ESC HEART FAILURE
ESC Heart Failure 2016; **3**: 77–85
Published online 30 November 2015 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12079

ORIGINAL RESEARCH ARTICLE

Associations of dipeptidyl peptidase-4 inhibitors with mortality in hospitalized heart failure patients with diabetes mellitus

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Abstract

Background Heart failure (HF) and diabetes mellitus (DM) often co-exist. Treatment of DM in HF patients is challenging because some therapies for DM are contraindicated in HF. Although previous experimental studies have reported that dipeptidyl peptidase-4 (DPP-4) inhibitors improve cardiovascular function, whether DPP-4 inhibition improves mortality of HF patients with DM remains unclear. Therefore, we examined the impact of DPP-4 inhibition on mortality in hospitalized HF patients using propensity score analyses.

Methods and results We performed observational study analysed by propensity score method with 962 hospitalized HF patients. Of these patients, 293 (30.5%) had DM, and 122 of these DM patients were treated with DPP-4 inhibitors. Propensity scores for treatment with DPP-4 inhibitors were estimated for each patient by logistic regression with clinically relevant baseline variables. The propensity-matched 1:1 cohorts were assessed based on propensity scores (DPP-4 inhibitors, $n = 83$, and non-DPP-4 inhibitors, $n = 83$). Kaplan–Meier analysis in the propensity score-matched cohort demonstrated that cardiac and all-cause mortality was significantly lower in the DPP-4 inhibitor group than in the non-DPP-4 inhibitor group (cardiac mortality: 4.8% vs. 18.1%, $P = 0.015$; all-cause mortality: 14.5% vs. 41.0%, $P = 0.003$, by a log-rank test). In the multivariable Cox proportional hazard analyses, after adjusting for other potential confounding factors, the use of DPP-4 inhibitors was an independent predictor of all-cause mortality (pre-matched cohort: hazard ratio 0.467, $P = 0.010$; post-matched cohort: hazard ratio 0.370, $P = 0.003$) in HF patients with DM.

Conclusions Our data suggest that DPP-4 inhibitors may improve cardiac and all-cause mortality in hospitalized HF patients with DM.

Keywords Heart failure; Diabetes mellitus; Dipeptidyl-peptidase-4 inhibitors; Prognosis; Propensity score analyses

Received: 6 August 2015; Revised: 8 October 2015; Accepted: 13 October 2015
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Introduction

Patients with heart failure (HF) are suggested to have a diabetes mellitus (DM) prevalence of 8–41%,[1] which is associated with increased mortality and morbidity.[2,3] Treatment of DM in HF patients is controversial, because many contemporary therapies used for DM treatment, including thiazolidine, are contraindicated in HF.[4–6]

Dipeptidyl peptidase-4 (DPP-4) inhibitors prolong the action of incretin hormones, including glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide, by inhibiting their breakdown. Inhibiting DPP-4 enzymatic function in DM animal models seems to suggest that DPP-4 inhibition may possibly have a beneficial cardiovascular effect in humans.[7–9] Many, but not all, studies in experimental animals have found that DPP-4 inhibition improves cardiac

function and survival following cardiac damage.[10] Pre-clinical and clinical studies have investigated the cardiovascular effects of DPP-4 inhibitors or glucagon-like peptide-1 analogues in HF experimental models or HF patients[7,11,12] and have shown improvements in cardiac function and protection against the development of adverse remodelling. This suggests that DPP-4 inhibitor could have potential as a novel therapeutic strategy in HF patients with DM.

Recent major DPP-4 inhibitor randomized control trials for DM patients [Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53[13,14] and Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE)[15,16]] have raised the hypothesis that HF may be precipitated with the use of DPP-4 inhibitor in DM patients.[17,18] On the other hand, the Trial Evaluating Cardiovascular Outcomes with Sitagliptin study has recently revealed that DPP-4 inhibitor does not increase hospitalization rate for HF patients.[19]

Furthermore, there is no evidence based on randomized clinical trials that DPP-4 inhibitor may improve or worsen mortality in HF patients with DM. However, in light of the unacceptably high cardiac event rates reported by previous studies on DPP-4 inhibitors of DM patients,[13–16] a prospective randomized clinical trial in HF patients with DM using DPP-4 inhibitors seems ethically unjustified. Therefore, we aimed to assess the association of DPP-4 inhibitor with cardiac and all-cause mortality in HF patients with DM based on an observational study using propensity score (PS) analyses to reduce selection bias.

