WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 7, Issue 03, 1356-1364. Review Article ISSN 2277–7105

A PROPENSITY-MATCHED STUDY OF THE EFFECT OF DIABETES ON THE NATURAL HISTORY OF HEART FAILURE: VARIATIONS BY SEX AND AGE

Laigy George*

India.

Article Received on
20 Dec. 2017,

Revised on 10 Jan. 2018,
Accepted on 31 Jan. 2018
DOI: 10.20959/wjpr20183-10846

***Corresponding Author**
Laigy George
India.

ABSTRACT

Poor prognosis in heart failure (HF) patients with diabetes is often attributed to increased comorbidity and advanced disease. Further, this effect may be worse in women. To determine whether the effect of diabetes on outcomes and the sex-related variation persisted in a propensity score-matched HF population, and whether the sex-related variation was a function of age. Of the 7788 HF patients in the Digitalis Investigation Group trial, 2218 had a history of diabetes. Propensity score for diabetes was calculated for each patient using a non-parsimonious logistic regression model incorporating all measured baseline covariates, and was used to match 2056 (93%) diabetic patients with 2056 non-diabetic patients. All-cause mortality occurred in 135 (25%) and 216 (39%) women without and with diabetes (adjusted HR = 1.67; 95% CI = 1.34 to 2.08; p,0.001). Among men, 535 (36%) and 609 (41%) patients without and with diabetes died from all causes (adjusted HR = 1.21; 95% CI = 1.07 to 1.36; p = 0.002). Sex– diabetes interaction (overall adjusted p,0.001) was only significant in patients >65 years (15% absolute risk increase in women; multivariable p for interaction = 0.005), but not in younger patients (2% increase in women; p for interaction = 0.173). Risk-adjusted HR (95% CI) for all-cause hospitalisation for women and men were 1.49 (1.28 to 1.72) and 1.21 (1.11 to 1.32), respectively, also with significant sex–diabetes interaction (p = 0.011). Diabetes-associated increases in morbidity and mortality in chronic HF were more pronounced in women, and theses sex-related differences in outcomes were primarily observed in elderly patients

INTRODUCTION

Diabetes is common in heart failure (HF) and is associated with poor outcomes.[1,2] HF

patients with diabetes are sicker and have a higher burden of co-morbidity than those without diabetes.[1,2] Diabetes is also associated with activation of the renin–angiotensin–aldosterone and sympathetic nervous systems.[3,4] There is mounting evidence that diabetes adversely affects collagen production in fibroblasts and calcium homeostasis in cardiac myocytes.[5,6] However, it is not clear to what extent the diabetes-associated poor outcomes in HF are due to the direct effects of diabetes. Although outcome-based multivariable risk adjustment models can account for these confounding covariates to some extent, concerns for residual bias limit interpretation of these results.[7] To address this concern, propensity score matching can be used to assemble cohorts of patients with and without an exposure who would be well balanced in all measured baseline covariates.[8-10] More importantly, as investigators remain blinded during the design phase of a randomised clinical trial, this process of bias reduction and study cohort assembly can be done without any knowledge or use of the outcomes data, and the magnitude of bias reduction may be objectively assessed using standardised differences.[7, 9–11] Data from patients with coronary artery disease and elderly patients hospitalised with systolic HF suggest that the effect of diabetes might be worse in women than in men.[12–14] However, little is known about the sex-related variation in the effect of diabetes on outcomes in a more stable younger ambulatory patient population with mild to moderate systolic and diastolic HF. It is also unknown if this sex-related difference in the effect of diabetes on HF is a function of age. The purpose of this study thus is to determine the effect of diabetes on mortality and hospitalisation in propensity score-matched ambulatory HF patients and to determine if the effect varies by sex and if the sex-related differences vary by age.

METHODS

Data source and patients We conducted a secondary analysis of the Digoxin Investigation Group (DIG) data set. A detailed description of the rationale, design, implementation, patient characteristics and results of the DIG trial has been published previously.[15,16] Briefly, DIG recruited 7788 ambulatory patients with systolic (ejection fraction (45%; n = 6800) and diastolic (ejection fraction. 45%; n = 988) HF patients from 302 centres in the USA and Canada during 1991–1993. These patients were randomised to receive either digoxin or placebo, and were followed-up for a median of 38 months. Diabetes The presence of baseline diabetes as a co-morbid condition was ascertained by investigators based on chart documentation of diabetes. Data on baseline diabetes were available on all 7788 participants, of which 2218 (28.5%) had diabetes. Outcomes The primary outcomes for this analysis are

