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Effect of Dipeptidyl Peptidase-4 Inhibitor on All-Cause Mortality and Coronary Revascularization in Diabetic Patients

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Background: Anti-atherosclerotic effect of dipeptidyl peptidase-4 (DPP-4) inhibitors has been suggested from previous studies, and yet, its association with cardiovascular outcome has not been demonstrated. We aimed to evaluate the effect of DPP-4 inhibitors in reducing mortality and coronary revascularization, in association with baseline coronary computed tomography (CT).

Methods: The current study was performed as a multi-center, retrospective observational cohort study. All subjects with diabetes mellitus who had diagnostic CT during 2007–2011 were included, and 1866 DPP-4 inhibitor users and 5179 non-users were compared for outcome. The primary outcome was all-cause mortality and secondary outcome included any coronary revascularization therapy after 90 days of CT in addition to all-cause mortality.

Results: DPP-4 inhibitors users had significantly less adverse events [0.8% vs. 4.4% in users vs. non-users, adjusted hazard ratios (HR) 0.220, 95% confidence interval (CI) 0.102–0.474, p = 0.0001 for primary outcome, 4.1% vs. 7.6% in users vs. non-users, HR 0.517, 95% CI 0.363–0.735, p = 0.0002 for secondary outcome, adjusted variables were age, sex, presence of hypertension, high sensitivity C-reactive protein, glycated hemoglobin, statin use, coronary artery calcium score and degree of stenosis]. Interestingly, DPP-4 inhibitor seemed to be beneficial only in subjects without significant stenosis (adjusted HR 0.148, p = 0.0013 and adjusted HR 0.525, p = 0.0081 for primary and secondary outcome).

Conclusion: DPP-4 inhibitor is associated with reduced all-cause mortality and coronary revascularization in diabetic patients. Such beneficial effect was significant only in those without significant coronary stenosis, which implies that DPP-4 inhibitor may have beneficial effect in earlier stage of atherosclerosis.

KEY WORDS: Dipeptidyl peptidase-4 inhibitor · Mortality · Cardiovascular outcome · Computed tomography.

Introduction

Dipeptidyl peptidase-4 (DPP-4) inhibitor, a novel class of oral antidiabetic agent, has received much attention recently, with its excellent glucose-lowering effect. It increases bioavailability and activates receptor signaling of incretin hormones in response to oral food intake,[1)] and thus lowers blood glucose level without risk of hypoglycemia. In addition, DPP-4 inhibitors have shown several ancillary effects including blood pressure-lowering,[2)] lipid-lowering,[3)] endothelial cell protection,[4)] and anti-atherogenic effect that might have favorable cardiovascular implication. A few meta-analyses suggested that DPP-4 inhibitors are safe from a cardiovascular standpoint and decrease

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myocardial infarction and all-cause mortality, but the results were not consistent.[5-9] It still remains to be elucidated whether such excellent glucose control and possible pleiotropic effect of DPP-4 inhibitors affect all-cause mortality in consequence, since none of the antidiabetic agents has shown a consistent benefit in reducing macrovascular complications and mortality despite adequate control of diabetes mellitus (DM) and reduced microvascular complications.[10-12]

Coronary artery disease is a common macrovascular complication and major cause of death in patients with DM.[13)14)] Therefore, it is of paramount importance to establish a therapeutic strategy targeting not only glucose lowering but also improving cardiovascular outcome in these patients. Recently published two clinical trials have failed to show beneficial effect of DPP-4 inhibitors in cardiovascular outcome,[15)16)] but the results were derived from rather short-term clinical trials performed in selected patients. In addition, it is unclear whether the presence of combined coronary disease has an impact on the potential cardiovascular benefit of DPP-4 inhibitors because most of the previous trials were performed in patients without coronary disease, as assessed by computed tomography (CT).

In this study, we aimed to evaluate the effect of DPP-4 inhibitors on all-cause mortality and coronary revascularization in unselected 'real-world' diabetic patients. In addition, we evaluated the impact of combined significant coronary disease on the cardiovascular effect of DPP-4 inhibitors using our coronary CT cohort.

METHODS

STUDY SUBJECTS

It is a multi-center, retrospective observational cohort study. We identified 11376 diabetic patients among 49027 consecutive patients who underwent either coronary CT angiography or calcium scoring CT between January 2007 and December 2011 in Seoul National University Hospital and its two affiliated hospitals, Seoul National University Bundang Hospital and Healthcare System Gangnam Center. Those who underwent percutaneous coronary artery intervention (PCI) or coronary artery bypass graft surgery (CABG) before CT were excluded. We also excluded patients who did not take antidiabetic agents regularly and thus 7045 diabetic patients remained for the analysis. Baseline laboratory test results were recorded from the medical record.

DATA SOURCE FROM HEALTH INSURANCE REVIEW AND ASSESSMENT SERVICE

The current study used the database from Korean Health Insurance Review and Assessment (HIRA) Service's claims data. As the National Health Insurance program provides universal coverage of the population in Korea,[17] the HIRA database contains all of the information on healthcare utilization and prescribed medications for all registered Korean subjects. The resident registration numbers of our study cohort were used to match the patients' medical record with claims data including all prescriptions, diagnosis, hospital visit information and survival data between January 2007 and December 2011. The HIRA provided the claims data with each individual's personal information concealed and the matched raw data were kept securely at HIRA database.

