Korean Circ J. 2018 May;48(5):395-405
https://doi.org/10.4070/kcj.2017.0324
pISSN 1738-5520·eISSN 1738-5555

kcj
Korean Circulation Journal

Original Article

Check for updates

Comparative Cardiovascular Risks of Dipeptidyl Peptidase-4 Inhibitors: Analyses of Real-world Data in Korea

Kyoung Hwa Ha, PhD[1,2], Bongseong Kim, BS[3], Hae Sol Shin, BS[4], Jinhee Lee, MS[1], Hansol Choi, PhD[5,6], Hyeon Chang Kim, PhD[5,6], and Dae Jung Kim, MD[1,2]

[1]Department of Endocrinology and Metabolism, Ajou University School of Medicine, Suwon, Korea
[2]Cardiovascular and Metabolic Disease Etiology Research Center, Ajou University School of Medicine, Suwon, Korea
[3]Department of Statistics and Actuarial Science, Soongsil University, Seoul, Korea
[4]Department of Biostatistics, Yonsei University College of Medicine, Seoul, Korea
[5]Department of Preventive Medicine, Yonsei University College of Medicine, Seoul, Korea
[6]Cardiovascular and Metabolic Disease Etiology Research Center, Yonsei University College of Medicine, Seoul, Korea

OPEN ACCESS

Received: Oct 25, 2017
Revised: Jan 4, 2018
Accepted: Jan 25, 2018

Correspondence to
Dae Jung Kim, MD
Department of Endocrinology and Metabolism, Ajou University School of Medicine, 164, World cup-ro, Yeongtong-gu, Suwon 16499, Korea.
E-mail: djkim@ajou.ac.kr

ORCID iDs
Kyoung Hwa Ha
https://orcid.org/0000-0002-3408-7568
Bongseong Kim
https://orcid.org/0000-0002-1022-3553
Hae Sol Shin
https://orcid.org/0000-0003-4124-1946
Jinhee Lee
https://orcid.org/0000-0002-5357-3481
Hansol Choi
https://orcid.org/0000-0003-4244-6644
Hyeon Chang Kim
https://orcid.org/0000-0001-7867-1240

ABSTRACT

Background and Objectives: To compare cardiovascular disease (CVD) risk associated with 5 different dipeptidyl peptidase-4 inhibitors (DPP-4is) in people with type 2 diabetes.
Methods: We identified 534,327 people who were newly prescribed sitagliptin (n=167,157), vildagliptin (n=67,412), saxagliptin (n=29,479), linagliptin (n=220,672), or gemigliptin (n=49,607) between January 2013 and June 2015 using the claims database of the Korean National Health Insurance System. A Cox proportional hazards model was used to estimate hazard ratios (HRs) for major CVD events (myocardial infarction, stroke, or death) among users of different DPP-4is. The model was adjusted for sex, age, duration of DPP-4i use, use of other glucose-lowering drugs, use of antiplatelet agents, hypertension, dyslipidemia, atrial fibrillation, chronic kidney disease, microvascular complications of diabetes, Charlson comorbidity index, and the calendar index year as potential confounders.
Results: Compared to sitagliptin users, the fully adjusted HRs for CVD events were 0.97 (95% confidence interval [CI], 0.94–1.01; p=0.163) for vildagliptin, 0.76 (95% CI, 0.71–0.81; p<0.001) for saxagliptin, 0.95 (95% CI, 0.92–0.98; p<0.001) for linagliptin, and 0.84 (95% CI, 0.80–0.88; p<0.001) for gemigliptin.
Conclusions: Compared to sitagliptin therapy, saxagliptin, linagliptin, and gemigliptin therapies were all associated with a lower risk of cardiovascular events.

Keywords: Type 2 diabetes mellitus; Cardiovascular diseases; Dipeptidyl-peptidase IV inhibitors

INTRODUCTION

Type 2 diabetes is a chronic and progressive disease that is an increasing global health problem. It has considerable impact on morbidity and mortality, particularly on cardiovascular complications.[1] To delay or prevent these complications, the management of type 2 diabetes through lifestyle modifications and the selection of appropriate glucose-lowering drugs are necessary.[2]

kcj
Korean Circulation Journal

Dae Jung Kim
https://orcid.org/0000-0003-1025-2044

Funding

This study used National Health Insurance Service (NHIS) data (NHIS-2017-1-059) made by NHIS. This research was supported by a grant of the Korea Health Technology R&D project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health and Welfare, Republic of Korea (grant number: HI13C0715).

This research was supported by LG Chem, Ltd. The funder did not play any role in the study design, data collection and analysis, decisions regarding data release, or manuscript preparation.

Conflict of Interest

The authors have no financial conflicts of interest.

Author Contributions

Conceptualization: Kim HC, Kim DJ; Data curation: Choi H, Kim HC; Formal analysis: Kim B, Shin HS, Lee J; Funding acquisition: Kim HC; Investigation: Kim HC, Kim DJ; Methodology: Ha KH, Kim HC, Kim DJ; Project administration: Kim HC; Resources: Choi H; Software: Ha KH, Shin HS; Supervision: Kim HC, Kim DJ; Validation: Ha KH, Kim B, Kim HC, Kim DJ; Writing - original draft: Ha KH; Writing - review & editing: Ha KH, Kim HC, Kim DJ.