Methods

Subjects and study protocol

This was an observational study analysed by PS methods, which enrolled consecutive symptomatic HF patients with DM, who were hospitalized with decompensated HF and discharged from Fukushima Medical University between 2009 and 2013. The diagnosis of decompensated HF was defined based on the Framingham criteria.[20] Patients with acute coronary syndrome and dialysis were excluded. Blood samples were obtained at hospital discharge. Diabetes was defined as the recent use of antidiabetic drugs, a fasting blood glucose value of $\geq$126 mg/dL and/or a haemoglobin A1c (HbA1c) value of $\geq$6.5%. Patients were divided into two groups based on use of DPP-4 inhibitors at hospital discharge: a DPP-4 inhibitor group and a non-DPP-4 inhibitor group. We compared the clinical features, results from laboratory tests, and echocardiography, which were performed at discharge. Hypertension was defined as the recent use of antihypertensive drugs, systolic blood pressure $\geq$140 mmHg, and/or diastolic blood pressure $\geq$90 mmHg. Dyslipidemia was defined as the recent use of cholesterol-lowering drugs, a triglyceride value of $\geq$150 mg/dL, a low-density lipoprotein cholesterol value of $\geq$140 mg/dL, and/or a high-density lipoprotein cholesterol value of $<$40 mg/dL. The estimated glomerular filtration rate (GFR) was measured by the Modification of Diet in Renal Disease formula.[21] Chronic kidney disease was defined as estimated GFR of $<$60 mL/min/1.73 cm^2. Anaemia was defined as haemoglobin of $<$12.0 g/dL in female patients and $<$13.0 g/dL in male patients.[22] The left ventricular ejection fraction (LVEF) was calculated using the Simpson's method, and recording was performed on ultrasound systems (ACUSON Sequoia; Siemens Medical Solutions USA, Inc., Mountain View, CA, USA). Reduced LVEF was defined as less than 50%. All patients were followed up for all-cause and cardiac death. The primary endpoint of this study was all-cause death, while the secondary endpoint was cardiac death in the present study. Cardiac death was adjudicated by independent experienced several cardiologists including worsening HF, which met the Framingham criteria,[20] and ventricular fibrillation documented by electrocardiogram or implantable devices. Survival time was calculated from the date of discharge until the date of death or last follow-up. Status and dates of deaths were obtained from the patients' medical records. If these data were unavailable, status was ascertained by a telephone call to the patient's referring hospital cardiologist. This survey was performed blindly to the analyses of this study. Written informed consent was obtained from all study subjects. The study protocol was approved by the Ethics Committee of Fukushima Medical University. The investigation conforms with the principles outlined in the Declaration of Helsinki. Reporting of the study conforms to Strengthening the Reporting of Observational Studies in Epidemiology along with references to Strengthening the Reporting of Observational Studies in Epidemiology and the broader Enhancing the QUAlity and Transparency Of health Research (EQUATOR) guidelines.[23]

Statistical analysis

Normally distributed data are presented as mean ± standard deviation, and non-normally distributed data (e.g. BNP) are presented as log transformed. Categorical variables are expressed as numbers and percentages, and the χ^2 test was used for their comparisons. Characteristics and data of the two groups were compared using an independent Student's *t*-test for normally distributed data. The Kaplan–Meier method was used for presenting the mortality, and the log-rank test was used for initial comparisons.

To eliminate imbalances in the measurement of baseline characteristics because of selection bias associated with use of DPP-4 inhibitors, we used PS. The PS for treatment with DPP-4 was estimated for each patient by logistic regression with the following nine clinically relevant variables associated with introduction of DPP-4 inhibitors: age, gender, body mass index, HbA1c, estimated GFR, use of α2-glucosidase inhibitors, biguanides, sulfonyl urea, and insulin. The PS is the

propensity from 0 to 1 to receive treatment, given a set of known variables, and is used to adjust for potential selection bias, confounding, and differences between treatment groups in observational studies.[24] The PS was then used to match patients who received and who did not receive DPP-4 therapy, using a 1:1 nearest neighbour-matching algorithm with calliper width = 0.2 of the pooled standard deviation of the logit of the PS (calliper = 0.03) as previously suggested.[25] The PS-matched datasets were compared using pairwise analysis.[26] We assessed the effectiveness of our post-matched model by estimating absolute standardized differences, which were presented as a Love plot. As previously reported, a standardized difference below 10% was considered for adequate balance.[27]