The date of CT was the begin of follow up, and using prescription claims data and database from the Ministry of Security and Public Administration and HIRA, we checked the last day of follow up and the date of death. Using the prescription claims data, we defined the patients who had taken DPP-4 inhibitors for longer than 12 weeks as DPP-4 inhibitor users (the users) and those with less than 12 weeks of DPP-4 inhibitors as DPP-4 inhibitor non-users (the non-users). The patients were categorized into four groups according to the statin prescription; those who were never prescribed any type of statin, those with less than 30% of prescription during the follow up period, those with 30–80% of prescription and those with ≥ 80% of prescription during follow up.

OUTCOME MEASURES

The primary outcome was all-cause mortality. Both database from HIRA and the Ministry of Security and Public Administration were used and cross-checked to confirm the death and the date of death. The secondary outcome included all PCI or CABG performed at least 90 days after CT in addition to all-cause mortality. We excluded CT-derived revascularization procedure within 90 days of CT from the outcome measures.[18)19)]

CORONARY CT

64-slice MDCT (SOMATOM Sensation 64 and SOMATOM Definition, Siemens Medical Solutions, Forchheim, Germany or Brilliance 64, Philips Medical Systems, Best, the Netherlands) was used for CT coronary angiography with 64 × 0.625 mm section collimation, 420 ms rotation time, 120 kV tube voltage, and 800 mA tube current under electrocardiographic-gated dose modulation. The heart rate was controlled using either intravenous esmolol or oral metoprolol. Image data sets were reviewed at a commercially available workstation (Brilliance, Philips Medical Systems). At each center, two experienced radiologists reviewed all the images. The severity of luminal stenosis of the epicardial coronary artery was classified as 0%, 1–49%, 50–69%, or ≥ 70%, and ≥ 50% stenosis was considered as "significant".[20-22] The number of vessels with significant stenosis was also counted. Coronary artery calcium score (CACS) was measured using the scoring system by Agatston et al.[23] and categorized into three groups of 0–100, 100–400, and ≥ 400. CT coronary angiography was performed in 6873 patients (97.6%) and CACS was measured in 5698 (80.9%) patients.

STATISTICAL ANALYSIS

Data are expressed as mean ± standard deviation for contin-

uous variables and frequencies and percentages for categorical variables. To compare DPP-4 inhibitor users with non-users, Student's t-test was used for continuous parameters and chi-square test for categorical variables. For survival analysis, Kaplan-Meier method with the log-rank test and cox-regression survival analysis were applied. The effect of DPP-4 inhibitors was evaluated according to the presence of significant stenosis. For all statistical analyses, statistical software package (SAS 9.3, SAS Institute Inc., Cary, NC, USA) was used and a *p*-value of less than 0.05 was considered statistically significant.

Ethics statement

The study protocol was reviewed and approved by the Institutional Review Board (IRB) of Seoul National University Hos-

Table 1. Baseline characteristics

	DPP-4 inhibitor user (n = 1866)	DPP-4 inhibitor non-user (n = 5179)	*p*-value
Age, mean ± SD	61 ± 10	63 ± 11	< 0.0001
Male, n (%)	1235 (66.2)	3221 (62.2)	0.0022
HTN, n (%)	1487 (79.7)	4162 (80.4)	0.5313
Statin use in percent*			< 0.0001
Statin < 30%	333 (17.9%)	839 (16.2%)	
Statin 30–80%	318 (17.0%)	664 (12.8%)	
Statin ≥ 80%	648 (34.7%)	1421 (27.4%)	
SU use, n (%)	1008 (54.0)	2798 (54.0)	0.9961
Laboratory data			
FBS, mg/dL	142 ± 47	133 ± 48	< 0.0001
HbA1C, %	7.6 ± 1.4	7.2 ± 1.4	< 0.0001
T.chol, mg/dL	189 ± 43	188 ± 44	0.3371
TG, mg/dL	165 ± 128	158 ± 112	0.0351
HDL-cholesterol, mg/dL	48 ± 11	49 ± 12	0.0618
LDL-cholesterol, mg/dL	108 ± 33	109 ± 33	0.2001
hsCRP, mg/dL	0.5 ± 2.2	0.8 ± 2.7	0.0038
Cr, mg/dL	1.0 ± 0.2	1.0 ± 0.5	0.0091
CT finding			
CACS, mean ± SD	155 ± 409	159 ± 488	0.7263
0 ≤ CACS < 100	1136 (74.4%)	3043 (73.0%)	0.5434
100 ≤ CACS < 400	235 (15.4%)	688 (16.5%)	
CACS ≥ 400	157 (10.3%)	439 (10.5%)	
CT stenosis = 0%	802 (44.1%)	2205 (43.6%)	0.7494
0% < CT stenosis < 50%	643 (35.4%)	1788 (35.4%)	
50% ≤ CT stenosis < 70%	152 (8.4%)	464 (9.2%)	
CT stenosis ≥ 70%	222 (12.2%)	597 (11.8%)	
Number of vessels with significant stenosis			0.5354
1VD	199 (11.0%)	600 (11.9%)	
2VD	93 (5.1%)	227 (4.5%)	
3VD	82 (4.5%)	234 (4.6%)	
Outcome measures			
All-cause mortality			
Follow up duration, median, days	927 (IQR 459–1382)	978 (IQR 492–1433)	0.1238
Duration of medication	453 ± 294	43 ± 21	< 0.0001
Event, n (%)	15 (0.8)	226 (4.4)	< 0.0001
All-cause mortality + PCI/CABG			
Follow up duration, median, days	823 (IQR 351–1330)	861 (IQR 360–1389)	0.0696
Event, n (%)	76 (4.1)	393 (7.6)	< 0.0001