mortality and hospitalisation due to all causes. We also studied mortality and hospitalisations due to cardiovascular causes and worsening HF Estimation of propensity scores Because of the significant imbalances in baseline covariates between patients with and without diabetes (table 1), we used propensity scores to reduce imbalance.[7-9] 11 17–20 We used a nonparsimonious multivariable logistic regression model to estimate propensity scores for diabetes for all patients. Covariates included in the model were age, sex, race, body mass index, HF duration, HF aetiology, co-morbidities (myocardial infarction, current angina and hypertension), medications (ACE inhibitors, pretrial digoxin, potassium-sparing diuretic, non-potassium-sparing diuretic, potassium supplement, and nitrates, hydralazine and other vasodilators), functional status (New York Heart Association (NYHA) functional class), symptoms (dyspnoea at rest and dyspnoea on exertion), physical signs (jugular venous distension, third heart sound, pulmonary raˆles and lower extremity oedema) and radiological signs (cardiothoracic ratio and pulmonary congestion) of HF, vital signs (heart rate, and systolic and diastolic blood pressure), laboratory data (serum creatinine and potassium levels) and left ventricular ejection fraction.

The model had an appropriate fit (Hosmer–Lemeshow goodness-of-fit x2 6.12 and p = 0.634) and discriminated well (c statistic, 0.711). However, because propensity score models are sample-specific adjusters, and are not used for out-of-sample prediction or estimation of coefficients, measures of calibration and discrimination are less relevant to the assessment of the model's quality.21 Propensity score matching Using an SPSS macro, we matched pairs of patients with and without diabetes who had very similar propensity scores.9 10 20 22 Before matching, the median propensity scores for patients with and without diabetes were 0.34402 and 0.22793, respectively (Mann–Whitney test p,0.0001). After matching, the median propensity scores for patients with and without diabetes were 0.29830 and 0.29877, respectively (Mann– Whitney test p = 0.898). The covariate balance achieved in the matching was assessed by absolute standardised differences in covariates between patients with and without diabetes. Standardised differences measure the degree of bias in covariate means across exposures.[11] It is more appropriate than significance test results for assessing balance in observational studies and is also an important measure of the quality of a propensity score model. Absolute standardised differences of, 10% for all measured covariates suggest that these covariates are well balanced between patients with and without diabetes (fig 1). According to Rubin, "If this balance is achieved in an observational study—that is, if the treatment and control groups have very similar distributions of the observed covariates within

blocks (subclasses, matched pairs, etc.) of the propensity score (perhaps crossed by blocks on critical covariates)—then it really makes no difference, for estimation of effects controlling for these covariates, as to how this balance was achieved.”23 Statistical analysis The analyses were done in two stages for each of the outcome variables of interest. In the first stage, we investigated the effect of diabetes with follow-up analyses on the interaction effect of diabetes with sex. To achieve these aims, several models were fitted. One model only had diabetes as an independent variable. To test for interaction between diabetes and sex, we calculated absolute risk differences and then formally tested for interactions using Mantel–Haenszel tests of homogeneity. We then fitted a Cox proportional hazards model with sex, diabetes and their interaction as covariates. Because we found a significant interaction effect between sex and diabetes, we performed separate analyses for men and women. In particular, we used Kaplan–Meier survival analyses and log-rank tests to compare the survival functions, and fitted bivariate and multivariable Cox proportional hazards models with only diabetes and then added the rest of the covariates (same baseline covariates used in estimating the propensity scores) to estimate the hazard ratios (HRs), separately for men and women, to determine the effect of diabetes on all-cause mortality and all-cause hospitalisations. Our multivariate models incorporated the same baseline covariates as were used in the multivariable logistic regression model used to estimate propensity scores. The second stage of the analyses aims to understand the role of age in sex-related differences in the effect of diabetes. To achieve this, we repeated the above analyses separately for patients ,65 years and >65 years. All statistical tests were evaluated using a two-tailed 95% confidence level. Analyses were performed using SPSS for Windows (Release 14.0).24 RESULTS Patient characteristics The mean (SD) age of 4112 propensity-matched patients was 64 (11) years, 27% were women and 17% were non-whites. Before matching, patients with diabetes were more likely to be women, non-whites, have higher NYHA class, pulmonary congestion, ischaemic cardiomyopathy, hypertension and chronic kidney disease, defined as estimated glomerular filtration rate ,60 ml/1.73 m2 , 2 25 26 and be treated with nonpotassium-sparing diuretics (table 1). There were no imbalances among the matched patients (table 1 and fig 1). Regardless of diabetes, women were more likely to be elderly, non-whites, have higher NYHA class, pulmonary congestion, hypertension and chronic kidney disease, and be treated with diuretics (table 2) Diabetes and mortality During a median 38 months of follow-up, 36% patients died from any cause, 29% died from cardiovascular causes and 13% died from worsening HF. Compared with 33% deaths among patients without diabetes, 40% of those with diabetes died from all causes (HR = 1.29; 95% CI = 1.16 to 1.42; p,0.001). Diabetes-