To further assess the associations of DPP-4 inhibitor use on cardiac and all-cause mortality, Cox proportional hazard models were constructed in the pre-matched cohort using three different approaches (unadjusted, adjusted using PS as a covariate, and multivariable-adjusted using several confounders) and constructed in the post-matched cohort to validate the findings of the Cox analyses. To prepare for potential confounding in the Cox regression analyses, in addition to the previous factors to calculate PS, we considered the following clinical factors, which are known to affect the risk of mortality in HF patients: New York Heart Association (NYHA) functional class III or IV, systolic blood pressure, heart rate, presence of ischaemic aetiology, atrial fibrillation, anaemia, LVEF, B-type natriuretic peptide (BNP), haemoglobin, use of renin–angiotensin–aldosterone system (RAS) inhibitors, and beta-blockers. Among these factors, which independently predicted mortality with a value of $P < 0.05$, the following

Table 1 Comparisons of clinical features

	Pre-matched cohort			Post-matched cohort		
	DPP-4 inhibitors (–) (n = 171)	DPP-4 inhibitors (+) (n = 122)	P-value	DPP-4 inhibitors (–) (n = 83)	DPP-4 inhibitors (+) (n = 83)	P-value
Demographics						
Age (years)	68.1 ± 12.3	68.7 ± 12.4	0.658	68.3 ± 12.5	68.5 ± 13.6	0.906
Male gender (n, %)	108 (63.2)	79 (64.8)	0.806	48 (57.8)	56 (60.2)	0.875
Body mass index (kg/cm^2)	24.2 ± 4.6	24.2 ± 4.3	0.895	24.5 ± 5.1	24.3 ± 4.6	0.777
NYHA class III or IV (n, %)	37 (21.6)	22 (18.8)	0.465	25 (30.1)	16 (19.3)	0.149
Systolic blood pressure (mmHg)	119.2 ± 18.9	120.2 ± 17.3	0.659	121.9 ± 19.0	122.0 ± 17.0	0.962
Diastolic blood pressure (mmHg)	68.1 ± 13.9	67.8 ± 12.9	0.867	69.2 ± 15.0	68.3 ± 13.4	0.696
Heart rate (bpm)	72.8 ± 13.0	72.5 ± 13.4	0.838	73.4 ± 13.4	73.8 ± 13.5	0.845
Reduced LVEF (n, %)	104 (60.8)	86 (70.5)	0.107	44 (53.0)	56 (67.5)	0.081
Duration of DM (years)	5.1 (IQR 8.0)	7.0 (IQR 9.6)	0.092	8.4 (IQR 8.2)	7.0 (IQR 9.0)	0.808
Aetiology of heart failure			0.046			0.084
Ischaemic (n, %)	59 (34.5)	55 (45.1)		28 (32.2)	32 (36.8)	
Valvular (n, %)	37 (21.6)	20 (16.4)		25 (28.7)	19 (21.7)	
Cardiomyopathy (n, %)	41 (24.0)	32 (26.2)		16 (18.4)	26 (29.9)	
Others (n, %)	34 (19.9)	15 (12.3)		18 (20.6)	10 (11.5)	
Co-morbidity						
Hypertension (n, %)	138 (80.7)	99 (81.1)	1.000	74 (89.2)	65 (78.3)	0.416
Dyslipidemia (n, %)	148 (86.5)	101 (82.8)	0.409	69 (83.1)	67 (80.7)	0.840
Chronic kidney disease (n, %)	113 (66.1)	89 (73.0)	0.249	58 (69.9)	61 (73.5)	0.731
Atrial fibrillation (n, %)	68 (39.8)	49 (42.0)	1.000	38 (45.8)	36 (43.4)	0.876
Anaemia (n, %)	109 (63.7)	74 (60.7)	0.625	59 (71.1)	53 (63.9)	0.408
Medications						
RAS inhibitors (n, %)	144 (84.2)	106 (86.9)	0.616	71 (85.5)	72 (86.7)	1.000
Beta-blockers (n, %)	139 (81.3)	99 (81.1)	0.105	65 (78.3)	74 (89.2)	0.091
Diuretics (n, %)	131 (76.6)	92 (75.4)	0.809	65 (78.3)	60 (72.3)	0.472
Inotropic agents (n, %)	30 (17.5)	17 (13.9)	0.425	15 (18.1)	14 (16.9)	1.000
α2-Galactosidase inhibitors (n, %)	46.2 (26.9)	45 (36.9)	0.074	23 (27.7)	27 (32.5)	0.612
Biguanides (n, %)	6 (3.5)	22 (18.0)	<0.001	3 (3.6)	4 (4.8)	1.000
Sulfonylurea (n, %)	33 (19.3)	48 (39.3)	<0.001	24 (28.9)	22 (26.5)	0.472
Insulin (n, %)	40 (23.4)	27 (22.1)	0.888	22 (26.5)	18 (21.7)	0.586
Laboratory data and echocardiography						
Haemoglobin (g/dL)	11.8 ± 1.97	11.9 ± 1.96	0.709	11.5 ± 2.05	11.8 ± 2.02	0.345
Log (BNP)	2.17 ± 0.38	2.21 ± 0.34	0.432	2.19 ± 0.39	2.18 ± 0.36	0.888
Estimated GFR (mL/min/m^2)	52.7 ± 20.2	49.3 ± 21.5	0.159	50.1 ± 20.4	50.7 ± 21.6	0.848
HbA1c (%)	6.88 ± 0.99	7.33 ± 1.33	0.001	6.97 ± 1.09	6.88 ± 0.930	0.562
Sodium (mmol/L)	137.4 ± 3.3	137.4 ± 3.6	0.983	137.8 ± 3.4	137.5 ± 3.7	0.509
Total bilirubin (mg/dL)	0.806 ± 0.408	0.805 ± 0.423	0.985	0.813 ± 0.470	0.825 ± 0.430	0.864
LVEF (%)	45.9 ± 14.7	43.9 ± 11.7	0.187	48.6 ± 14.9	45.0 ± 12.2	0.061
Propensity score for introduction of DPP-4 inhibitors	0.362 ± 0.135	0.499 ± 0.210	<0.001	0.389 ± 0.134	0.391 ± 0.136	0.871