*The use of statin categorized into percent. CABG: coronary artery bypass graft, CACS: coronary artery calcium score, Cr: serum creatinine, CT: computed tomography, DPP-4: dipeptidyl peptidase-4, FBS: fasting blood sugar, HbA1C: glycated hemoglobin, HDL: high density lipoprotein, hsCRP: high sensitivity C-reactive protein, HTN: hypertension, IQR: interquartile range, LDL: low density lipoprotein, PCI: percutaneous coronary artery intervention, SD: standard deviation, SU: sulfonylurea, T.chol: total cholesterol, TG: triglyceride, VD: vessel disease

pital (IRB No. H 1307-157-507) and Seoul National University Bundang Hospital (IRB No. B-1307/212-107). Since the current study was performed as a retrospective study using the database and medical records, informed consent was waived by the board. The study was carried out according to the principles of the Declaration of Helsinki.

RESULTS

BASELINE CHARACTERISTICS AND CT FINDINGS

As shown in Table 1, 1866 patients were the users and 5179 were the non-users. The users were younger than non-users, with more male population (66.2% vs. 62.2%, p = 0.0022), and more patients under statin treatment (p < 0.0001). The prevalence of hypertension was not different between the groups (p = 0.5313). Both fasting blood sugar and glycated hemoglobin (HbA1C) levels were higher in the users (142 ± 47 vs. 133 ± 48, p < 0.0001 and 7.6 ± 1.4 vs. 7.2 ± 1.4, p < 0.0001). Total cholesterol, high density lipoprotein-cholesterol and low density lipoprotein-cholesterol level were not different between the groups (p = 0.3371, 0.0618, and 0.2001, respectively), whereas high sensitivity C-reactive protein (hsCRP) level was significantly lower in the users (p = 0.0038).

There was no significant difference in baseline CT findings between the users and non-users. The CACS and the degree of coronary artery stenosis did not show significant difference between the groups (74.4% vs. 73.0% for CACS < 100, 15.4% vs. 16.5% for 100 ≤ CACS < 400, 10.3% vs. 10.5% for CACS ≥ 400, in users vs. non-users, overall p = 0.5434 for CACS and 44.1% vs. 43.6% for no stenosis, 35.4% vs. 35.4% for < 50% stenosis, 8.4% vs. 9.2% for 50–70% stenosis, and 12.2% vs. 11.8% for ≥ 70% stenosis in users vs. non-users, overall p = 0.7494 for degree of stenosis). The number of vessels with significant stenosis did not differ between the groups (p = 0.5354).

EFFECT OF DPP-4 INHIBITORS ON ALL-CAUSE MORTALITY

Mean follow-up duration was 928 ± 524 days for the users and 950 ± 539 days for the non-users (p = 0.1238, median follow up duration is given in Table 1). Among 7045 patients, 241 (3.42%) died, of which 15 were the users (15/1866, 0.8%) and 226 were the non-users (226/5179, 4.4%) (p < 0.0001).

From univariate cox-regression survival analysis, the use of DPP-4 inhibitor was associated with decreased all-cause mortality, with 81% risk reduction [hazard ratios (HR) 0.190, 95% confidence interval (CI) 0.113–0.320, p < 0.0001] (Table 2). Advanced age, presence of hypertension and higher hsCRP level was associated with increased all-cause mortality. From baseline CT findings, greater CACS was associated with higher mortality (HR 1.943, 95% CI 1.615–2.337, p < 0.0001). The presence of any coronary artery calcium was associated with increased mortality (HR 2.612, 95% CI 1.836–3.716, p < 0.0001). Both greater degree of stenosis (HR 1.446, 95% CI 1.292–1.619, p < 0.0001) and more number of vessels with

Table 2. Univariate cox-regression survival analysis for all-cause mortality

	HR	95% CI	p-value
Age, years	1.100	1.086–1.114	< 0.0001
Male sex	1.184	0.906–1.547	0.2153
HTN	1.752	1.182–2.599	0.0053
Statin use*	0.854	0.766–0.953	0.0049
FBS, mg/dL	1.001	0.999–1.004	0.3101
HbA1C, %	1.083	0.987–1.188	0.0913
T.chol, mg/dL	0.990	0.987–0.993	< 0.0001
TG, mg/dL	0.999	0.997–1.001	0.1774
HDL-cholesterol, mg/dL	1.000	0.987–1.012	0.9450
LDL-cholesterol, mg/dL	0.989	0.984–0.995	0.0001
hsCRP, mg/dL	1.117	1.096–1.138	< 0.0001
CACS†	1.943	1.615–2.337	< 0.0001
Presence of any coronary calcium	2.612	1.836–3.716	< 0.0001
Coronary artery stenosis‡	1.446	1.292–1.619	< 0.0001
Number of vessels with significant stenosis§	1.506	1.332–1.702	< 0.0001
DPP-4 inhibitor user	0.190	0.113–0.320	< 0.0001
Metformin user	0.412	0.304–0.557	< 0.0001
SU user	1.074	0.827–1.394	0.5943

*Statin never-user vs. < 30% user vs. 30–80% user vs. ≥ 80% user, †CACS as a categorical variable defined as CACS 0–100 vs. 100–400 vs. ≥ 400, ‡Coronary artery stenosis as a categorical variable defined as 0% vs. 1–49% vs. 50–69% vs. ≥ 70%, §1 vessel disease vs. 2 vessel disease vs. 3 vessel disease. CACS: coronary artery calcium score, CI: confidence interval, DPP-4: dipeptidyl peptidase-4, FBS: fasting blood sugar, HbA1C: glycated hemoglobin, HR: hazard ratio, HDL: high density lipoprotein, hsCRP: high sensitivity C-reactive protein, HTN: hypertension, LDL: low density lipoprotein, SU: sulfonylurea, T.chol: total cholesterol, TG: triglyceride

significant stenosis (HR 1.506, 95% CI 1.332–1.702, p < 0.0001) were associated with increased all-cause mortality. Among medications, statin and metformin were associated with lower mortality (p = 0.0049 for statin and p < 0.0001 for metformin) whereas sulfonylurea was not (p = 0.5943).

