Association Between Dipeptidyl Peptidase-4 Inhibitors and Diabetic Retinopathy in Korean Patients With Type 2 Diabetes Mellitus: Nationwide Population-Based Cohort Study

Gyu Chul Oh
Seoul National University Hospital
You-Jeong Ki
Seoul National University Hospital
Kyung Woo Park
Seoul National University Hospital
Kyung-Do Han
Soongsil University
Hyo-Soo Kim (hyosoo@snu.ac.kr)
Seoul National University Hospital https://orcid.org/0000-0003-0847-5329

Original investigation

Keywords: diabetes mellitus, dipeptidyl peptidase-4 inhibitors, retinopathy, vascular permeability

Posted Date: August 17th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-666003/v1

Abstract

BACKGROUND

Dipeptidyl peptidase-4 (DPP4) inhibitors are widely used to treat type 2 diabetes mellitus (T2DM). In a previous study, we demonstrated a plausible mechanism how DPP4 inhibitors may cause accumulation of stroma derived factor-1 (SDF1) in ischemic retina, leading to vascular permeability and diabetic retinopathy (DR). We sought to investigate the association of DPP4 inhibitors with DR in patients using the Korean National Health Insurance Service (NHIS) data.

METHODS

This was a retrospective, population-based cohort study using the Korean NHIS database. The Korean NHIS is a government-run, mandatory medical insurance service and keeps records of patient sociodemographic data, inpatient and outpatient medical services and prescriptions. The database consists of records from the entire Korean, totaling 51 million people, regardless of the medical institution from which they received service.

RESULTS

Among the total study population, 26.0% (152,149 of 585,191) received prescriptions of DPP4 inhibitors. The incidence of DR in the DPP4 inhibitor group was 55.03 per 1,000 person-years (PPY), compared to 50.17 PPY in the non-DPP4 group ($P < 0.001$). Patients prescribed with DPP4 inhibitors as second-line therapy had a 9% increased risk of developing DR compared to those on other medications after adjustment for age, gender, hypertension, dyslipidemia, and duration of disease (adjusted HR 1.09, 95% CI 1.07–1.11, $P < 0.001$).

CONCLUSIONS

In Korean T2DM patients that received second line oral hypoglycemic agents, DPP4 inhibitor prescription was associated with a higher risk of newly-developed DR, suggesting that the effect of DPP4 inhibitors on vascular permeability and neovascularization may have clinical implications.

Background

Diabetes mellitus affects many people and has a huge socioeconomic burden worldwide [1]. Treatment for type 2 diabetes mellitus (T2DM) is mainly dependent on oral hypoglycemic agents. Metformin is recommended as first line therapy with the option to add second line agents when glucose control is inadequate [2]. Among the various classes of hypoglycemic agents, the dipeptidyl peptidase-4 (DPP4) inhibitors are very broadly used second-line drugs.

DPP4 is an enzyme that degrades a group of gastrointestinal hormones called incretins. Incretins stimulate postprandial insulin secretion and reduce fasting glucagon production. They are also known to reduce motility of the digestive tract and decrease appetite [3]. DPP4 inhibitors, by blocking the DPP4 enzyme, have beneficial effects on diabetic patients without the side effects of weight gain or hypoglycemia. Since the approval of sitagliptin in 2006, many DPP4 inhibitors have been developed and approved for patients with T2DM. In Korea, there are currently nine types of DPP4 inhibitors on the market and as of 2015, this class of drugs accounts for 40% of the revenue for diabetic medications.

Diabetes-related microvascular complications such as retinopathy, nephropathy and neuropathy, occur frequently and are the major causes of morbidity. In particular, diabetic retinopathy (DR) is the leading cause of acquired blindness among people of occupational age [4]. The first stage of DR is characterized by increased retinal blood flow and decreased retinal vascular response due to high blood glucose [5]. This, in turn, leads to increased vascular permeability and abnormal microvasculature, resulting in retinal ischemia [6]. We recently reported the molecular biologic mechanism, high Jagged1 and low Notch activity in retinal endothelial cells, leading to diabetic retinal vasculopathy [7]. Although landmark studies have shown that strict control of blood glucose prevents the development and progression of retinopathy, it is uncertain whether different drugs have different effects for DR [8, 9]. Up to now, the effects of DPP4 inhibitors have been regarded as mostly neutral or slightly protective if any, on microvascular complications. However, we previously showed using in vitro cell biologic experiments and in vivo murine DR model, that DPP4 inhibitors may block degradation of angiogenic stroma derived factor-1 (SDF-1), a substrate of the DPP4 enzyme, leading to angiogenesis and vascular leakage in the retina [10]. In an era where DPP4 inhibitor use is so ubiquitous, we decided to pursue this issue further with clinical data.

We hypothesized that DPP4 inhibitor use may be associated with an increased risk of the development and progression of DR. Using a nationwide population-based health insurance database, we sought to assess the association between DPP4 inhibitor prescription and DR in Korean T2DM patients.