BNP, B-type natriuretic peptide; DM, diabetes mellitus; DPP-4, dipeptidyl peptidase-4; GFR, glomerular filtration rate; IQR, interquartile range; Log; common logarithm; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RAS, renin–angiotensin–aldosterone system.

DOI: 10.1002/ehf2.12079

factors were selected in the final adjusted model for predictors of all-cause mortality: NYHA III or IV, haemoglobin, log (BNP), presence of beta-blockers, and PS. The proportional hazards assumption for the model was checked by examining log-minus-log transformed Kaplan–Meier estimates of the survival curves for two groups plotted against time to follow-up period. In addition, the scaled Schoenfeld residuals from the proportional hazards regression model were investigated to assess the proportional hazards assumption.

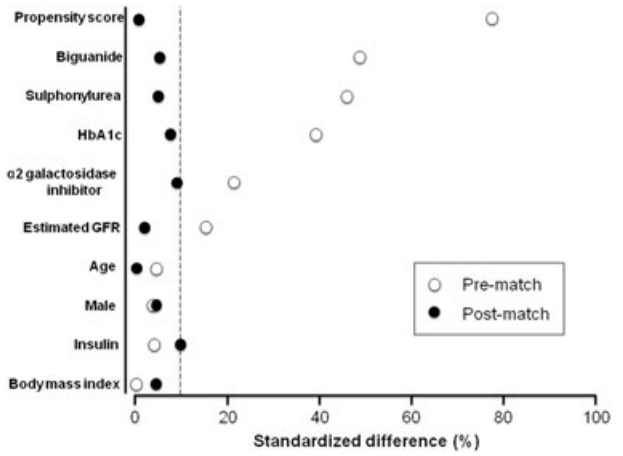
To assess potential heterogeneity of DPP-4 inhibitor treatment effect on all-cause mortality, we conducted subgroup analyses in the post-matched cohort. We formally tested for first-order interactions using multivariable Cox proportional hazard models by entering interaction terms between DPP-4 inhibitor use and the subgroup variables. Missing values were handled by estimating one logistic regression model for each pattern of missing values. Interactions between DPP-4 inhibitors and clinically relevant variables including age, gender, body mass index, duration of DM, NYHA class, log (BNP), LVEF, presence of ischaemic aetiology, atrial fibrillation, chronic kidney disease, anaemia, use of RAS inhibitors, and use of beta-blockers were estimated by a Cox proportional hazards regression model and are shown in a Forest plot. A value of $P < 0.05$ was considered significant for all comparisons. Analyses were performed using a statistical software package (SPSS ver. 21.0; IBM, Armonk, NY, USA).