An adjusted model to evaluate the beneficial effect of DPP-4 inhibitor for all-cause mortality is shown in Table 3. After adjusting age, male sex, presence of hypertension, HbA1C, statin use, hsCRP, CACS and the degree of stenosis, the use of DPP-4 inhibitors still showed significant risk reduction in all-cause mortality (HR 0.220, 95% CI 0.102–0.474, p = 0.0001) (Fig. 1A).

Effect of DPP-4 inhibitors on secondary outcome

During follow up, 228 PCI and CABG were reported 90 days after CT. The non-users experienced more adverse events which included mortality and coronary revascularization (4.1% vs. 7.6%, p < 0.0001 in DPP-4 inhibitor users vs. non-users).

The use of DPP-4 inhibitor was associated with reduced secondary outcome (HR 0.554, 95% CI 0.433–0.708, p < 0.0001). Advanced age (HR 1.071, 95% CI 1.061–1.080, p < 0.0001), male sex (HR 1.468, 95% CI 1.204–1.789, p = 0.0001), hypertension (HR 2.505, 95% CI 1.830–3.428, p < 0.0001) and higher hsCRP levels (HR 1.096, 95% CI 1.078–1.115, p < 0.0001) were all associated with increased adverse events. Also, higher fasting blood sugar and HbA1C and lower high density lipoprotein-cholesterol was also associated with more events defined as secondary outcome (p = 0.0346, p < 0.0001 and p = 0.0005, respectively). The baseline CT findings that reflect coronary atherosclerosis such as CACS, degree of stenosis, number of vessels with significant stenosis all increased risk of secondary outcome (HR 2.219, 95% CI 1.947–2.530, p < 0.0001 for CACS, HR 2.015, 95% CI 1.857–2.186, p < 0.0001 for degree of stenosis, HR 2.031, 95% CI 1.873–2.203, p < 0.0001 for number of vessel with significant stenosis). Metformin was associated with reduced events (HR 0.595, 95% CI 0.467–0.758, p < 0.0001), whereas statin and sulfonylurea were not (p = 0.7572 and 0.1091, respectively).

Table 3. Adjusted model showing multivariate cox-regression survival analysis for primary and secondary outcomes

	Primary outcome			Secondary outcome		
	Adjusted HR	95% CI	p-value	Adjusted HR	95% CI	p-value
Age, years	1.102	1.083–1.121	< 0.0001	1.058	1.045–1.071	< 0.0001
Male sex	1.388	0.962–2.003	0.0799	1.550	1.177–2.040	0.0018
HTN	0.770	0.449–1.321	0.3423	1.319	0.871–1.996	0.1910
HbA1C, %	1.157	1.023–1.308	0.0203	1.175	1.083–1.276	0.0001
Statin use*	0.904	0.782–1.046	0.1751	0.960	0.868–1.063	0.4341
hsCRP, mg/dL	1.091	1.065–1.119	< 0.0001	1.059	1.033–1.085	< 0.0001
CACS†	1.083	0.840–1.396	0.5384	1.089	0.907–1.308	0.3598
Degree of stenosis‡	1.201	0.977–1.477	0.0827	1.7257	1.495–1.995	< 0.0001
DPP-4 inhibitor user	0.220	0.102–0.474	0.0001	0.517	0.363–0.735	0.0002

*Statin never-user vs. < 30% user vs. 30–80% user vs. ≥ 80% user, †CACS as a categorical variable defined as CACS 0–100 vs. 100–400 vs. ≥ 400, ‡Coronary artery stenosis as a categorical variable defined as 0% vs. 1–49% vs. 50–69% vs. ≥ 70%. CACS: coronary artery calcium score, CI: confidence interval, DPP-4: dipeptidyl peptidase-4, HbA1C: glycated hemoglobin, HR: hazard ratio, hsCRP: high sensitivity C-reactive protein, HTN: hypertension