Methods

Study Design

This study was a retrospective, population-based cohort study using the Korean National Health Insurance Service (NHIS) claims database. As DPP4 inhibitors were first introduced to the Korean market in 2008, cases from 2009 were selected for analysis. Patients prescribed with second line oral hypoglycemic agents for the first time from 2009 to 2014 were included in the retrospective cohort and follow up data were obtained until 2015. During the study period, DPP4 inhibitors were approved for use as second-line therapy, and the NHIS reimbursement policy allowed DPP4 inhibitors to be reimbursed only when used in combination with metformin or sulfonylureas. Additionally, patients who underwent NHIS-provided health check-ups and whose relevant data were available, were selected for further analysis of validation.

NHIS database

The Korean NHIS is a government-run, mandatory medical insurance service and keeps records of patient sociodemographic data, all inpatient and outpatient medical services, surgery, procedures, and prescriptions. Patient diagnoses are classified using the International Classification of Disease, Tenth Revision, Clinical Modification (ICD-10-CM) codes.

The Korean healthcare system is a one payer system where the NHIS serves as the single payer. Therefore, the NHIS database consists of records from the entire Korean population, totaling 51 million people, regardless of the medical institution from which they received medical service. The data includes variables such as age, gender, socioeconomic status, death, diagnostic codes issued for clinic visits and hospitalizations, and prescription medications. On top of this database, we combined additional medical records from state-provided, annual routine health check-ups. The annual routine health check-up data includes variables such as body mass index (BMI), smoking, alcohol consumption, and estimated glomerular filtration values. The NHIS database is open to all researchers upon approval of study protocols by the institution's official review committee.

Study Population

From the NHIS database, patients over 18 years of age with pharmacy and hospital claims data for a continuous period of 12 months or more from January 2009 to 2014 were screened. First, among patients with diagnosis codes related to T2DM, those prescribed with second line oral hypoglycemic agents for the first time during the study period were selected (n = 805,214). Among these patients, those with neoplasms of the pancreas or with two or more drugs added to the initial therapy were excluded. Patients already diagnosed with DR or chronic kidney disease (CKD) were also excluded. Finally, annual health check-up data was obtained for patients who underwent the examination. Although annual health check-ups are provided by the government free of charge, not all patients receive the check-ups. We performed a separate analysis on patients with health check-up data. Detailed description of the study design is shown in Fig. 1.

Variables and Endpoint Definitions

The primary outcome was defined as time to onset (event-free survival) of DR, Secondary outcomes were defined as time to onset of all cause death, myocardial infarction (MI), ischemic stroke, and end stage renal disease (ESRD).

The presence of T2DM was defined as having at least one claim under ICD-10 codes E11-14, and DR was defined as having at least one claim under ICD-10 code of H36.0. MI and ischemic stroke were defined as having at least one claim under relevant ICD-10 codes. Chronic kidney disease was defined as either having at least one claim under ICD codes of N18, N19, or having claims for dialysis treatment. Detailed definitions of study outcomes and comorbidities are described in Supplementary Table 1.

The index date was defined as the prescription date for the first claim for a second line oral hypoglycemic agent during the study period. Observation was terminated at the occurrence of the outcome event. Patients were divided into two groups according to prescription of DPP4 inhibitors.

Statistical Analysis

To compare the risk of an outcome between treatment groups, time to event analysis was performed. We recorded the time from the index date to the relevant event, death, or end of follow-up, whichever came first. Analysis was performed on an intent-to-treat approach.

Event incidence was calculated as the number of events divided by 1,000 person-years. Cox regression analysis was used to compare event rates between groups, with the non-DPP4 inhibitor group as the reference. All adjusted hazard ratios (HRs) given in the study were adjusted with age, gender, hypertension, dyslipidemia, and duration of disease unless otherwise specified. In the case of analysis performed with data from health check-ups, HRs were additionally adjusted with smoking, alcohol consumption, BMI, and estimated glomerular filtration rate. Propensity score matching (PSM) was performed to account for the difference in baseline characteristics. All statistical analysis was performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Secondary analyses

Additional analyses were performed to assess the robustness of our findings. First, in order to adjust for differences in baseline characteristics, PSM was performed with age, gender, hypertension, dyslipidemia, atrial fibrillation, heart failure, history of ischemic heart disease / MI / stroke, and duration of disease. Secondly, in order to account for differences in rate of death between two groups, analysis was performed on patients who survived the whole study period. Lastly, sensitivity analysis was performed on a subset of patients with health check-up data.

Patient and public involvement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Results

Patient Characteristics

According to the NHIS data, the number of T2DM patients in Korea increased from 2,134,278 in 2009 to 2,864,795 in 2014. During the same period, patients with DR rose from 327,140 to 506,682, accounting for 1/6 of the total T2DM population. After the first introduction of DPP4 inhibitors to the Korean market in December 2008, its prescription rate has steadily increased over the years, rising to 46.2% of all oral hypoglycemic agent prescriptions in 2014. The annual trend of oral hypoglycemic agent prescription is shown in Supplementary Fig. 1.