Results

Clinical features of the overall and post-matched population are summarized in *Table 1*. In our hospitalized HF patients who were discharged ($n = 962$), 293 (30.5%) had DM and were divided into two groups based on present use of DPP-4 inhibitors (DPP-4 inhibitor group, $n = 122$, and non-DPP-4 inhibitor group, $n = 171$). The DPP-4 inhibitors used were as follows: sitagliptin ($n = 58$, 47.5%), vildagliptin ($n = 44$, 36.0%), alogliptin ($n = 10$, 8.2%), linagliptin ($n = 6$, 4.9%), and teneligliptin ($n = 4$, 3.3%). HbA1c was higher, and the prevalence of taking biguanides and sulfonylurea was significantly higher in the DPP-4 group than in the non-DPP-4 group in the pre-matched cohort. After PS matching for DPP-4 inhibitor use, as shown in *Figure 1*, the absolute standardized differences were minimized except for insulin use, suggesting substantial bias reduction. In the post-matched cohort (DPP-4 inhibitor group, $n = 83$, and non-DPP-4 inhibitor group, $n = 83$), use of beta-blockers tended to be higher, and LVEF tended to be lower in the DPP-4 group than in the non-DPP-4 group (*Table 1*).

In the follow-up period (mean 858 days), cardiac and all-cause mortality was significantly lower in the DPP-4 inhibitor group than in the non-DPP-4 inhibitor group of both the pre-matched and post-matched cohorts ($P < 0.05$), as shown in *Figures 2* and *3*. There was no significant difference in cardiac and all-cause mortality among DPP-4 inhibitors.

Figure 1 Love plot for absolute standardized differences. GFR, glomerular filtration rate; HbA1c, haemoglobin A1c.



The Cox proportional hazard model was used to examine the prognostic value of DPP-4 inhibitors as shown in *Table 2*. We have checked that the Cox models support the assumption of proportional odds. DPP-4 inhibitor use was a predictor of cardiac and all-cause mortality in the pre-matched cohort within the crude model, pre-matched cohort adjusted for PS as covariate model, and post-matched cohort ($P < 0.05$, respectively).

Interactions between DPP-4 inhibition therapy and clinically relevant variables were modelled with Cox regression and presented in *Figure 4* as a Forest plot for all-cause mortality in the matched population. Interaction analyses rendered similar results to subgroup analyses, with the additional benefit of being able to statistically test for differences in associations between DPP-4 use and outcomes between subgroups. In *Figure 4*, a Forest plot illustrates the association between DPP-4 use and all-cause mortality in subgroups after adjustment for interactions between pre-specified clinically important variables and DPP-4 inhibitors. There was no interaction between DPP-4 inhibitor use and other important variables to affect all-cause mortality.

Our findings, both in a matched population based on PS and in an overall population adjustment for PS, were consistent. Importantly, with regard to DPP-4 inhibitor use, there was no interaction between other variables associated with all-cause mortality.

Discussion

To the best of our knowledge, the present study is the first to show the association of DPP-4 inhibitors and low cardiac and

DOI: 10.1002/ehf2.12079

Figure 2 Kaplan–Meier analyses for (A) cardiac death and (B) all-cause mortality between the two groups [dipeptidyl peptidase-4 (DPP)-4 group and non-DPP-4 group] in pre- propensity score-matched cohort.