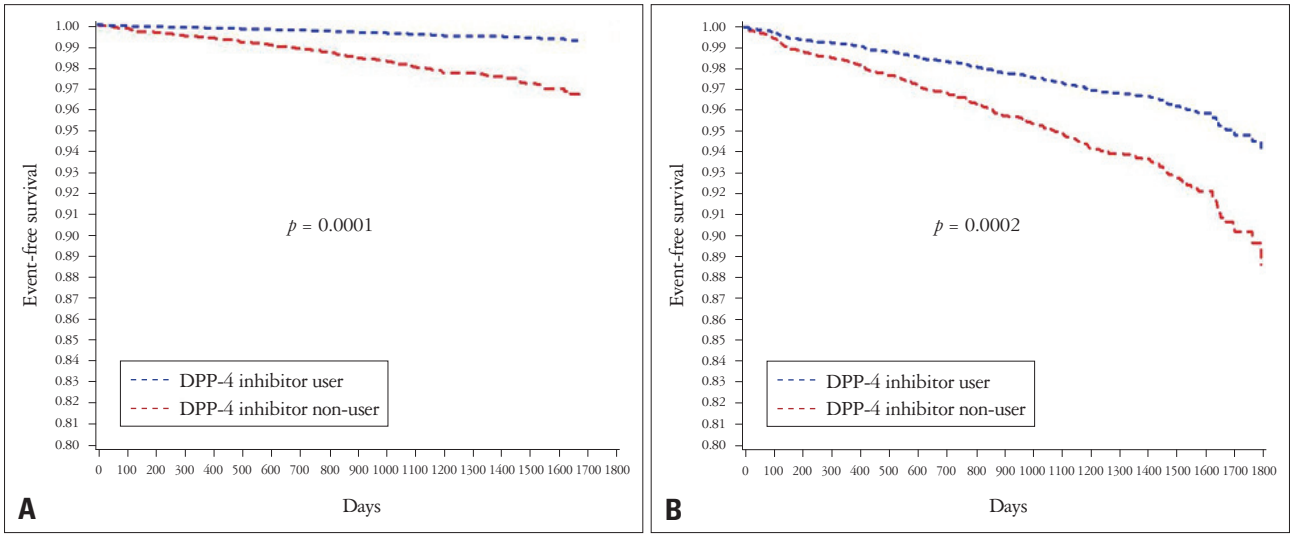

Fig. 1. Adjusted survival curve of DPP-4 inhibitor use for primary outcome (A) and secondary outcome (B). DPP-4: dipeptidyl peptidase-4.

After adjusting age, male sex, presence of hypertension, HbA1C, statin use, hsCRP, CACS and degree of stenosis, the use of DPP-4 inhibitors still showed significantly less secondary outcome (HR 0.517, 95% CI 0.363–0.735, p = 0.0002) (Table 3, Fig. 1B).

EFFECT OF DPP-4 INHIBITORS ACCORDING TO THE PRESENCE OF SIGNIFICANT CORONARY STENOSIS

A total of 5438 patients did not show significant stenosis at baseline CT. The unadjusted survival analysis showed that DPP-4 inhibitor was associated with lower all-cause mortality in both groups (Table 4), but when adjusted with other covariables, the use of DPP-4 inhibitors was associated with better primary outcome only in those without significant stenosis (Table 5, Fig. 2).

The secondary outcome was reduced in the users without significant stenosis (unadjusted HR 0.440, 95% CI 0.306–0.632, p < 0.0001 and adjusted HR 0.525, 95% CI 0.325–0.846, p = 0.0081). However, in patients with significant stenosis, the use of DPP-4 inhibitors did not affect outcome (p = 0.0916 and 0.0701, unadjusted and adjusted multivariate model).

DOSE-RESPONSE RELATIONSHIP OF DPP-4 INHIBITORS ON OUTCOME

To evaluate whether the duration of DPP-4 inhibitor use is associated with outcome, the patients were categorized into four groups according to the percent of DPP-4 inhibitors prescribed during the total follow up period; those who were never exposed to DPP-4 inhibitors, those with < 30% of use during follow up,

Table 4. Univariate cox-regression survival analysis for all-cause mortality according to the baseline degree of coronary stenosis

	Patients with stenosis < 50%			Patients with stenosis ≥ 50%		
	HR	95% CI	p-value	HR	95% CI	p-value
Age, years	1.102	1.084–1.119	< 0.0001	1.095	1.070–1.120	< 0.0001
Male sex	1.135	0.811–1.589	0.460	1.049	0.663–1.658	0.8386
HTN	1.791	1.106–2.901	0.0178	0.882	0.408–1.910	0.7509
Statin use*	0.871	0.754–1.006	0.0596	0.735	0.618–0.875	0.0005
FBS, mg/dL	1.002	0.999–1.005	0.1955	0.998	0.994–1.002	0.3415
HbA1C, %	1.017	0.893–1.157	0.8033	1.079	0.938–1.241	0.2891
T.chol, mg/dL	0.990	0.986–0.994	< 0.0001	0.990	0.985–0.995	0.0001
TG, mg/dL	0.998	0.996–1.001	0.1536	0.999	0.997–1.002	0.6233
HDL-cholesterol, mg/dL	1.008	0.992–1.024	0.3433	0.995	0.972–1.018	0.6568
LDL-cholesterol, mg/dL	0.985	0.978–0.993	< 0.0001	0.994	0.986–1.003	0.1784
hsCRP, mg/dL	1.110	1.081–1.139	< 0.0001	1.117	1.087–1.148	< 0.0001
CACS†	1.815	1.350–2.442	< 0.0001	1.282	0.931–1.766	0.1277
Presence of any coronary artery calcium	2.192	1.446–3.323	0.0002	1.287	0.466–3.555	0.6263
DPP-4 inhibitor user	0.144	0.068–0.308	< 0.0001	0.285	0.138–0.590	0.0007
Metformin user	0.382	0.260–0.560	< 0.0001	0.497	0.299–0.826	0.0070

*Statin use in percentiles defined as 0% (never use) vs. < 30% vs. 30–80% vs. ≥ 80%, †CACS as a categorical variable defined as CACS 0–100 vs. 100–400 vs. ≥ 400. CACS: coronary artery calcium score, CI: confidence interval, DPP-4: dipeptidyl peptidase-4, FBS: fasting blood sugar, HbA1C: glycated hemoglobin, HR: hazard ratio, HDL: high density lipoprotein, hsCRP: high-sensitivity C-reactive protein, HTN: hypertension, LDL: low density lipoprotein, T.chol: total cholesterol, TG: triglyceride