Patients meeting pre-defined criteria were included in the retrospective cohort and grouped into either the DPP4 inhibitor group or the non-DPP4 inhibitor group. Among the 585,191 subjects included in the final

analysis, 152,149 (26.0%) subjects were prescribed with DPP4 inhibitors. As shown in Table 1, the study population showed significant differences between the two groups. The DPP4 inhibitor group was younger, more likely to be male, had lower proportion of patients with prolonged duration of DM, and lower prevalence of heart failure or ischemic stroke than the non-DPP4 inhibitor group. Overall, the baseline profiles of the DPP4 inhibitor group were milder than those of the non-DPP4 inhibitor one.

Table 1
Patient characteristics

	Total population				*Propensity score matched population*		
	Total (n = 585,191)	**DPP4-I (n = 152,149)**	**non-DPP4-I (n = 433,042)**	**P value**	**DPP4-I (n = 152,149)**	**non-DPP4-I (n = 152,149)**	**P value**
Age	58.8 ± 12.4	56.3 ± 12.1	59.7 ± 12.4	< 0.0001	56.3 ± 12.1	56.3 ± 12.1	0.718
Sex (male)	316,617 (54.1)	85,357 (56.1)	231,260 (53.4)	< 0.0001	85,357 (56.1)	85,131 (56.0)	0.409
Duration (> 5 years)	133,694 (22.9)	23,833 (15.7)	109,861 (25.4)	< 0.0001	23,833 (15.7)	23,874 (15.7)	0.838
Follow-up Duration (years)	2.3 ± 1.8	2.2 ± 1.6	2.3 ± 1.8	< 0.001	2.2 ± 1.6	2.3 ± 1.8	< 0.001
Hypertension	345,875 (59.1)	85,584 (56.3)	260,291 (60.1)	< 0.0001	85,584 (56.3)	85,561 (56.2)	0.933
Dyslipidemia	281,277 (48.1)	87,877 (57.8)	193,400 (44.7)	< 0.0001	87,877 (57.8)	87,902 (57.8)	0.927
IHD	86,163 (14.7)	22,416 (14.7)	63,747 (14.7)	0.908	22,416 (14.7)	22,372 (14.7)	0.822
MI	6,298 (1.1)	1,674 (1.1)	4,624 (1.1)	0.291	1,674 (1.1)	1,623 (1.1)	0.372
Atrial fibrillation	8,849 (1.5)	2,373 (1.6)	6,476 (1.5)	0.078	2,373 (1.6)	2,109 (1.4)	< 0.001
Heart failure	3,805 (0.7)	810 (0.5)	2,995 (0.7)	< 0.0001	810 (0.5)	567 (0.4)	< 0.0001
Ischemic stroke	5,244 (0.9)	1,067 (0.7)	4,177 (1.0)	< 0.0001	1,067 (0.7)	941 (0.6)	0.005

DPP4-I dipeptidyl peptidase 4 inhibitors, *IHD* ischemic heart disease, *MI* myocardial infarction.

The study protocol was approved by the Institutional Review Board of Seoul National University Hospital, Seoul, Korea (IRB No. E-1704-130-848), and the National Health Information Data Request Review Committee.

Diabetic Retinopathy

The incidence rate of DR in the DPP4 group was 55.03 per 1,000 person-years (PPY), compared to 50.17 PPY in the non-DPP4 group. Patients prescribed with DPP4 inhibitors had a 9% increase in risk of developing DR compared to those prescribed with other medications, after adjustment for age, gender, hypertension, dyslipidemia, duration of disease, and socioeconomic status (adjusted HR 1.09, 95% CI 1.07–1.11, $P < 0.001$). Kaplan-Meier survival curves showed continuous divergence of the two groups evident from year 1 with slight separation at 7 years of follow-up (log rank $P < 0.001$) (Fig. 2A).

Additional analysis was performed to account for the difference in baseline characteristics between two groups. After PSM using age, gender, hypertension, dyslipidemia, atrial fibrillation, heart failure, history of ischemic heart disease / MI / stroke, and duration of disease, we confirmed that association between DPP4 prescription and DR was consistent with the initial study population (HR 1.09, 95% CI 1.07–1.11, $P < 0.001$). The baseline demographics and results of the outcome analysis in the PSM population are also shown in Tables 1 and 2.

Table 2
Incidence of diabetic retinopathy, overall death, and chronic kidney disease

	Total subjects			*Propensity score matched subjects*		
	DPP4-I (n = 152,149)	**non-DPP4-I (n = 433,042)**	**P value**	**DPP4-I (n = 152,149)**	**non-DPP4-I (n = 152,149)**	**P value**
Diabetic retinopathy						
-Number of patients	18,117	49,990		18,117	17,246	
-Incidence rate (PPY)	55.03	50.17		55.03	49.98	
-Crude HR (95% CI)	1.09 (1.07, 1.11)	-	< 0.001	1.09 (1.07, 1.11)	-	< 0.001
-Adjusted HR* (95% CI)	1.09 (1.07, 1.11)	-	< 0.001			
Death						
-Number of patients	3,968	30,065		3,968	7,455	
-Incidence rate (PPY)	11.00	27.63		11.00	19.81	
-Crude HR (95% CI)	0.39 (0.38, 0.40)	-	< 0.001	0.54 (0.52, 0.56)	-	< 0.001
-Adjusted HR* (95% CI)	0.50 (0.48, 0.52)	-	< 0.001			
Myocardial infarction						
-Number of patients	666	3,755		666	1,186	
-Incidence rate (PPY)	1.34	1.94		1.34	1.74	
-Crude HR (95% CI)	0.70 (0.65, 0.76)	-	< 0.001	0.77 (0.70, 0.85)	-	< 0.001

DPP4-I dipeptidyl peptidase 4 inhibitors, *ESRD* End Stage Renal Disease, *HR* hazard ratio, *PPY* per 1,000 person-years.