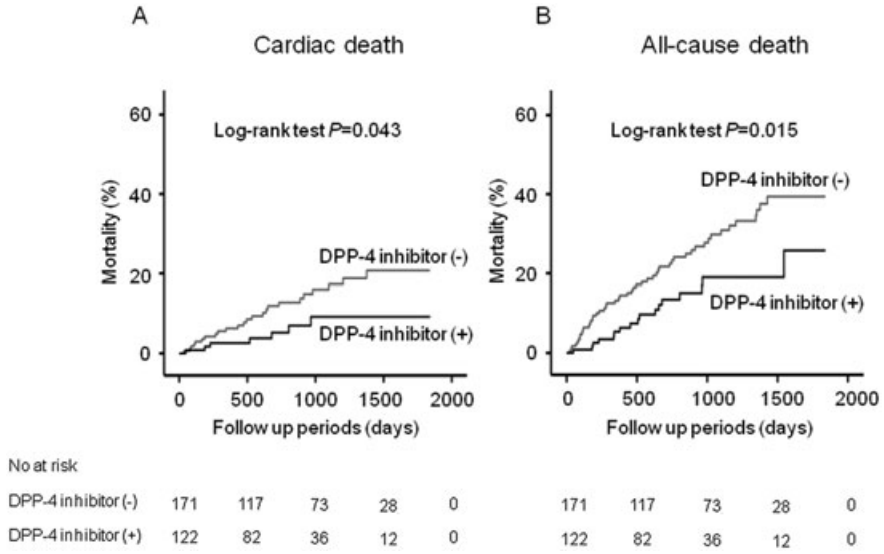
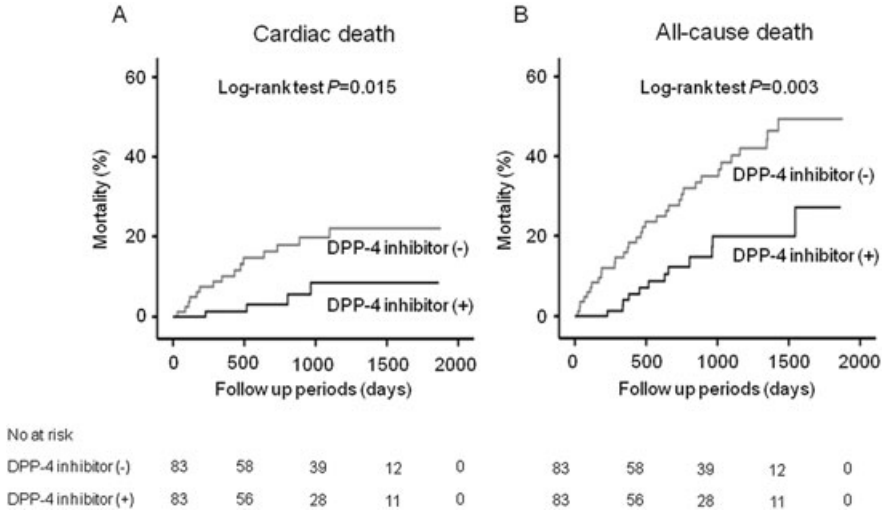


Figure 3 Kaplan–Meier analyses for (A) cardiac death and (B) all-cause mortality between the two groups [dipeptidyl peptidase-4 (DPP)-4 group and non-DPP-4 group] in post-matched cohort.



all-cause mortality of hospitalized HF patients with DM based on PS analyses.

Diabetes mellitus probably impairs cardiac function and causes additional myocardial damage,[6,28] and an increase of HbA1c is associated with prevalence of HF.[29] Some antidiabetic drugs, such as thiazolidinediones, worsen fluid retention and exacerbate HF,[6,30–32] whereas sulfonylureas and insulin potentially exacerbate the dysregulation of myocardial metabolism and worsen left ventricular function.[33–35] Hence, treating HF and DM together is challenging.[4–6,33,34] Based on pre-clinical and early clinical work, DPP-4 inhibitors should, in theory, have beneficial effects on left ventricular reverse remodelling[36] and renal amelioration[36,37] resulting in improvement of HF.[7–9,38] DPP-4 stimulates activation of proinflammatory cytokines,[39] independent drivers of progression of left ventricular systolic dysfunction, because of their prohypertrophic and profibrotic effect.[40] DPP-4 inhibition should direct BNP metabolism towards an increase in active BNP rather than biologically inactive BNP precursor fragments.[39] There also seems to be interaction between DPP-4 inhibitors and RAS inhibitors.[41]