associated higher mortality persisted after multivariable risk adjustment (adjusted HR = 1.31; 95% CI = 1.18 to 1.45; p,0.001). Adjusted HR for cardiovascular and HF mortality for patients with diabetes were 1.31 (95% CI = 1.16 to 1.46; p,0.001) and 1.42 (95% CI = 1.20 to 1.69; p,0.001), respectively. Sex-related variations in mortality associated with diabetes Kaplan–Meier plots for total mortality are displayed in fig 2A. Compared with men (38%), fewer women (32%) died from all causes during the study (adjusted HR = 0.81; 95% CI = 0.72 to 0.93, p,0.001). Among patients without diabetes, compared with men (36%), fewer women (25%) died from all causes (x2 p,0.001). However, among patients with diabetes, there was no significant difference in mortality between men (41%) and women (39%; x2 p = 0.401). The absolute increase in mortality due to diabetes was more pronounced in women (39% and 25%, respectively, for patients with and without diabetes; x2 p,0.001) than in men (41% and 36%, respectively, in patients without diabetes; x2 p = 0.003). The Mantel–Haenszel test of heterogeneity revealed a significant heterogeneity in the effect of diabetes between the sexes (p = 0.004). A bivariate Cox proportional regression analysis also confirmed a significant interaction between diabetes and sex (p = 0.002). The effect of diabetes on mortality was more pronounced in women (adjusted HR = 1.67; 95% CI = 1.34 and 2.08; p,0.001) than in men (adjusted HR = 1.21; 95% CI = 1.07 to 1.36; p = 0.002) (table 3). These sex-related differences were significant (p for interaction = 0.005). Mortality and age-related variations in sex–diabetes interaction Among HF patients ,65 years, the effect of diabetes on mortality was similar in both women and men with 6% and 8% absolute increases in mortality, respectively (Mantel–Haenszel test for heterogeneity p = 0.524; fig 3). Diabetes significantly increased mortality in both women (adjusted HR = 1.69; p = 0.001) and men (adjusted HR = 1.21; p = 0.036), with no significant sex–diabetes interaction (adjusted p = 0.173; fig 3). Among HF patients >65 years, absolute increases in diabetes-related mortality were 19% and 4%, respectively, for women and men (Mantel–Haenszel test for heterogeneity p = 0.001; fig 3). The increased mortality associated with diabetes persisted after multivariable risk adjustment in elderly women (adjusted HR = 1.87; p,0.001), but was attenuated and lost significance for elderly men (adjusted HR = 1.20; p = 0.021). The sex-related difference in the effect of diabetes on mortality was significant in HF patients >65 years (adjusted p for interaction = 0.005; fig 3). Diabetes and hospitalisation Overall, 69% patients were hospitalised from all causes: 55% were due to cardiovascular causes, 33% due to worsening HF. Compared with 65% hospitalisations among patients without diabetes, 73% of those with diabetes were hospitalised due to all causes (unadjusted HR = 1.28; 95% CI = 1.19 to 1.38; p,0.001). Diabetes-related increased hospitalisation remained unchanged after