Table 5. Adjusted multivariate cox-regression survival analysis for all-cause mortality according to the baseline degree of coronary stenosis

	Patients with stenosis < 50%			Patients with stenosis ≥ 50%		
	Adjusted HR	95% CI	p-value	Adjusted HR	95% CI	p-value
Age, years	1.116	1.092–1.140	< 0.0001	1.082	1.049–1.116	< 0.0001
Male sex	1.325	0.848–2.071	0.2169	1.662	0.832–3.320	0.1503
HTN	0.742	0.397–1.386	0.3497	0.697	0.240–2.023	0.5070
hsCRP, mg/dL	1.080	1.040–1.122	< 0.0001	1.113	1.073–1.153	< 0.0001
HbA1C, %	1.113	0.950–1.303	0.1853	1.177	0.951–1.456	0.1342
Statin use*	0.911	0.752–1.104	0.3426	0.914	0.725–1.152	0.4466
CACS†	1.075	0.779–1.484	0.6590	0.967	0.667–1.402	0.8600
DPP-4 inhibitor user	0.148	0.046–0.473	0.0013	0.356	0.126–1.009	0.0519

*Statin use in percentiles defined as 0% (never use) vs. < 30% vs. 30–80% vs. ≥ 80%, †CACS as a categorical variable defined as CACS 0–100 vs. 100–400 vs. ≥ 400. CACS: coronary artery calcium score, CI: confidence interval, DPP-4: dipeptidyl peptidase-4, HbA1C: glycated hemoglobin, HR: hazard ratio, hsCRP: high-sensitivity C-reactive protein, HTN: hypertension

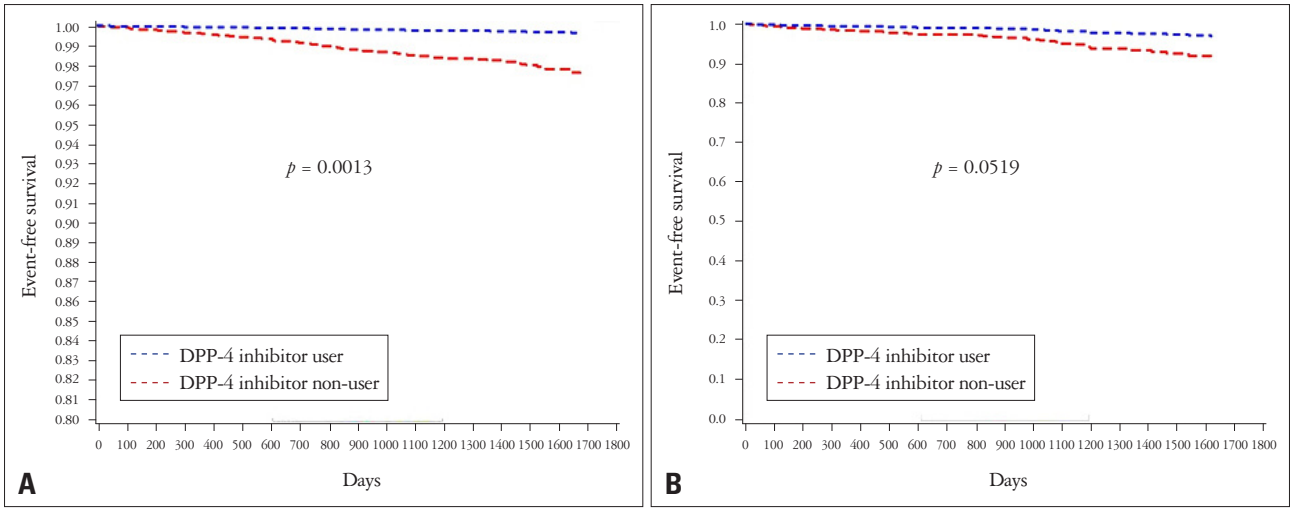

Fig. 2. Adjusted survival curve of DPP-4 inhibitor use for primary outcome in subjects with < 50% (A) and ≥ 50% (B) stenosis at baseline computed tomography. DPP-4: dipeptidyl peptidase-4.