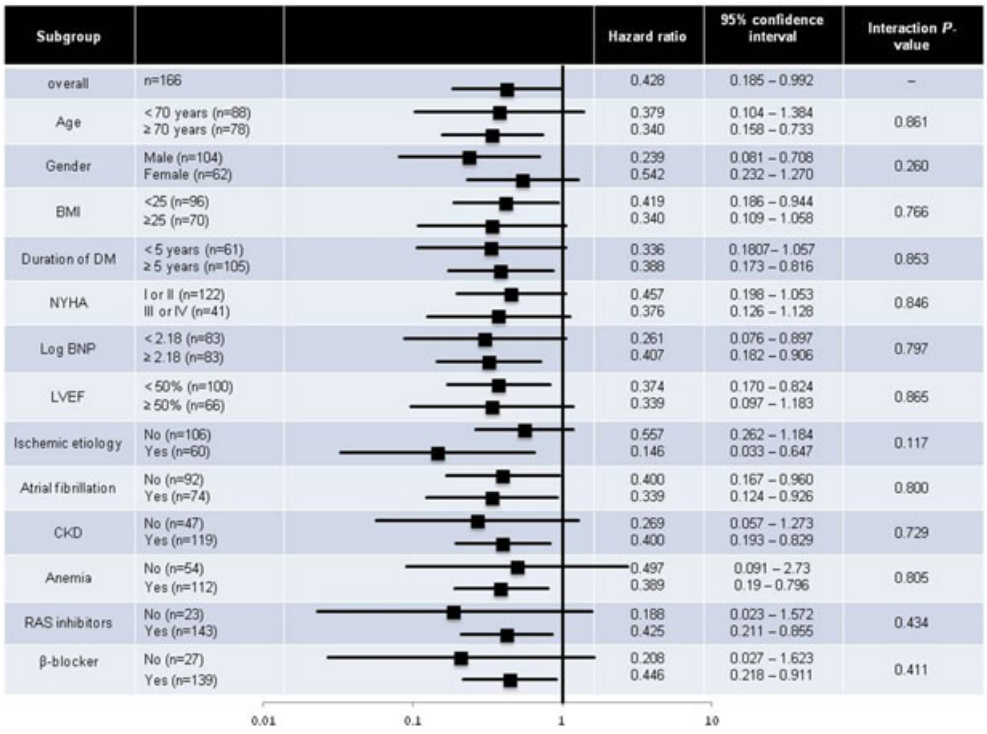
DOI: 10.1002/ehf2.12079

Table 2 Cox proportional hazard models of cardiac death and all-cause mortality in pre-matched cohort and post-matched cohort

	Pre-matched cohort			
	Events	Hazard ratio	95% CI	*P*-value
Cardiac death				
Unadjusted	32/293	0.428	0.185–0.992	0.048
Adjusted for PS as covariate	32/293	0.313	0.124–0.788	0.014
All-cause mortality				
Unadjusted	68/293	0.511	0.295–0.885	0.012
Adjusted for PS as covariate	68/293	0.402	0.220–0.732	0.003
Final adjusted model[a]	68/293	0.467	0.263–0.830	0.010
	Pre-matched cohort			
	n events/*n*	Hazard ratio	95% CI	*P*-value
Cardiac death	19/166	0.268	0.089–0.810	0.020
All-cause mortality	46/166	0.370	0.191–0.716	0.003

CI, confidence interval; PS, propensity score.
[a]New York Heart Association (over III), haemoglobin, log (BNP), beta-blocker, and PS.

Figure 4 Forest plot with subgroup analyses for all-cause mortality. BMI, body mass index; BNP, B-type natriuretic peptide; CKD, chronic kidney disease; DM, diabetes mellitus; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RAS, renin–angiotensin–aldosterone system.



To date, there have only been three random clinical trials regarding associations of DPP-4 inhibitors and cardiovascular events in DM patients, and the hospital admission for HF results differs among the three trials. First, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53 trial was designed to evaluate long-term cardiovascular efficacy in 16 492 patients with DM (HbA1c of 6.5–12.0%) who were at risk of cardiovascular events, including 13% with a previous HF episode.[13,14] Over a median of 2.1 year follow-up, saxagliptin did not increase or decrease the rate of major adverse cardiovascular events, although the rate of unexpected hospitalization for HF was increased.[13,14] This increase in risk was the highest among patients with elevated levels of natriuretic peptides, previous HF, or chronic kidney disease.[13] The second trial, EXAMINE,[15,16] enrolled 5380 patients with DM (HbA1c 6.5–11.0%) and a recent acute coronary syndrome event, including 29% who had previous HF. Over a median of 1.5 year follow-up, alogliptin did not increase or decrease the rate of major adverse cardiovascular events.[16]