Dipeptidyl peptidase-4 inhibitors (DPP-4is) are a relatively new class of oral hypoglycemic agents for treating type 2 diabetes; their effects are mediated through the incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Previous studies have suggested that DPP-4i as a monotherapy or in combination with other oral hypoglycemic agents has potentially beneficial effects on cardiovascular outcomes.[3-6] A recent study by Ha et al.,[6] based on the 2011–2015 Korean National Health Insurance Service (NHIS) database, reported that people with type 2 diabetes who added a DPP-4i as a second-line drug to metformin had lower risks of cardiovascular disease (CVD) and all-cause mortality, compared to those who added sulfonylurea. However, there are some practical differences between the DPP-4is such as duration of action, metabolism, elimination, and isolated compound-specific characteristics.[7] Although there have been randomized controlled trials studying the effects of each DPP-4i on CVD, the results have been inconsistent,[8-10] and there is little evidence comparing the effects of DPP-4i on CVD using large-scale observational studies.[11-13]

We conducted a real-world cohort study to compare the CVD risks of different DPP-4is among people with type 2 diabetes through an analysis of a nationwide health insurance database in Korea.

METHODS

The current analyses were based on a dataset from the NHIS, the compulsory single-payer national health care coverage system in South Korea. The NHIS claims database includes a de-identified research dataset of demographic information, disease diagnoses, therapeutic procedures, and drug prescriptions. In addition, the NHIS requires biennial health screening tests that include health questionnaire surveys, physical examinations, and biochemical test results.

Among people with type 2 diabetes (International Classification of Diseases, 10th Edition [ICD-10] codes E11–E14), we selected a subset who were newly prescribed DPP-4is for at least 90 days between January 2013 and June 2015. DPP-4is were limited to the 5 most common drugs: sitagliptin, vildagliptin, saxagliptin, linagliptin, and gemigliptin. The start date of medication administration was defined as the index date. We excluded people aged <30 years or >90 years at the index date, and/or who had a history of CVD or cancer between the year prior to the index date and within 90 days after the index (**Figure 1**). The outcome was the modified major adverse cardiovascular events, defined as hospitalized myocardial infarction (ICD-10 codes I21–I23), hospitalized stroke (ICD-10 codes I60–I69), or all-cause death. The date of CVD onset was the date of the first occurrence of the event. This study was performed as an "intention to treat" analysis. The end of follow-up was the CVD diagnosis or the end of the study period (June 30, 2015), or whichever occurred first.

We used Kaplan-Meier analyses to compare cumulative incidence of CVD by the 5 different DPP-4is. A Cox proportional hazards model was used to estimate the relationships between the 5 different DPP-4is and CVD risk, calculating hazard ratios (HRs) and 95% confidence intervals (CIs) and adjusting for potential confounders. Although the NHIS claims database included major risk factor variables, there may be some unmeasured confounding factors. Therefore, we utilized 2 approaches. First, we conducted the main analysis, including the following factors as confounders: sex, age, duration of DPP-4i use, use of other

https://doi.org/10.4070/kcj.2017.0324

kcj
Korean Circulation Journal

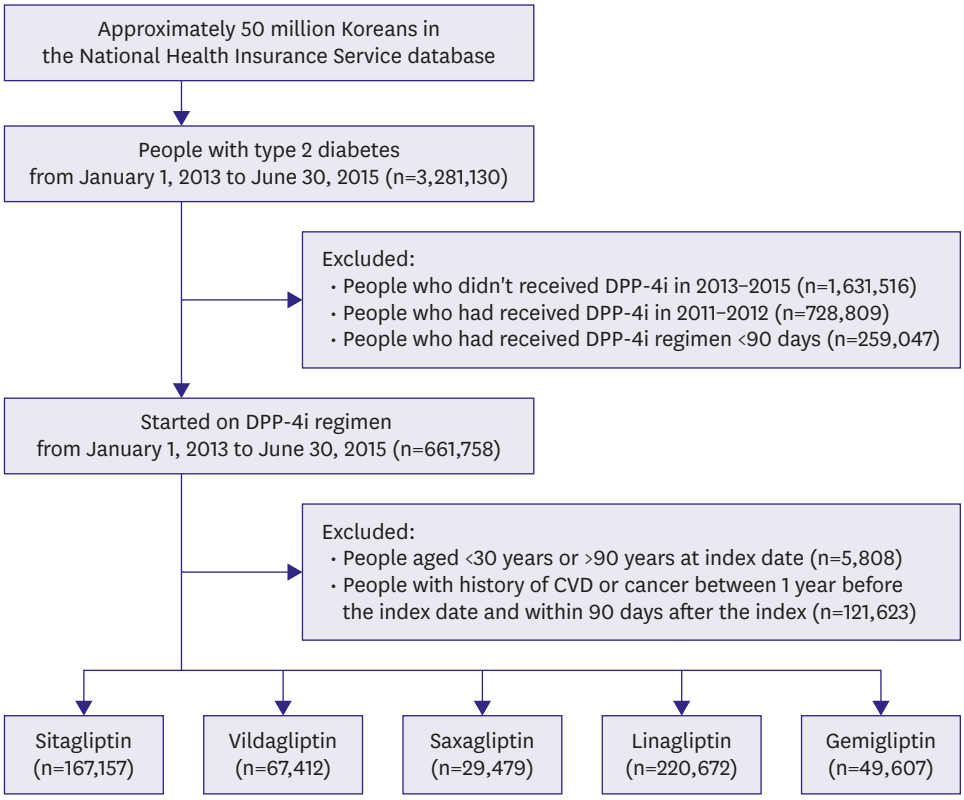


Figure 1. Flow of people through study.
CVD = cardiovascular disease; DPP-4i = dipeptidyl peptidase-4 inhibitor.