*Adjusted for age, sex, hypertension, dyslipidemia, duration of disease, and socioeconomic status.

	Total subjects			*Propensity score matched subjects*		
-Adjusted HR* (95% CI)	0.77 (0.71, 0.83)	-	< 0.001			
Ischemic stroke						
-Number of patients	1,542	10,194		1,542	2,740	
-Incidence rate (PPY)	3.11	5.31		3.11	4.04	
-Crude HR (95% CI)	0.58 (0.55, 0.61)	-	< 0.001	0.77 (0.72, 0.82)	-	< 0.001
-Adjusted HR* (95% CI)	0.70 (0.66, 0.74)	-	< 0.001			
ESRD						
-Number of patients	272	1,053		272	280	
-Incidence rate (PPY)	0.75	0.97		0.75	0.75	
-Crude HR (95% CI)	0.79 (0.70, 0.91)	-	< 0.001	1.03 (0.87, 1.22)	-	0.726
-Adjusted HR* (95% CI)	0.97 (0.85, 1.11)	-	0.660			

DPP4-I dipeptidyl peptidase 4 inhibitors, *ESRD* End Stage Renal Disease, *HR* hazard ratio, *PPY* per 1,000 person-years.

*Adjusted for age, sex, hypertension, dyslipidemia, duration of disease, and socioeconomic status.

Overall survival and cardiovascular outcomes

Interestingly, the incidence rates of the other clinical outcomes were lower in the DPP4 inhibitor group than in the non-DPP4 inhibitor group, for example, all-cause death (11.00 vs. 27.63 PPY), MI (1.34 vs. 1.94 PPY), ischemic stroke (3.11 vs. 5.31 PPY), and ESRD (0.75 vs. 0.97 PPY). In the multi-variable adjusted analysis, the DPP4 inhibitor group was associated with a significantly lower risk for death (adjusted HR 0.50, 95% CI 0.48–0.52, $P < 0.001$), MI (adjusted HR 0.77, 95% CI 0.71–0.83, $P < 0.001$), and ischemic stroke (adjusted HR 0.70, 95% CI 0.66–0.74, $P < 0.001$) (Fig. 2B-D), while reduction in risk for ESRD was not significant (adjusted HR 0.97, 95% CI 0.85–1.11, $P = 0.660$) (Table 2). PSM analysis showed similar trends with the multi-variable adjusted analysis.

Subgroup analysis

According to explorative subgroup analysis, the trend of association between DPP4 inhibitor use and DR development was consistent across age and sex subpopulations. Like the results from whole population, DPP4 inhibitor use was associated with the lower rates of death, MI, or ischemic stroke consistently in all the subgroups (Supplementary Fig. 2).

Sensitivity analysis

To account for the increased number of deaths in the non-DPP4 inhibitor group, separate analysis was performed on patients who survived the whole study period. Among 269,962 patients who are alive, the risk of developing diabetic retinopathy showed same results as the primary analysis of the whole population (HR 1.11, 95% CI 1.08–1.13, $P < 0.001$).

Among 585,191 patients included in the study, medical records of annual health check-up data were available for analysis in 193,522 (33.1%) patients (Supplementary Table 2). Additional parameters were used to adjust for differences in baseline characteristics, such as, age, sex, hypertension, dyslipidemia, duration of disease, smoking, alcohol consumption, BMI, socioeconomic status, and estimated glomerular filtration rate. Primary outcome analysis of this sub-population having more detailed health data showed same results as the initial whole population, showing an 8% increase in risk of DR in the DPP4 inhibitor group (adjusted HR 1.08, 95% CI 1.05–1.11, $P < 0.001$). The trend for death was also consistent with the initial whole population (adjusted HR 0.58, 95% CI 0.54–0.62, $P < 0.001$), as well as for MI and ischemic stroke (Supplementary Table 3).

Discussion

In this nationwide, retrospective cohort study utilizing the Korean NHIS database, we observed a positive association between use of DPP4 inhibitors and development of DR in T2DM patients. To our knowledge, this is the first study to assess the development of DR according to use of hypoglycemic agents and to find the potential hazard of DPP4 inhibitors increasing DR in a robust, real-world population. This nation-wide population based clinical data are consistent with the biologic hypothesis that DPP4 inhibitors may accumulate SDF-1 and induce angiogenesis and retinal vasculopathy [10]. Previous studies have reported several beneficial effects of DPP4 inhibitors, which have not been confirmed by several large clinical trials suggesting non-inferiority to non-DPP4 inhibitor medications. Neither basic nor clinical studies have paid attention to or evaluated the impact of DPP4 inhibitors on DR. Despite the innate limitations that arise from a retrospective analysis, we were able to obtain some novel findings that have not been previously addressed in any other trial. Although hypothesis generating at best, we believe that our findings warrant further analysis and investigation.