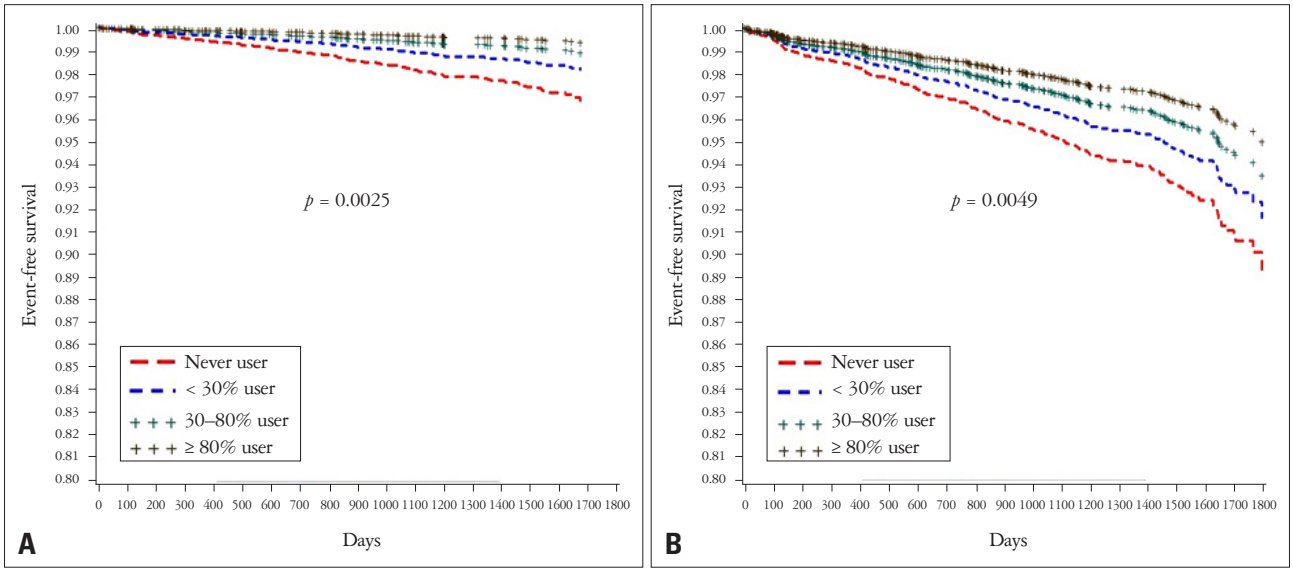

Fig. 3. Adjusted survival curve of DPP-4 inhibitor cumulative use for primary (A) and secondary outcome (B). DPP-4: dipeptidyl peptidase-4.

those with 30–80% use, those with ≥ 80%.

DPP-4 inhibitor was never used in 4957 patients, < 30% in 775 patients, 30–80% in 749 patients and ≥ 80% in 564 patients. From the baseline CT, the degree of stenosis did not differ among the four groups (p = 0.0967). During follow-up, 218 (4.4%) among never users, 10 (1.29%) among < 30% users, 8 (1.07%) among 30–80% users, and 5 (0.89%) among ≥ 80% users died (p < 0.0001).

In univariate cox-regression analysis, longer exposure to DPP-4 inhibitors was associated lower primary and secondary outcome (unadjusted HR 0.478, 95% CI 0.310–0.745, p = 0.0008 for primary outcome, unadjusted HR 0.781, 95% CI 0.621–0.980, p = 0.0332 for secondary outcome). To adjust other possible confounding variables, a multivariate cox-regression survival analysis was performed including age, sex, presence of hypertension, hsCRP, HbA1C, statin use, CACS, degree of stenosis and percent use of DPP-4 inhibitors, and longer use of DPP-4 inhibitors was associated with lower mortality and coronary revascularization (adjusted HR 0.579, 95% CI 0.406–0.825, p = 0.0025 for primary outcome, adjusted HR 0.766, 95% CI 0.636–0.922, p = 0.0049 for secondary outcome) (Fig. 3).

Then we grouped these patients according to the CT findings. In subjects with < 50% coronary artery stenosis at baseline, longer use of DPP-4 inhibitors was associated with significant risk reduction for primary and secondary outcome both before and after adjusting covariables which were age, male sex, presence of hypertension, hsCRP, HbA1C, statin use and CACS (unadjusted HR 0.426, 95% CI 0.293–0.619, p < 0.0001 and adjusted HR 0.449, 95% CI 0.259–0.780, p = 0.0045 for primary outcome, HR 0.693, 95% CI 0.568–0.845, p = 0.0003 and adjusted HR 0.755, 95% CI 0.584–0.976, p = 0.0320 for secondary outcome) (Supplementary Table 1 and 2).

In subjects with ≥ 50% stenosis at baseline CT, longer use of DPP-4 inhibitors was not associated with better primary nor secondary outcome, both before and after adjustment (adjusted HR 0.783, 95% CI 0.492–1.244, p = 0.3000 and adjusted HR 0.829, 95% CI 0.639–1.076, p = 0.1579 for primary and secondary outcome).

Discussion

In this study, we demonstrated for the first time, that 1) DPP-4 inhibitors are associated with less all-cause mortality in DM patients, 2) the longer use of DPP-4 inhibitors have greater protective effect, and 3) such possible beneficial effect of DPP-4 inhibitors is observed only in patients without significant coronary artery stenosis, defined as < 50% stenosis at CT.

DPP-4 inhibitors and all-cause mortality

The novel finding of our study is that we have shown reduced all-cause mortality in DM patients with DPP-4 inhibitors. Reduced mortality may be explained by reduced hypoglycemic events and excellent glucose control as well as cardiovascular effect by DPP-4 inhibitors. Previous studies of the intensive and rapid glucose lowering therapy have shown a paradoxically increased mortality compared with standard therapy,[24] which is known to be associated with hypoglycemic event. DPP-4 inhibitors act by prolonging bioavailability of incretins which are only secreted in response to oral meal uptake, thus are free from hypoglycemia. As reported from UKPDS 80 (United Kingdom Prospective Diabetes Study), better control of blood glucose is associated with continued risk reduction for all-cause death, in addition to risk reduction for myocardial infarction,[25] which could also be an explanation to the survival benefit in our study.