glucose-lowering drugs (metformin, sulfonylurea, thiazolidinedione, or insulin), use of antiplatelet agents (Anatomical Therapeutic Chemical [ATC] code B01), calendar year, Charlson comorbidity index (CCI), and comorbidities.[14] The comorbid conditions included hypertension (ICD-10 codes I10–I15 and/or ATC codes C02–C03, or C07–C09), dyslipidemia (ICD-10 code E78 and/or ATC code C10), atrial fibrillation (ICD-10 code I48), chronic kidney disease (ICD-10 code N18), and microvascular complications of diabetes including retinopathy (ICD-10 codes E11.3, E12.3, E13.3, E14.3, or H36.0), neuropathy (ICD-10 codes E11.4, E12.4, E13.4, E14.4, or G63.2), or nephropathy (ICD-10 codes E11.2, E12.2, E13.2, E14.2, or N08.3) within the year prior to the index date. Second, we conducted additional analysis only on those who had health screening data collected within the 2 years prior to the index date. These analyses included sex, age, duration of DPP-4i use, use of other glucose-lowering drugs (metformin, sulfonylurea, thiazolidinedione, or insulin), calendar year, body mass index (BMI), waist circumference, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, fasting glucose, serum creatinine, smoking status (yes or no), family history of stroke and heart disease, and CCI. All of the analyses were conducted using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Ethical consideration

This study used a de-identified dataset that was prepared and monitored by the Korea NHIS. The study protocol was reviewed and approved by the Institutional Review Board (IRB) of Severance Hospital at Yonsei University College of Medicine (IRB No. 4-2015-1023).

https://doi.org/10.4070/kcj.2017.0324

kcj
Korean Circulation Journal

RESULTS

A total of 534,327 people with type 2 diabetes who were newly prescribed DPP-4is (167,157 sitagliptin users, 67,412 vildagliptin users, 29,479 saxagliptin users, 220,672 linagliptin users, and 49,607 gemigliptin users) were identified. The age and sex distribution of the users of each DPP-4i were similar, with a mean age of approximately 60 years; approximately 57.1% of the people were male (**Table 1**). The baseline characteristics of the analysis of the health screening data was summarized in **Supplementary Table 1**.

Table 2 and **Figure 2** shows the CVD risk for users of each DPP-4i compared to those treated with sitagliptin. In the main analysis, CVD risk was significantly lower in saxagliptin users (HR, 0.76; 95% CI, 0.71–0.81; p<0.001), linagliptin users (HR, 0.95; 95% CI, 0.92–0.98; p<0.001) and gemigliptin users (HR, 0.84; 95% CI, 0.80–0.88; p<0.001) than in sitagliptin users after adjusting for all of the confounding variables. However, vildagliptin users were not significantly different from sitagliptin users in terms of CVD risk (HR, 0.97; 95% CI, 0.94–1.01; p=0.163). In addition, this statistical significance was retained saxagliptin, linagliptin, and gemigliptin users in the propensity score-matching analysis (data not shown). There was a difference in the significant associations of each events (death, myocardial infarction, and stroke) for each DPP-4i use (**Supplementary Table 2**). Because our analysis defined wash-out period as 90 days, we did a further analysis with 180, 270, and 360 days wash-out period. And, different wash-out period did not severely influence the association (**Supplementary Table 3**). When we divided subgroup by duration of DPP-4i, saxagliptin and gemigliptin users had lower risk of CVD in all groups (**Supplementary Table 4**).

In the analysis of health screening data, saxagliptin and gemigliptin users had significantly lower CVD risk than sitagliptin users after adjusting for sex, age, duration of DPP-4i use, use

Table 1. Baseline characteristics by DPP-4is

	Sitagliptin (n=167,157)	Vildagliptin (n=67,412)	Saxagliptin (n=29,479)	Linagliptin (n=220,672)	Gemigliptin (n=49,607)	p value
Age (years)	59.1±12.0	59.7±12.1	59.7±11.9	60.2±12.0	60.1±11.9	<0.001
Men	97,754 (58.5)	38,957 (57.8)	16,835 (57.1)	124,053 (56.2)	27,492 (55.4)	<0.001
Duration of DPP-4i use (years)	1.0±0.6	1.0±0.7	1.0±0.6	1.1±0.6	0.9±0.6	<0.001
Use of other glucose-lowering drugs						
Metformin	106,862 (63.9)	42,231 (62.7)	18,192 (61.7)	139,940 (63.4)	31,573 (63.7)	<0.001
Sulfonylurea	93,743 (56.1)	39,432 (58.5)	15,080 (51.2)	131,894 (59.8)	27,268 (55.0)	<0.001
Thiazolidinedione	11,236 (6.7)	4,729 (7.0)	2,286 (7.8)	16,281 (7.4)	4,554 (9.2)	<0.001
Insulin	16,187 (9.7)	9,027 (13.4)	2,865 (9.7)	21,271 (9.6)	6,132 (12.4)	<0.001
Use of antiplatelet agents	10,068 (6.0)	4,977 (7.4)	2,737 (9.3)	13,525 (6.1)	3,276 (6.6)	<0.001
Comorbidities						
Hypertension	110,088 (65.9)	44,742 (66.4)	19,600 (66.5)	152,464 (69.1)	32,938 (66.4)	<0.001
Dyslipidemia	132,600 (79.3)	54,321 (80.6)	24,350 (82.6)	178,145 (80.7)	40,150 (80.9)	<0.001
Atrial fibrillation	3,620 (2.2)	1,803 (2.7)	792 (2.7)	4,903 (2.2)	1,042 (2.1)	<0.001
Chronic kidney disease	14,673 (8.8)	7,748 (11.5)	2,964 (10.1)	26,797 (12.1)	5,613 (11.3)	<0.001
Diabetic retinopathy	33,078 (19.8)	15,417 (22.9)	6,094 (20.7)	46,351 (21.0)	9,452 (19.1)	<0.001
Diabetic neuropathy	26,087 (15.6)	12,576 (18.7)	5,184 (17.6)	37,828 (17.1)	9,440 (19.0)	<0.001
Diabetic nephropathy	4,275 (2.6)	2,387 (3.5)	2,048 (7.0)	6,230 (2.8)	1,512 (3.1)	<0.001
CCI score (unit)	4.9±2.5	5.2±2.6	5.1±2.5	5.2±2.6	5.2±2.5	<0.001
Inclusion year						
2013	73,308 (43.9)	31,480 (46.7)	11,735 (39.8)	114,368 (51.8)	18,245 (36.8)	
2014	67,550 (40.4)	24,339 (36.1)	12,156 (41.2)	81,532 (37.0)	21,610 (43.6)	<0.001
2015	26,299 (15.7)	11,593 (17.2)	5,588 (19.0)	24,772 (11.2)	9,752 (19.7)	