Post-hoc analyses from the EXAMINE trial, with regard to HF, recently reported that alogliptin had no effect on hospital admission for HF and that cardiovascular mortality differed by baseline BNP concentration.[15] Although the rate of cardiovascular mortality was similar in the alogliptin and placebo group in the first to third quartiles of baseline BNP concentration, cardiovascular mortality was significantly lower in the alogliptin group in the highest BNP quartiles.[15] These results are concordant with lower mortality in the DPP-4 group of our hospitalized HF patients with DM. The third trial, Trial Evaluating Cardiovascular Outcomes with Sitagliptin,[19] enrolled 14 671 patients with DM (HbA1c 6.5–8.0%) and established cardiovascular disease, including 18% with a past history of HF. Over a median of 3 year follow-up, sitagliptin did not increase the risk of major adverse cardiovascular events, hospitalization for HF, or other adverse events.[19] The reasons that our results differ from previous studies may relate to the differences in the patients who were enrolled, background therapy including RAS inhibitors, and intrinsic pharmacologic differences among DPP-4 inhibitors, or it may simply represent the role of chance in previous findings. In addition, there may be a potential class effect among each DPP-4 inhibitor.[42] Most of our study population received sitagliptin or vildagliptin, and these results may positively affect prognosis. Another study, entitled Vildagliptin in Ventricular Dysfunction Diabetes Trial,[43] tested the effects of vildagliptin in 254 patients with DM and HF with systolic dysfunction (LVEF $<$ 40%). The primary endpoint was the change in LVEF over 52 weeks, to demonstrate non-inferiority compared with placebo. There was no difference between vildagliptin and placebo in the LVEF at 12 months and, interestingly, no excess of HF hospitalization with vildagliptin. Another ongoing trial, the Cardiovascular Outcome Study of Linagliptin versus Glimepiride in Patients with Type 2 Diabetes, is expected to clarify this issue.

Study strengths and limitations

Our study has several strengths and differs from previous studies[13–16,19] in many ways. For instance, the present study is the first to show the association of DPP-4 inhibitors with lower cardiac and all-cause mortality in hospitalized HF patients with DM, including non-ischaemic HF, with a relatively long follow-up period. Our study population included only hospitalized HF patients with DM, many of whom had higher levels of natriuretic peptide, had higher prevalence of chronic kidney disease, and had received higher prevalence of RAS inhibitors than previous studies.[13–16,19] In addition, diagnosis of HF and causes of death including cardiac and all-cause mortality were accurately made by our experienced cardiologists.

There are some potential limitations. First, our study is a non-randomized and observational study of a single institution, so the number of subjects was relatively small, and there are potential biases and confounders that may be responsible for our findings. Although propensity analyses are powerful, they are inherently limited by the number and accuracy of variables evaluated. Importantly, we cannot rule out residual confounding from unknown or unmeasured variables, and the effects of differences in backgrounds between the two groups might not be completely adjusted. However, because of the worse outcome for HF patients with DM using DPP-4 inhibitors in previous studies,[13,14] the enforcement of randomized clinical trials to determine the impact of DPP-4 on the prognosis of patients with HF and DM is ethically difficult. Second, we have assessed this study using only index hospitalization variables, without consideration for changes in medical parameters and post-discharge treatment. Changes in DPP-4 inhibitor use were not considered, and there might be little crossover between the two groups. However, if a crossover bias was present, it would have led to underestimation of the association between DPP-4 inhibitor use and survival. Third, a standardized difference between matched groups of less than 10% is generally considered inconsequential. Of all the nine variables assessed, only use of insulin had a standardized difference of $>$10%. For these reasons, the results of our study should be viewed as preliminary. Hence, further clinical trials for HF patients with DM using DPP-4 inhibitors are required, with a larger population.

Conclusions

Our findings suggest that use of DPP-4 inhibitors may be associated with lower cardiac and all-cause mortality than without DPP-4 inhibitors in hospitalized HF patients with DM.

Acknowledgements

The authors acknowledge the efforts of Dr Tetsuya Ohira (Department of Epidemiology) for his invaluable advice on medical statistics, as well as Ms Kumiko Watanabe and Yuko Niimura for their outstanding technical assistance.

Conflict of interest

The authors declare no conflicts of interest.

Funding

This study was supported in part by a grant-in-aid for Scientific Research (no. 25461061) from the Japan Society for the Promotion of Science and grants-in-aid from the Japanese Ministry of Health, Labor, and Welfare, Tokyo, Japan.

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