DPP4 inhibitors have only been on the market for around 10 years, but their use as a second line drug in T2DM patients has exploded due to its efficacy and lack of side effects. We however, previously published results of molecular and cellular biologic experiments with validation in animal study, where we raised concerns about DPP4 inhibitors and suggested that use of DPP4 inhibitors mechanistically may be related to increased permeability in mouse retinal arteries [10]. In order to investigate this issue further,

we utilized medical claims data from the Korean NHIS database to study the association between DPP4 inhibitors and development of DR.

In the present study, DPP4 inhibitor prescription was associated with a 9% increase in risk of developing DR in Korean T2DM patients. Oral hypoglycemic agents act in different pathways to lower blood glucose, and although all agents have the same goal, side effects vary among drug types. The increased risk of developing DR may be explained due to effects that the drug has on vascular permeability and angiogenesis as we showed in our previous study [10]. DPP4 inhibitors increase SDF-1 and Src-induced tyrosine phosphorylation of VE-cadherin, which in turn leads to increased vascular permeability and neovascularization [10]. Although previous studies have reported that use of DPP4 inhibitors are protective against development of microvascular complications in diabetic patients, they have failed to show a specific mechanism other than glucose lowering to support the results. We have previously reported that DPP4 inhibitors increase vascular permeability in mice retinal arteries, which is the first step in the development of DR. Although the negative effects of DPP4 inhibitors might be partially neutralized by improved glucose lowering capabilities, our results show that the use of DPP4 inhibitors could be associated with poor long term ocular outcomes.

The benefit of tight glucose control on macrovascular or cardiovascular complications have been investigated in several previous trials [11, 12]. In terms of microvascular complications, landmark prospective trials like the UK Prospective Diabetes Study (UKPDS) and the Diabetes Control and Complications Trial (DCT) have reported that every 1% reduction in HbA1c correlated to 37% and 54% reduction in risk of microvascular complications, respectively [13, 14]. But the effect of DPP4 inhibitors on microvascular complications have not been well evaluated. Two animal studies suggested positive effects of DPP4 inhibitors on diabetic nephropathy [15, 16]. One small clinical study suggested that saxagliptin treatment just for 6 weeks may change retinal arteriolar structure or retinal capillary flow [17].

Although there have been no reports of definite association between DPP4 inhibitors and ocular complications, the TECOS trial has reported a significant higher incidence of diabetic eye disease (RR 1.25, 95% CI 1.04–1.50) compared with placebo [18]. Furthermore, use of glucagon-like peptide-1 (GLP-1) analogues, also an incretin-based therapy, were associated with increased incidence of DR in SUSTAIN-6 and LEADER trials [19, 20]. Although the mechanism of action of DPP4 inhibitors are different from that of GLP-1 analogues, when the results of the current analysis are taken together with the results of our preclinical study, we cannot ignore the possibility of DPP4 inhibitors to increase the risk of development of DR. There is no doubt in the fact that ‘the glucose-lowering effect’ of DPP4 inhibitors will have beneficial effects in preventing DR. However, it may have ‘the adverse extra-glucose effects’ that warrant further clinical investigation. If similar results are reproduced in other diabetic cohorts, physicians may need to be more vigilant in monitoring DR progression in patients receiving DPP4 inhibitors.

However, there have been no definite studies linking either glucose control and DR or certain hypoglycemic agent and DR in a large and long-term population-based cohort. Our cohort study followed

up over 500,000 patients for a mean period of 2.3 years, and could be a reference for the future treatment strategies of T2DM and its complications especially DR.

Our study population generally represents patients in the early stages DM, with over 75% having a disease duration less than 5 years. Patients with previous history suggesting DR were excluded from the study. According to our analysis, although DPP4 inhibitors were associated with increased risk of DR, it was also associated with reduced risk of death and cardiovascular disease such as MI and ischemic stroke. In our analysis, patients on DPP4 inhibitors were associated with a reduced risk of cardiovascular (CV) outcomes, which is in discordance with previous large-scale trials, where DPP4 inhibitors have failed to show any CV benefit [18, 21, 22]. Few studies have shown good results on the CV risk of DPP4 inhibitors. Prior to the publication of the major randomized controlled trials dealing with DPP4 inhibitors, there was a meta-analysis showing the reduction of CV risk by DPP4 inhibitors [23]. The post-hoc analysis of randomized controlled EXAMINE trial with alogliptin showed that alogliptin could reduce the risk of CV death in a group with the normal renal function, but not in patient with impaired renal function [24]. In the present study, as opposed to previous studies of DPP4 inhibitors [18, 21, 22] but similar to meta-analysis and post-hoc analysis [23, 24], the reduced risk of DPP4 inhibitors may have been driven by better baseline characteristics in DPP4 inhibitor group than in the non-DPP4 inhibitor group. Despite having better baseline characteristics and clinical outcomes of cardiovascular events in the DPP4 inhibitor group, the high prevalence of retinopathy in the DPP4 inhibitor group suggests an association between DPP4 inhibitors and retinopathy. Further prospective studies related to retinopathy are needed.