Data are reported as means±standard deviations or numbers (percentages) unless otherwise stated.
CCI = Charlson comorbidity index; DPP-4i = dipeptidyl peptidase-4 inhibitor.

https://doi.org/10.4070/kcj.2017.0324

Table 2. HRs for CVD risk among users of different DPP-4is

	Number of persons	PY	Number of events	Event rate (per 100,000 PY)	Adjusted HR (95% CI)	p value
Main analysis*						
Sitagliptin	167,157	300,327	8,218	2,736	1.00	
Vildagliptin	67,412	121,177	3,700	3,053	0.97 (0.94–1.01)	0.163
Saxagliptin	29,479	50,566	1,151	2,276	0.76 (0.71–0.81)	<0.001
Linagliptin	220,672	419,113	11,809	2,818	0.95 (0.92–0.98)	<0.001
Gemigliptin	49,607	82,704	2,118	2,561	0.84 (0.80–0.88)	<0.001
Analysis of health screening data†						
Sitagliptin	22,741	43,127	999	2,316	1.00	
Vildagliptin	9,868	18,507	493	2,664	1.06 (0.95–1.18)	0.312
Saxagliptin	3,885	7,010	117	1,669	0.71 (0.58–0.86)	<0.001
Linagliptin	30,303	60,099	1,451	2,414	1.00 (0.92–1.08)	0.923
Gemigliptin	6,736	11,665	250	2,143	0.80 (0.69–0.91)	0.001

BMI = body mass index; CCI = Charlson comorbidity index; CI = confidence interval; CVD = cardiovascular disease; DPP-4i = dipeptidyl peptidase-4 inhibitor; HDL = high-density lipoprotein; HR = hazard ratio; LDL = low-density lipoprotein; PY = person-years.
*Adjusted for sex, age, duration of DPP-4i use, use of other glucose-lowering drugs (metformin, sulfonylurea, thiazolidinedione, or insulin), use of antiplatelet agents, hypertension, dyslipidemia, atrial fibrillation, chronic kidney disease, and microvascular complications of diabetes (retinopathy, neuropathy, or nephropathy), the CCI score, and calendar index year, †Adjusted for sex, age, duration of DPP-4i use, use of other glucose-lowering drugs (metformin, sulfonylurea, thiazolidinedione, or insulin), BMI, waist circumference, systolic blood pressure, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, fasting glucose, serum creatinine level, smoking status, family history of stroke and heart disease, the CCI score, and calendar index year.

of other glucose-lowering drugs, calendar year, CCI, BMI, waist circumference, systolic blood pressure, blood lipid profile, fasting glucose, serum creatinine, cigarette smoking, and family histories of stroke and heart disease, which were measured ≤2 years before DPP-4i therapy initiation (saxagliptin users, HR, 0.71; 95% CI, 0.58–0.86; p<0.001; gemigliptin users, HR, 0.80; 95% CI, 0.69–0.91; p=0.001) (**Table 2** and **Figure 2**).

We repeated the main analysis for subgroups categorized by sex, age, hypertension, dyslipidemia, and microvascular complication. Sex, age, microvascular complication did not modify the associations. However, when classified as hypertension, saxagliptin, linagliptin, and gemigliptin users had significantly lower risk of CVD compare to sitagliptin users in people with hypertension. However, this statistical significance was retained only saxagliptin users in people without hypertension. When classified as dyslipidemia, saxagliptin, linagliptin, and gemigliptin users had significantly lower risk of CVD compare to sitagliptin users in people with dyslipidemia. However, this statistical significance was not found in people without dyslipidemia (**Figure 3**). When classified as use of statin, saxagliptin, linagliptin, and gemigliptin users had significantly lower risk of CVD compare to sitagliptin users regardless of use of statin (data not shown).