multivariable risk adjustment (adjusted HR = 1.28; 95% CI = 1.19 to 1.38; p,0.001). Adjusted HR for cardiovascular and HF hospitalisations for patients with versus without diabetes were 1.31 (95% CI = 1.20 to 1.43: p,0.001) and 1.54 (95% CI = 1.38 to 1.72; p,0.001), respectively. Sex-related variations in hospitalisations associated with diabetes Kaplan–Meier plots for hospitalisations due to all causes are displayed in fig 2B. The absolute increase in all-cause hospitalisations due to diabetes was more pronounced in women (74% and 61%, respectively, for patients with and without diabetes; x2 p ,0.001) than in men (72% and 66%, respectively, for patients with and without diabetes; x2 p,0.001), with a significant Mantel–Haenszel test for heterogeneity (p = 0.032). A bivariate Cox proportional regression analysis also confirmed a significant interaction between diabetes and sex (p = 0.008). The effect of diabetes on allcause hospitalisation was more pronounced in women (adjusted HR = 1.49; 95% CI = 1.28 to 1.72; p,0.001) than in men (adjusted HR = 1.21; 95% CI = 1.11 to 1.32; p,0.001) (table 3). These sex-related differences were significant (p for interaction = 0.011). Hospitalisation and age-related variations in sex– diabetes interaction Among HF patients ,65 years, there was a 17% and 9% increase in all-cause hospitalisations among women and men with diabetes (Mantel–Haenszel test for heterogeneity p = 0.097). However, the relative risk of all-cause hospitalisation due to diabetes was higher among women (adjusted HR = 1.58; 95% CI = 1.25 to 1.99; p,0.001) than in men (adjusted HR = 1.29; 95% CI = 1.14 to 1.47; p,0.001). However, these differences were not significant (multivariable adjusted p for interaction = 0.395). Among HF patients >65 years, absolute increases in diabetes-related all-cause hospitalisations were 10% and 4%, respectively, for women and men (Mantel–Haenszel test for heterogeneity p = 0.112). However, the relative risk of all-cause hospitalisation due to diabetes was higher among women (adjusted HR = 1.53; 95% CI = 1.27 to 1.85; p,0.0001) than in men (adjusted HR = 1.16; 95% CI = 1.03 to 1.31; p = 0.018), with significant interaction (multivariable adjusted p for interaction = 0.002). DISCUSSION In the current study we found that diabetes was associated with a significant increase in the risk of death and hospitalisation among a propensity score-matched cohort of ambulatory HF patients. Importantly, we also observed that the significantly increased diabetes-related mortality and hospitalisations in women were restricted in patients >65 years, which was primarily due to an attenuated effect of diabetes in men >65 years. These results in a relatively stable HF cohort with an excellent balance in all measured baseline covariates suggest that diabetes has a significant negative impact on the natural history of HF, and an early diagnosis and a more stringent control of diabetes is necessary to improve outcomes in HF, especially in elderly women. The findings of our study are consistent with previous

reports on the effect of diabetes on cardiovascular disease in general and HF in particular.1 2 14 27 Gustafsson et al demonstrated a significant effect of diabetes and sex interaction on mortality in elderly hospitalised acute systolic HF patients.14 However, diabetic patients in those studies were sicker and had a higher burden of co-morbidity, as is also evident from the prematch cohort of our study (table 1). Our study confirms the existence of a similar effect of this interaction, but in ambulatory and relatively younger chronic systolic and diastolic HF patients, on both mortality and hospitalisation. Since our propensity score matching achieved an excellent balance in all measured covariates, the deleterious effects of diabetes are probably due to its direct metabolic effects. It is now well appreciated that hyperglycaemia, in addition to the haemodynamic stress of HF can activate neurohormonal systems and reactive oxygen species that promote apoptosis and fibrosis in the heart and kidney.[3,4] These changes at the myocardial level result in more severe left ventricular remodelling and lethal arrhythmias that could account for the increased overall and cardiovascular morbidity and mortality in our cohort of ambulatory HF patients. The differential effect of diabetes on morbidity and mortality in men versus women is quite striking. We noted that compared with men, women with diabetes were older and were also more likely to have higher NYHA class, chronic kidney disease and be receiving diuretics, suggesting a more advanced stage of HF. However, among HF patients without diabetes, women also shared these same characteristics relative to men (table 2) but this did not result in an increased mortality and hospitalisation. These results suggest an effect of diabetes in the female population that is not related to the underlying severity of heart disease or presence of kidney disease. However, our data also indicate that the differential increase in mortality in women with diabetes was largely a function of age, and lack of effect of diabetes in elderly men. Thus, diabetes negates the female sex advantage in elderly HF patients, which is primarily due to a lack of effect of diabetes in elderly men and a greater effect in elderly women. This is important as .80% of all HF patients are >65 years and the prevalence of diabetes increases with age. Although many other studies have shown that diabetes imposes a greater risk of heart disease and HF in women than in men, the effect of age on the greater risk in women with diabetes is less clearly defined. The median age of our patient population was 65 years. It was of interest that there was a significant interaction of diabetes and sex among HF patients >65 years, but not among younger patients. Studies in rat models of diabetes demonstrate that pro-survival signalling pathways and cardiac contractile function were preserved in young females but depressed in age-matched males with streptozotocin-induced diabetes.28 29 However, the protective effects of female gender were negated by advanced age in rodent models of