Limitations

There are several limitations to this study. As the study was retrospective in its design, utilizing data from insurance claims, it lacks results such as HbA1c and fasting glucose levels. Thus, we were unable to assess the disease state of each patient. Second, there was also no data on compliance or the effectiveness of the prescribed medications for the patients. Third, the outcome events were captured through pre-defined criteria from the claims data. The failure to screen patients for DR or failure to input correct diagnostic codes might have led to underestimation of events, which are innate to these types of analyses. The rate of ischemic stroke was generally high in our study population, which might be due to input of unconfirmed diagnostic codes. Fourth, although we tried our best to adjust for significant baseline differences, the two groups were mostly heterogeneous. Finally, this study was not designed to assess the causal relationship. At best, our findings are positive association between prescription of DPP4 inhibitors and DR, and thus the results should be interpreted with caution. Long term data from randomized and prospective trials are needed to better understand the causal relationship between DPP4 inhibitors and DR.

Conclusions

DPP4 inhibitor prescription as second-line therapy for T2DM patients may be associated with an increased risk of developing DR. Further prospective studies are required to confirm our findings.

Abbreviations

BMI
body mass index; CKD:chronic kidney disease; CV:cardiovascular; DCT:Diabetes Control and Complications Trial; DPP4:dipeptidyl peptidase-4; DR:diabetic retinopathy; ESRD:end stage renal disease; GLP-1:glucagon-like peptide-1; HRs:hazard ratios; MI:myocardial infarction; NHIS:national health insurance service; PPY:per 1,000 person-years; PSM:propensity score matching; SDF-1:stroma derived factor-1; T2DM:type 2 diabetes mellitus; UKPDS:UK Prospective Diabetes Study.

Declarations

Availability of data and materials: All data relevant to the study are included in the article or uploaded as additional file. No more additional data are available.

Acknowledgements: Not applicable.

Authors' contributions: GCO and KWP designed the trial, planned the analyses, and wrote the manuscript with assistance from HSK, and YJK. KDH carried out the statistical analyses. All authors participated in the review and critical revisions of the final manuscript. HSK is the guarantor of the manuscript.

Funding: This study was supported by a grant of the Korea Health Technology R&D Project "Strategic Center of Cell and Bio Therapy for Heart, Diabetes & Cancer" through the Korea Health Industry Development Institute (HI17C2085) as well as grant of ABC trial for retinal artery (SNUH-620102240).

Ethical approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

Competing interests: Not applicable.

References

1. American Diabetes Association. Economic Costs of Diabetes in the U.S. in 2017. Diabetes Care. 2018;41(5):917–28.
2. American Diabetes Association. Standards of Medical Care in Diabetes-2017 Abridged for Primary Care Providers. Clin Diabetes. 2017;35(1):5–26.
3. Sneha P, Doss CG. Gliptins in managing diabetes - Reviewing computational strategy. Life Sci. 2016;166:108–20.
4. Yamagishi S, Imaizumi T. Diabetic vascular complications: pathophysiology, biochemical basis and potential therapeutic strategy. Curr Pharm Des. 2005;11(18):2279–99.
5. Kohner EM. The effect of diabetic control on diabetic retinopathy. Eye (Lond). 1993;7(Pt 2):309–11.
6. Zhang X, Wang N, Schachat AP, Bao S, Gillies MC. Glucocorticoids: structure, signaling and molecular mechanisms in the treatment of diabetic retinopathy and diabetic macular edema. Curr Mol Med.

2014;14(3):376–84.