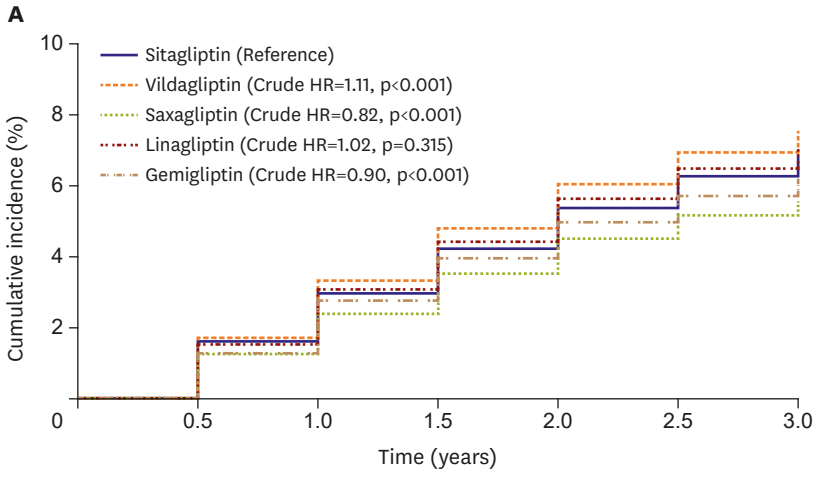
DISCUSSION

In this analysis of nationwide real-world data, we observed that the use of saxagliptin, linagliptin, or gemigliptin was significantly associated with decreased CVD risk compared to sitagliptin use.

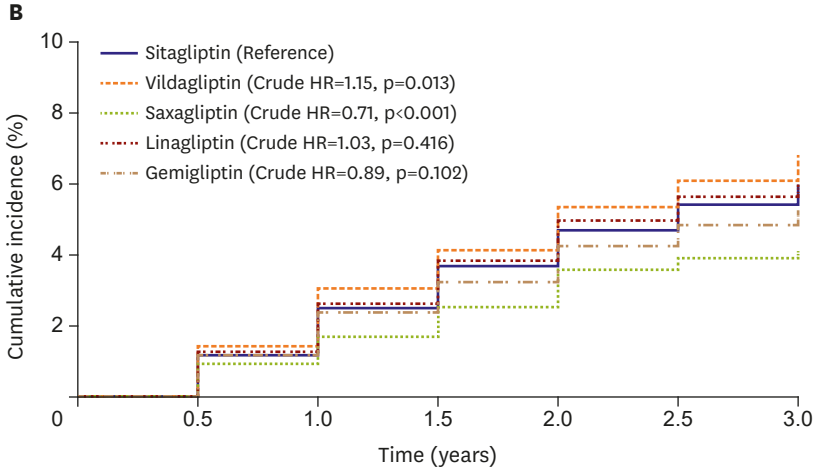
Previous studies have reported associations between specific DPP-4i agents and CVD risk. A large observational study in the United States demonstrated that new users of sitagliptin or saxagliptin had no associated risk for heart failure compared to pioglitazone users.[13] Based on a large national study using commercially insured claims and an integrated laboratory database in the United States, sitagliptin use did not increase the risks of all-cause hospital admission or death compared to other glucose-lowering agents.[15] In a clinical

https://doi.org/10.4070/kcj.2017.0324

kcj
Korean Circulation Journal



No. at risk							
Sitagliptin	167,157	164,491	139,425	107,800	72,156	42,190	4,356
Vildagliptin	67,412	66,243	55,030	43,156	30,544	17,819	1,608
Saxagliptin	29,479	29,099	23,885	17,410	11,570	6,357	725
Linagliptin	220,672	217,232	192,784	158,157	112,733	62,689	4,918
Gemigliptin	49,607	48,963	39,714	29,078	19,266	8,904	367



No. at risk							
Sitagliptin	22,741	22,461	19,346	15,724	11,265	7,002	764
Vildagliptin	9,868	9,726	8,165	6,711	4,962	3,059	295
Saxagliptin	3,885	3,849	3,212	2,482	1,747	1,000	115
Linagliptin	30,303	29,912	26,893	22,781	17,136	10,201	914
Gemigliptin	6,736	6,657	5,431	4,216	2,822	1,404	53

Figure 2. Cumulative incidence of cardiovascular events by different DPP-4is. (A) Main analysis. (B) Analysis of health screening data.
DPP-4i = dipeptidyl peptidase-4 inhibitor; HR = hazard ratio.

trial, using vildagliptin as an add-on medication to metformin resulted in a larger decrease in glycosylated hemoglobin than using pioglitazone as an add-on medication (−0.94% vs. −0.6%; p=0.010).[16] However, real-world data from 5 European electronic healthcare databases showed that vildagliptin had no association with CVD compared to other glucose-lowering agents (range of adjusted incidence rate ratios=0.22–1.02).[17] Using the Korean Health Insurance Review and Assessment Service database, new users of sitagliptin and

