22)	<0.0001	130 (±21)	130 (±21)	0.775
Diastolic	76 (±11)	74 (±11)	0.026	74 (±11)	75 (±12)	0.654
Serum potassium (mEq/L)	4.3 (±0.4)	4.4 (±0.5)	<0.0001	4.4 (±0.4)	4.4 (±0.5)	0.400
Chest radiograph						
Pulmonary congestion	195 (17%)	183 (17%)	0.683	119 (17%)	105 (15%)	0.346
CT ratio >0.5	680 (61%)	720 (66%)	0.011	438 (63%)	433 (62%)	0.823
LV ejection fraction	32 (±12)	33 (±12)	0.256	33 (±13)	32 (±12)	0.901
LV ejection fraction >45%	135 (12%)	150 (14%)	0.238	88 (13%)	88 (13%)	1.000

ACE=angiotensin-converting enzyme; CKD=chronic kidney disease; CT=cardiothoracic; DM=diabetes mellitus; HF=heart failure; JVD=jugular venous distension; LV=left ventricular; NYHA=New York Heart Association; PS=potassium sparing

Table 2
Association of multimorbidity due to both diabetes mellitus (DM) and chronic kidney disease (CKD), relative to DM alone, with mortality and hospitalization

	Rate per 10,000 Person-Years (Events/Total Follow-Up Years)		Absolute Rate Difference (per 10,000 person-years) [†]	Matched Hazard Ratio (95% Confidence Interval)	P value
	DM (n = 699)	DM and CKD (n = 699)			
Mortality					
All-cause	1,349 (272/2,017)	1,648 (310/1,881)	+ 299	1.34 (1.11–1.62)	0.003
Cardiovascular	1,026 (207/2,017)	1,249 (235/1,881)	+ 223	1.33 (1.07–1.66)	0.010
Progressive heart failure	436 (88/2,017)	569 (107/1,881)	+ 133	1.41 (1.02–1.96)	0.040
Hospitalization [*]					
All-cause	4,909 (510/1,039)	5,799 (530/914)	+ 890	1.16 (0.99–1.36)	0.064
Cardiovascular	3,151 (410/1,301)	3,759 (433/1,152)	+ 607	1.17 (0.99–1.39)	0.064
Worsening heart failure	1,469 (244/1,661)	1,950 (290/1,487)	+ 481	1.26 (1.03–1.55)	0.026

^{*} Absolute rate differences were calculated by subtracting the rates of death and hospitalization in the DM group from those in the DM and CKD group (before values were rounded)

[†] Data shown include the first hospitalization of each patient due to each cause