7. Yoon CH, Choi YE, Cha YR, Koh SJ, Choi JI, Kim TW, Woo SJ, Park YB, Chae IH, Kim HS. Diabetes-Induced Jagged1 Overexpression in Endothelial Cells Causes Retinal Capillary Regression in a Murine Model of Diabetes Mellitus: Insights Into Diabetic Retinopathy. Circulation. 2016;134(3):233–47.
8. Nathan DM, Genuth S, Lachin J, Cleary P, Crofford O, Davis M, Rand L, Siebert C. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329(14):977–86.
9. Action to Control Cardiovascular Risk in Diabetes Follow-On (ACCORDION) Eye Study Group and the Action to Control Cardiovascular Risk in Diabetes Follow-On (ACCORDION) Study Group. Persistent Effects of Intensive Glycemic Control on Retinopathy in Type 2 Diabetes in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Follow-On Study. Diabetes Care. 2016;39(7):1089–100.
10. Lee CS, Kim YG, Cho HJ, Park J, Jeong H, Lee SE, Lee SP, Kang HJ, Kim HS. Dipeptidyl Peptidase-4 Inhibitor Increases Vascular Leakage in Retina through VE-cadherin Phosphorylation. Sci Rep. 2016;6:29393.
11. ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008;358(24):2560–72.
12. ACCORD Study Group. Long-term effects of intensive glucose lowering on cardiovascular outcomes. N Engl J Med. 2011;364(9):818–28.
13. Stratton IM, Adler AI, Neil HAW, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000;321(7258):405–12.
14. de Boer IH, Rue TC, Cleary PA, Lachin JM, Molitch ME, Steffes MW, Sun W, Zinman B, Brunzell JD, Control D, et al. Long-term renal outcomes of patients with type 1 diabetes mellitus and microalbuminuria: an analysis of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications cohort. Arch Intern Med. 2011;171(5):412–20.
15. Liu WJ, Xie SH, Liu YN, Kim W, Jin HY, Park SK, Shao YM, Park TS. Dipeptidyl peptidase IV inhibitor attenuates kidney injury in streptozotocin-induced diabetic rats. J Pharmacol Exp Ther. 2012;340(2):248–55.
16. Mega C, Teixeira de Lemos E, Vala H, Fernandes R, Oliveira J, Mascarenhas-Melo F, Teixeira F, Reis F. Diabetic nephropathy amelioration by a low-dose sitagliptin in an animal model of type 2 diabetes (Zucker diabetic fatty rat). Exp Diabetes Res. 2011;2011:162092.
17. Ott C, Raff U, Schmidt S, Kistner I, Friedrich S, Bramlage P, Harazny JM, Schmieder RE. Effects of saxagliptin on early microvascular changes in patients with type 2 diabetes. Cardiovasc Diabetol. 2014;13:19.
18. Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, Josse R, Kaufman KD, Koglin J, Korn S, et al. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2015;373(3):232–42.

19. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, Lingvay I, Rosenstock J, Seufert J, Warren ML, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2016;375(19):1834–44.
20. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2016;375(4):311–22.
21. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, Ohman P, Frederich R, Wiviott SD, Hoffman EB, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013;369(14):1317–26.
22. White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, Perez AT, Fleck PR, Mehta CR, Kupfer S, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med. 2013;369(14):1327–35.
23. 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(2):112–20.
24. Ferreira JP, Mehta C, Sharma A, Nissen SE, Rossignol P, Zannad F. Alogliptin after acute coronary syndrome in patients with type 2 diabetes: a renal function stratified analysis of the EXAMINE trial. BMC Med. 2020;18(1):165.