https://doi.org/10.4070/kcj.2017.0324

	PY	No. of events	HR (95% CI)
Sex			
Men			
Sitagliptin	175,469	4,534	1.00 (reference)
Vildagliptin	70,192	2,107	0.98 (0.93–1.03)
Saxagliptin	28,870	619	0.73 (0.67–0.80)
Linagliptin	235,336	6,338	0.94 (0.90–0.97)
Gemigliptin	45,835	1,153	0.84 (0.79–0.90)
Women			
Sitagliptin	124,858	3,684	1.00 (reference)
Vildagliptin	50,985	1,593	0.94 (0.89–1.00)
Saxagliptin	21,695	532	0.77 (0.71–0.85)
Linagliptin	183,777	5,471	0.94 (0.90–0.98)
Gemigliptin	36,869	965	0.80 (0.74–0.86)
Age groups			
<65			
Sitagliptin	202,793	2,978	1.00 (reference)
Vildagliptin	79,370	1,288	0.95 (0.89–1.02)
Saxagliptin	33,423	368	0.68 (0.61–0.76)
Linagliptin	270,301	3,838	0.90 (0.86–0.95)
Gemigliptin	53,254	678	0.78 (0.72–0.85)
≥65			
Sitagliptin	97,534	5,240	1.00 (reference)
Vildagliptin	41,807	2,412	0.97 (0.92–1.02)
Saxagliptin	17,143	783	0.79 (0.73–0.85)
Linagliptin	148,811	7,971	0.97 (0.93–1.00)
Gemigliptin	29,449	1,440	0.85 (0.80–0.90)
Hypertension			
Yes			
Sitagliptin	200,564	7,206	1.00 (reference)
Vildagliptin	81,678	3,235	0.96 (0.92–1.00)
Saxagliptin	34,433	1,003	0.75 (0.70–0.80)
Linagliptin	291,095	10,483	0.95 (0.92–0.98)
Gemigliptin	55,893	1,859	0.83 (0.79–0.87)
No			
Sitagliptin	99,762	1,012	1.00 (reference)
Vildagliptin	39,499	465	1.04 (0.93–1.16)
Saxagliptin	16,133	148	0.79 (0.66–0.94)
Linagliptin	128,017	1,326	0.96 (0.88–1.04)
Gemigliptin	26,811	259	0.87 (0.76–1.00)
Dyslipidemia			
Yes			
Sitagliptin	245,306	7,035	1.00 (reference)
Vildagliptin	101,087	3,174	0.97 (0.93–1.01)
Saxagliptin	43,395	996	0.74 (0.69–0.79)
Linagliptin	345,427	10,074	0.94 (0.91–0.97)
Gemigliptin	68,994	1,770	0.81 (0.77–0.85)
No			
Sitagliptin	55,021	1,183	1.00 (reference)
Vildagliptin	20,090	526	1.01 (0.91–1.12)
Saxagliptin	7,171	155	0.92 (0.77–1.08)
Linagliptin	73,686	1,735	1.01 (0.94–1.09)
Gemigliptin	13,710	348	1.01 (0.90–1.14)

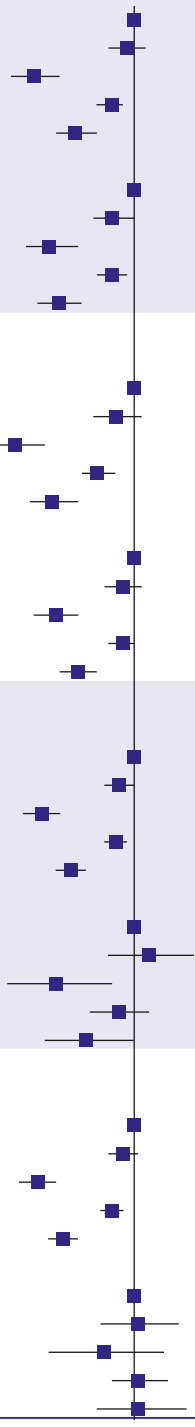


Figure 3. Subgroup analysis by sex, age group, hypertension, dyslipidemia, microvascular complication. These analyses were adjusted to address potential confounding by sex, age, duration of DPP-4i use, use of other glucose-lowering drugs (metformin, sulfonylurea, thiazolidinedione, or insulin), use of antiplatelet agents, hypertension, dyslipidemia, atrial fibrillation, chronic kidney disease, and microvascular complications of diabetes (retinopathy, neuropathy, or nephropathy), the CCI score, and calendar index year.
CCI = Charlson comorbidity index; CI = confidence interval; DPP-4i = dipeptidyl peptidase-4 inhibitor; HR = hazard ratio; PY = person-years.

(continued to the next page)

https://doi.org/10.4070/kcj.2017.0324

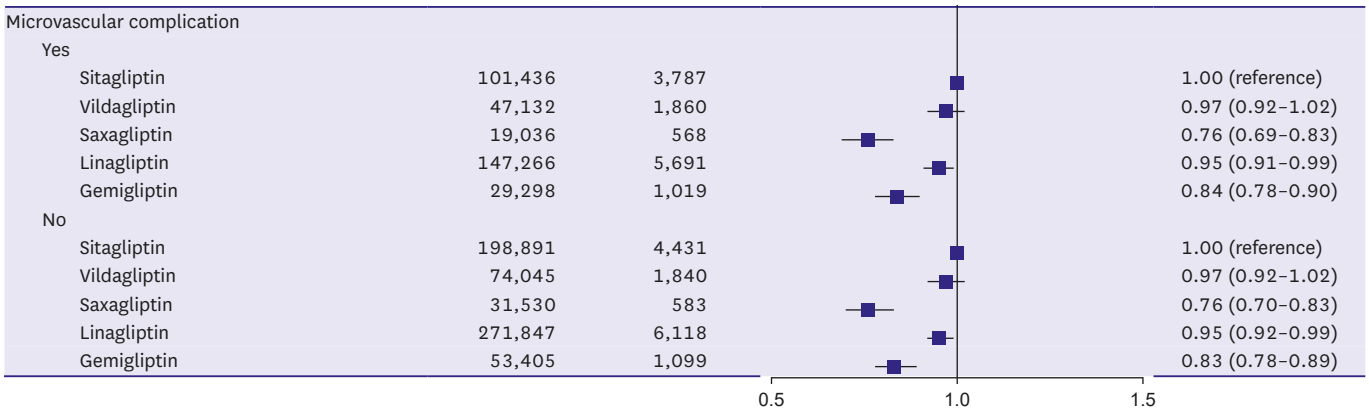


Figure 3. (Continued) Subgroup analysis by sex, age group, hypertension, dyslipidemia, microvascular complication. These analyses were adjusted to address potential confounding by sex, age, duration of DPP-4i use, use of other glucose-lowering drugs (metformin, sulfonylurea, thiazolidinedione, or insulin), use of antiplatelet agents, hypertension, dyslipidemia, atrial fibrillation, chronic kidney disease, and microvascular complications of diabetes (retinopathy, neuropathy, or nephropathy), the CCI score, and calendar index year.
CCI = Charlson comorbidity index; CI = confidence interval; DPP-4i = dipeptidyl peptidase-4 inhibitor; HR = hazard ratio; PY = person-years.