Mechanisms of DPP-4 inhibitors in coronary atherosclerosis

The cardioprotective effect of DPP-4 inhibitors can be explained by both its glucose-lowering effect and pleiotropic effect. In DM subjects, atherosclerosis is promoted by augmented reactive oxygen species, inflammatory responses, endothelial dysfunction, and lipid deposition in the vascular wall,[26] and subsequent macrovascular complications determine mortality. The main mechanism of DPP-4 inhibitors is glucose-lowering effect through two incretin hormones, which are secreted from small intestine and rapidly degraded by DPP-4 enzyme.[27-30] By lowering glucose level, attenuating fluctuation of serum glucose level and directly lowering lipid levels, DPP-4 inhibitors have shown antiatherogenic effect and beneficial effect in cardiovascular events.[3][7][30]

In addition to direct glucose lowering effect, DPP-4 inhibitors have shown pleiotropic effect via which cardiovascular comorbidities are affected.[6][31-33] DPP-4 inhibitors improve lipid profiles[34][35] and lower blood pressure by diuretic effect and vasodilatation effect of glucagon-like peptide-1.[36][37] By cardiovascular risk factor modifications, DPP-4 inhibitors have been suggested for an anti-atherosclerotic effect and possible cardioprotective effect, which is shown in our study.

The anti-inflammatory effect is another mechanism to explain anti-atherosclerotic effect of DPP-4 inhibitors. In various animal models and human studies, DPP-4 inhibitors have shown reduced inflammatory markers and cytokine production,[38] decreased infiltration and macrophage foam cell formation and macrophage content,[39][40] and reduced mRNA expression levels of proinflammatory mediators. Although not studied in coronary arteries, a previous study using carotid arteries also support the hypothesis, which suggested anti-inflammatory effect of DPP-4 inhibitors and reduced inflammatory markers as a mechanism to explain reduction in atherosclerotic changes in carotid arteries.[41] Moreover, DPP-4 inhibitors have shown beneficial effect in improving endothelial function and vascular relaxation, by modulating vascular tone through nitric oxide-dependent pathway,[33][42] which all contribute to possible cardiovascular protective effect of DPP-4 inhibitors.

Effect of DPP-4 inhibitors with or without significant coronary artery stenosis

Another novel finding of our study is that we observed a difference in the effect of DPP-4 inhibitors according to the presence of significant coronary stenosis. In all study subjects, baseline CT was performed, with which we were able to demonstrate an accurate degree of coronary artery stenosis at baseline, and evaluate the effect of DPP-4 inhibitors according to the presence of significant coronary artery stenosis using such advantages of imaging modality.

As we have shown, the beneficial effect of DPP-4 inhibitors was somewhat different in those with and without significant stenosis. The benefit of DPP-4 inhibitors was demonstrated only in subjects without significant stenosis. In presence of already documented significant stenosis, DPP-4 inhibitors did not affect survival or revascularization therapy significantly. Although our study cannot provide exact mechanism to explain the different effect of DPP-4 inhibitors according to the presence of significant coronary artery stenosis, it may be due to anti-inflammatory and anti-atherosclerotic effect of DPP-4 inhibitors that usually affect initial phase of atherosclerosis.[43] Currently atherosclerosis is understood as a specific form of chronic inflammatory process, and especially, early events in atherosclerosis is known to be triggered and mediated by proinflammatory factors, cytokines in arterial wall and atherogenic lipoproteins in plasma. Thus, anti-inflammatory effect of DPP-4 inhibitors may be more effective in earlier stage of atherosclerosis, which may explain the different cardioprotective effect in presence or absence of significant coronary artery stenosis. However, further study is needed to find out the exact mechanism.

Comparison with other clinical outcome studies of DPP-4 inhibitors

Recently, two clinical trial results of DPP-4 inhibitors were presented,[15)16)] the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)-Thrombolysis in Myocardial Infarction (TIMI) 53 study and the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) study. Both trials showed neither significant risk nor benefit of saxagliptin and alogliptin in study subjects. It may be due to a different patient enroll criteria and use of different types of DPP-4 inhibitors. In SAVOR-TIMI 53, the study subjects consisted of a 'selected' population with a history of or were at risk for cardiovascular events, and in EXAMINE study patients with recent acute coronary syndrome were evaluated, whereas in our study, those with previous revascularization were excluded. Our study population represents more of the 'real-world' diabetic subjects, and different study population may have caused a different result.

Study limitations

Our study has several limitations. First, the major limitation of our study lies in inherent problems with observational data. Due to the retrospective design of the study, we cannot clearly show 'causal relationship' between DPP-4 inhibitor use and outcome. It was not possible to account for changes in antidiabetic agents during follow up period. Randomized controlled trials of 'real-world' DM patients should be designed and performed, to further establish the effect of DPP-4 inhibitors along with other antidiabetic agents, in near future. Second, although all study subjects received antidiabetic agents during follow up, we do not have follow up blood test results to show adequate control of blood glucose levels. However, since the study subjects had regular prescriptions and were treated under medical guidance, we could assume that these patients were under control. Third, we do not have information regarding indications of CT taken in our study population. Fourth, due to the reimbursement policy in Korea, most of the DPP-4 inhibitor users were under combination therapy, which itself may have affected the outcomes. However, when we adjusted combination therapy using multivariate models, DPP-4 inhibitor users still showed significant risk reduction in both primary and secondary outcome.

Conclusion

DPP-4 inhibitors are associated with reduced all-cause mortality and coronary revascularization in DM patients. After adjustment of known cardiovascular risk factors, DPP-4 inhibitors seemed to be still beneficial in improving outcome. The duration of DPP-4 inhibitor exposure was also associated with outcome. Longer use of DPP-4 inhibitors had less events in all-cause mortality and revascularization. Interestingly, the benefit of DPP-4 inhibitors was found predominantly in subjects without significant coronary stenosis at baseline CT.

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