Figures

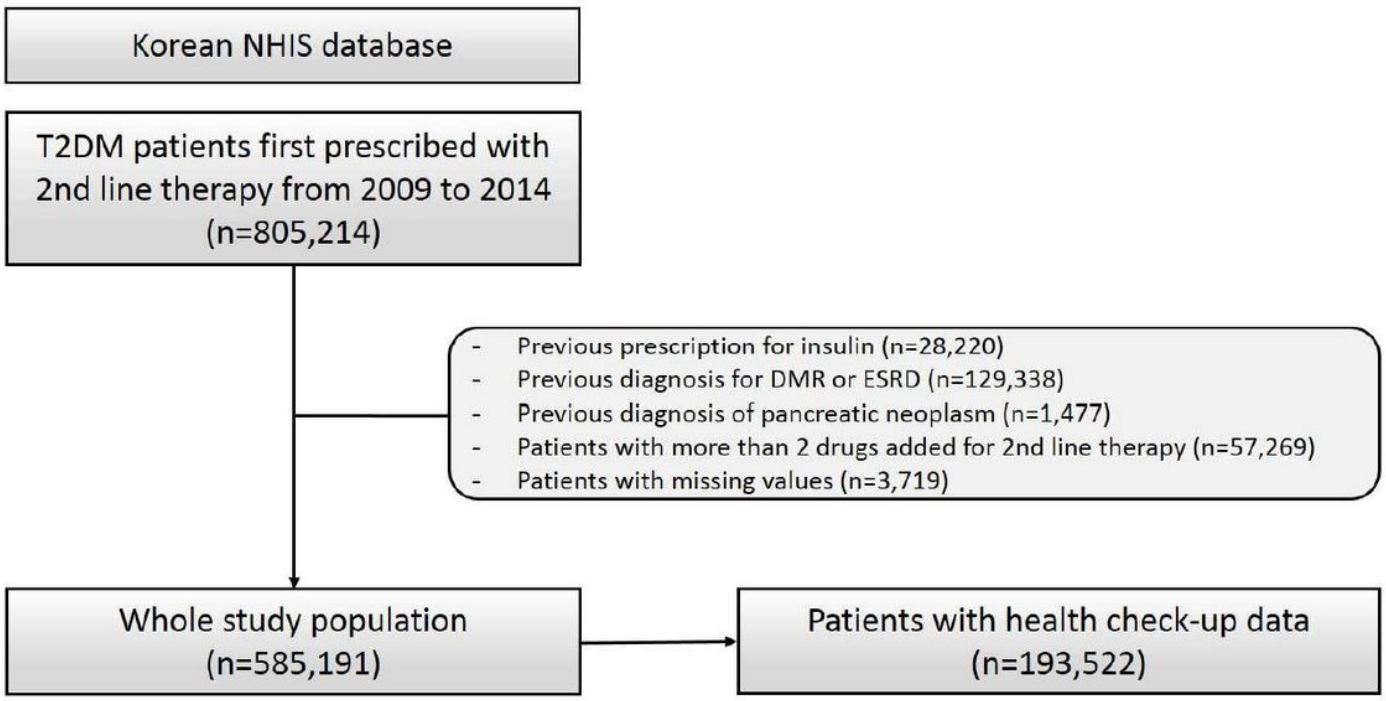

Figure 1

Study design DMR diabetic retinopathy, ESRD end stage renal disease, NHIS National Health Insurance Service, T2DM type 2 diabetes mellitus.

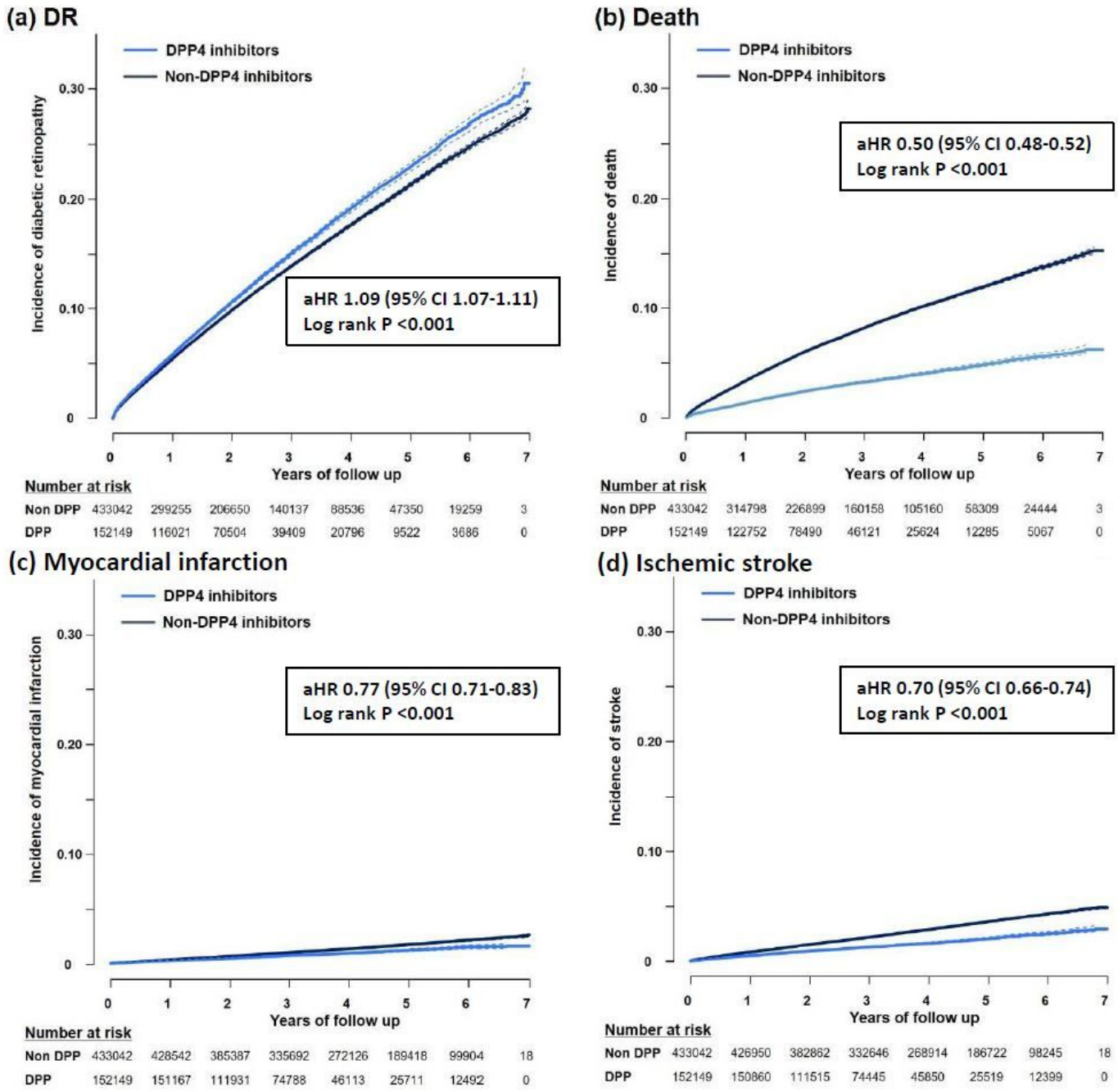

Figure 2

Kaplan Meier curve for outcomes according to DPP4 inhibitor use versus non-use aHR adjusted hazard ratio, CI confidence interval, DPP4 dipeptidyl peptidase 4, DR diabetic retinopathy.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CVdiabetologyDPP4Online20210625ver3.3.docx