vildagliptin had no associations with CVD compared to pioglitazone users.[12] In a clinical trial, linagliptin was associated with significantly lower risk of CVD than sulfonylurea glimepiride (relative risk=0.46; p=0.021).[18] Gemigliptin demonstrated a protective effect against CVD.[19] Pooled meta-analyses with DPP-4i (sitagliptin, vildagliptin, saxagliptin, and linagliptin) reported significant decreases in cardiovascular events.[20-24]

The risk of CVD, particularly heart failure, for DPP-4i users has been controversial in randomized controlled trials. The SAVOR-TIMI 53 trial reported that saxagliptin showed no significant associations with cardiovascular risks including cardiovascular death, nonfatal myocardial infarction, nonfatal ischemic stroke, hospitalization for unstable angina, coronary revascularization, or heart failure compared to a placebo group (HR, 1.02; p=0.660). When classified as subtypes of CVD, saxagliptin had a significantly increased risk for only heart failure (HR, 1.27; p=0.007), but not for other subtypes of CVD.[10] The TECOS trial showed that sitagliptin had no significant associations with CVD, comprising cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina (HR, 0.98; p=0.650); but also heart failure (HR, 1.00; p=0.980).[8] However, there were no significant differences in CVD risk between saxagliptin users and sitagliptin users based on a United States insurance claims database.[11]

DPP-4is are glucose-lowering agents that inhibit the metabolism of the incretin hormones GLP-1 and GIP.[25] Experimental and preliminary clinical data have reported that GLP-1 has beneficial cardiovascular effects.[26][27] Although different DPP-4is act on the human body in similar ways, there are some intrinsic pharmacological differences.[7] In particular, the differential selectivities among DPP-4is for non-GLP-1 substrates may cause a risk of hospitalizations for heart failure.[28] However, the reasons for the different effects on CVD among the classes of DPP-4i are unclear.

To the best of our knowledge, this study was the first to investigate the associations between DPP-4i and cardiovascular risk among people with type 2 diabetes using nationwide real-world data from Korea. Despite yielding several important findings, this study faced several limitations that should be considered when reviewing the results. First, there were potential misclassifications of outcomes because we used definitions based on diagnoses from health insurance claims data. However, previous validation studies for the identification of CVD events

https://doi.org/10.4070/kcj.2017.0324

showed 71.4% for myocardial infarction and 83.4% for ischemic stroke.[29][30] Second, as the mean follow-up period was relatively short, additional studies are needed to compare the long-term effects of the different DPP-4i. Finally, we cannot exclude the possibility of residual confounding by unmeasured or uncontrolled confounders such as duration of diabetes, time-varying confounders because this is an observational study using a health insurance claims database. Although the analysis of health screening data adjusting for clinical variables attenuate this concern, we still cannot completely rule out the possibility of residual confounding.

In conclusion, this analysis of nationwide real-world data from Korea suggests that compared to sitagliptin use, saxagliptin, linagliptin, and gemigliptin use was associated with a lower risk of cardiovascular events. Further large-scale observational studies evaluating the differences among DPP-4is in terms of cardiovascular benefits or risks are needed.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Baseline characteristics by DPP-4is in a subgroup with available health screening data

Click here to view

Supplementary Table 2

HRs for certain subtypes of modified major adverse cardiovascular events risk among users of different DPP-4is

Click here to view

Supplementary Table 3

HRs for CVD risk among users of different DPP-4is by wash-out period

Click here to view

Supplementary Table 4

HRs for CVD risk among users of different DPP-4is by duration of DPP-4is use

Click here to view

REFERENCES

1. Kim JH, Kim DJ, Jang HC, Choi SH. Epidemiology of micro- and macrovascular complications of type 2 diabetes in Korea. *Diabetes Metab J* 2011;35:571-7.
PUBMED | CROSSREF
2. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2015;38:140-9.
PUBMED | CROSSREF
3. Monami M, Ahrén B, Dicembrini I, Mannucci E. Dipeptidyl peptidase-4 inhibitors and cardiovascular risk: a meta-analysis of randomized clinical trials. *Diabetes Obes Metab* 2013;15:112-20.
PUBMED | CROSSREF