diabetes.30 This is believed to be in part due to increased insulin resistance and greater susceptibility to ischaemic injury in the ageing female type 2 diabetic heart.31 However, no such data are available from human HF. The disproportionate effect of diabetes in elderly women may also be a function of age and may in part be mediated by the menopause. Several limitations of our study must be acknowledged. Propensity score analyses cannot necessarily account for bias due to unmeasured covariates. Our matching protocol resulted in exclusion of some study participants. However, we were able to match 93% of all patients with diabetes. The diagnosis of diabetes was not centrally adjudicated and we had no data on the duration and control status of diabetes. It is also likely that patients developed diabetes during the follow-up, but these data were not available. This analysis is based on HF patients not receiving beta-blockers, thus limiting generalisability to contemporary HF patients. However, in retrospect, it allowed us to examine the effect of diabetes on the natural history of HF. Additionally, the diagnosis and treatment of diabetes has evolved during the same period. It is therefore important that the results of the current analysis be replicated in contemporary HF patients. In conclusion, we noted that in a wide spectrum of ambulatory patients with chronic mild to moderate systolic and diastolic HF, all measured covariates being balanced at baseline, the presence of diabetes was associated with increased risk of death and hospitalisation. We also noted that the effect of diabetes was significantly worse in women than in men, and that this sex-related variation was restricted to HF patients >65 years. These results suggest that HF patients should be thoroughly evaluated for the presence of diabetes and, if it is present, should be intensively managed based on published guidelines. Future studies should test existing interventions and develop new ones to reduce the adverse effect of diabetes in HF in general, and among older adults with HF, in particular

REFERENCES

1. Shindler DM, Kostis JB, Yusuf S, et al. Diabetes mellitus, a predictor of morbidity and mortality in the Studies of Left Ventricular Dysfunction (SOLVD) Trials and Registry. Am J Cardiol, 1996; 77: 1017–20.
2. Domanski M, Krause-Steinrauf H, Deedwania P, et al. The effect of diabetes on outcomes of patients with advanced heart failure in the BEST trial. J Am Coll Cardiol, 2003; 42: 914–922.
3. Miller JA. Impact of hyperglycemia on the renin angiotensin system in early human type 1 diabetes mellitus. J Am Soc Nephrol, 1999; 10: 1778–85.
4. Lim HS, MacFadyen RJ, Lip GY. Diabetes mellitus, the renin–angiotensin– aldosterone

system, and the heart. Arch Intern Med, 2004; 164: 1737–48.

5. Spiro MJ, Kumar BR, Crowley TJ. Myocardial glycoproteins in diabetes: type VI collagen is a major PAS-reactive extracellular matrix protein. J Mol Cell Cardiol, 1992; 24: 397–410.
6. Aronson D. Cross-linking of glycated collagen in the pathogenesis of arterial and myocardial stiffening of aging and diabetes. J Hypertens, 2003; 21: 3–12.
7. Rubin DB. Using propensity score to help design observational studies: application to the tobacco litigation. Health Serv Outcomes Res Methodol, 2001; 2: 169–88.
8. Rosenbaum PR, Rubin DB. Reducing bias in observational studies using subclassification on the propensity score. J Am Stat Assoc, 1984; 79: 516–24.
9. Ahmed A, Husain A, Love TE, et al. Heart failure, chronic diuretic use, and increase in mortality and hospitalization: an observational study using propensity score methods. Eur Heart J, 2006; 27: 1431–39.
10. Ahmed A, Rich MW, Love TE, et al. Digoxin and reduction in mortality and hospitalization in heart failure: a comprehensive post hoc analysis of the DIG trial. Eur Heart J, 2006; 27: 178–86.
11. Normand ST, Landrum MB, Guadagnoli E, et al. Validating recommendations for coronary angiography following acute myocardial infarction in the elderly: a matched analysis using propensity scores. J Clin Epidemiol, 2001; 54: 387–98.
12. Natarajan S, Liao Y, Sinha D, et al. Sex differences in the effect of diabetes duration on coronary heart disease mortality. Arch Intern Med, 2005; 165: 430–5.
13. Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. BMJ, 2006; 332: 73–8.
14. Gustafsson I, Brendorp B, Seibaek M, et al. Influence of diabetes and diabetes– gender interaction on the risk of death in patients hospitalized with congestive heart failure. J Am Coll Cardiol, 2004; 43: 771–7.
15. 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.