4. Morgan CL, Mukherjee J, Jenkins-Jones S, Holden SE, Currie CJ. Combination therapy with metformin plus sulphonylureas versus metformin plus DPP-4 inhibitors: association with major adverse cardiovascular events and all-cause mortality. *Diabetes Obes Metab* 2014;16:977-83.
PUBMED | CROSSREF
5. Ou HT, Chang KC, Li CY, Wu JS. Comparative cardiovascular risks of dipeptidyl peptidase 4 inhibitors with other second- and third-line antidiabetic drugs in patients with type 2 diabetes. *Br J Clin Pharmacol* 2017;83:1556-70.
PUBMED | CROSSREF
6. Ha KH, Kim B, Choi H, Kim DJ, Kim HC. Cardiovascular events associated with second-line anti-diabetes treatments: analysis of real-world Korean data. *Diabet Med* 2017;34:1235-43.
PUBMED | CROSSREF
7. Deacon CF. Dipeptidyl peptidase-4 inhibitors in the treatment of type 2 diabetes: a comparative review. *Diabetes Obes Metab* 2011;13:7-18.
PUBMED | CROSSREF
8. Green JB, Bethel MA, Armstrong PW, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2015;373:232-42.
PUBMED | CROSSREF
9. Zannad F, Cannon CP, Cushman WC, et al. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial. *Lancet* 2015;385:2067-76.
PUBMED | CROSSREF
10. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* 2013;369:1317-26.
PUBMED | CROSSREF
11. Fu AZ, Johnston SS, Ghannam A, et al. Association between hospitalization for heart failure and dipeptidyl peptidase 4 inhibitors in patients with type 2 diabetes: an observational study. *Diabetes Care* 2016;39:726-34.
PUBMED | CROSSREF
12. Suh S, Seo GH, Jung CH, et al. Increased risk of hospitalization for heart failure with newly prescribed dipeptidyl peptidase-4 inhibitors and pioglitazone using the Korean Health Insurance Claims Database. *Diabetes Metab J* 2015;39:247-52.
PUBMED | CROSSREF
13. Toh S, Hampp C, Reichman ME, et al. Risk for hospitalized heart failure among new users of saxagliptin, sitagliptin, and other antihyperglycemic drugs: a retrospective cohort study. *Ann Intern Med* 2016;164:705-14.
PUBMED | CROSSREF
14. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005;43:1130-9.
PUBMED | CROSSREF
15. Eurich DT, Simpson S, Senthilselvan A, Asche CV, Sandhu-Minhas JK, McAlister FA. Comparative safety and effectiveness of sitagliptin in patients with type 2 diabetes: retrospective population based cohort study. *BMJ* 2013;346:f2267.
PUBMED | CROSSREF
16. Kim JH, Kim SS, Baek HS, et al. Comparison of vildagliptin and pioglitazone in Korean patients with type 2 diabetes inadequately controlled with metformin. *Diabetes Metab J* 2016;40:230-9.
PUBMED | CROSSREF
17. Williams R, de Vries F, Kothny W, et al. Cardiovascular safety of vildagliptin in patients with type 2 diabetes: a European multi-database, non-interventional post-authorization safety study. *Diabetes Obes Metab* 2017;19:1473-8.
PUBMED | CROSSREF
18. Gallwitz B, Rosenstock J, Rauch T, et al. 2-year efficacy and safety of linagliptin compared with glimepiride in patients with type 2 diabetes inadequately controlled on metformin: a randomised, double-blind, non-inferiority trial. *Lancet* 2012;380:475-83.
PUBMED | CROSSREF
19. Kim SH, Yoo JH, Lee WJ, Park CY. Gemigliptin: an update of its clinical use in the management of type 2 diabetes mellitus. *Diabetes Metab J* 2016;40:339-53.
PUBMED | CROSSREF
20. Cobble ME, Frederich R. Saxagliptin for the treatment of type 2 diabetes mellitus: assessing cardiovascular data. *Cardiovasc Diabetol* 2012;11:6.
PUBMED | CROSSREF

21. Engel SS, Golm GT, Shapiro D, Davies MJ, Kaufman KD, Goldstein BJ. Cardiovascular safety of sitagliptin in patients with type 2 diabetes mellitus: a pooled analysis. *Cardiovasc Diabetol* 2013;12:3.
PUBMED | CROSSREF

22. Ferrannini E, DeFronzo RA. Impact of glucose-lowering drugs on cardiovascular disease in type 2 diabetes. *Eur Heart J* 2015;36:2288-96.
PUBMED | CROSSREF

23. Johansen OE, Neubacher D, von Eynatten M, Patel S, Woerle HJ. Cardiovascular safety with linagliptin in patients with type 2 diabetes mellitus: a pre-specified, prospective, and adjudicated meta-analysis of a phase 3 programme. *Cardiovasc Diabetol* 2012;11:3.
PUBMED | CROSSREF

24. Schweizer A, Dejager S, Foley JE, Couturier A, Ligueros-Saylan M, Kothny W. Assessing the cardio-cerebrovascular safety of vildagliptin: meta-analysis of adjudicated events from a large Phase III type 2 diabetes population. *Diabetes Obes Metab* 2010;12:485-94.
PUBMED | CROSSREF

25. Vanderheyden M, Bartunek J, Goethals M, et al. Dipeptidyl-peptidase IV and B-type natriuretic peptide. From bench to bedside. *Clin Chem Lab Med* 2009;47:248-52.
PUBMED | CROSSREF

26. Anagnostis P, Athyros VG, Adamidou F, et al. Glucagon-like peptide-1-based therapies and cardiovascular disease: looking beyond glycaemic control. *Diabetes Obes Metab* 2011;13:302-12.
PUBMED | CROSSREF

27. Saraiva FK, Sposito AC. Cardiovascular effects of glucagon-like peptide 1 (GLP-1) receptor agonists. *Cardiovasc Diabetol* 2014;13:142.
PUBMED | CROSSREF

28. Scirica BM. The safety of dipeptidyl peptidase 4 Inhibitors and the risk for heart failure. *JAMA Cardiol* 2016;1:123-5.
PUBMED | CROSSREF

29. Kimm H, Yun JE, Lee SH, Jang Y, Jee SH. Validity of the diagnosis of acute myocardial infarction in korean national medical health insurance claims data: the korean heart study (1). *Korean Circ J* 2012;42:10-5.
PUBMED | CROSSREF

30. Park JK, Kim KS, Kim CB, et al. The accuracy of ICD codes for cerebrovascular diseases in medical insurance claims. *Korean J Prev Med* 2000;33:76-82.