Dipeptidyl Peptidase-4 Inhibitors versus Other Antidiabetic Drugs Added to Metformin Monotherapy in Diabetic Retinopathy Progression: A Real World-Based Cohort Study

Yoo-Ri Chung[1], Kyoung Hwa Ha[2,3], Hyeon Chang Kim[4], Sang Jun Park[5], Kihwang Lee[1], Dae Jung Kim[2,3]

Departments of [1]Ophthalmology, [2]Endocrinology and Metabolism, [3]Cardiovascular and Metabolic Disease Etiology Research Center, Ajou University School of Medicine, Suwon,
[4]Department of Preventive Medicine, Yonsei University College of Medicine, Seoul,
[5]Department of Ophthalmology, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea

Background: To investigate the effects of dipeptidyl peptidase-4 inhibitor (DPP4i) as add-on medications to metformin on progression of diabetic retinopathy (DR) in patients with type 2 diabetes mellitus, compared with sulfonylurea (SU) or thiazolidinedione (TZD).

Methods: We identified 4,447 patients with DPP4i, 6,136 with SU, and 617 with TZD in addition to metformin therapy from the database of Korean National Health Insurance Service between January 2013 and December 2015. Cox proportional hazards regression models were used to calculate hazard ratios (HRs) for DR progression. The progression of DR was defined by the procedure code of panretinal photocoagulation, intravitreal injection or vitrectomy; or the addition of diagnostic code of vitreous hemorrhage, retinal detachment, or neovascular glaucoma.

Results: The age and sex-adjusted HR of DR progression was 0.74 for DPP4i add-on group compared with SU add-on group (95% confidence interval [CI], 0.62 to 0.89). This lower risk of DR progression remained significant after additional adjustments for comorbidities, duration of metformin therapy, intravitreal injections and calendar index year (HR, 0.80; 95% CI, 0.66 to 0.97).

Conclusion: This population-based cohort study showed that the use of DPP4i as add-on therapy to metformin did not increase the risk of DR progression compared to SU.

Keywords: Diabetes mellitus, type 2; Diabetic retinopathy; Dipeptidyl-peptidase IV inhibitors

INTRODUCTION

Diabetic retinopathy (DR) is the most frequent microvascular complication of diabetes, leading to severe visual impairment in working-age population [1]. Retinal neovascularization and its accompanying complications such as vitreous hemorrhage and neovascular glaucoma occurring in proliferative stage, as well as diabetic edema, contribute to major sources of severe visual loss in DR [1,2]. These late-stage complications require treatments as laser photocoagulation or intravitreal injections

Corresponding authors: Kihwang Lee https://orcid.org/0000-0003-0478-8758
Department of Ophthalmology, Ajou University School of Medicine, 164 World cup-ro, Yeongtong-gu, Suwon 16499, Korea
E-mail: kie114@ajou.ac.kr

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

of anti-vascular endothelial growth factor agents or corticosteroids, which need repeated treatments and result in high socioeconomic burden [3-5].

Metformin is commonly used antidiabetic drug as first-line therapy in United States as well as in Korea [6-8]. Sulfonylurea (SU) still remains the most commonly prescribed second-line agent, while the use of dipeptidyl peptidase-4 inhibitor (DPP4i) increased significantly over the past decade [6-8]. DPP4i have introduced at the end of 2008 in Korea and approved by the Ministry of Food and Drug Safety in 2012 [9], and their prescription has been increased to be 4-fold in 2013 (38.4% of total antidiabetic prescription) compared to 2009 [6]. The antidiabetic effect of DPP4i is based on the glucose-lowering activities of the gastrointestinal hormone, glucagon-like peptide-1 [10]. DPP4i seems to be protective in cardiovascular events as well as in nephropathy through previous studies [10-13], while few investigations have been performed on retinopathy.

We previously investigated the effect of DPP4i to the progression of DR as a pilot study, showing that DPP4i had protective effect on DR progression independently from glucose-lowering effect [14]. However, there are controversies concerning the effect of DPP4i in DR [15-17], which highlight further investigation for safety issue associated with DR and DPP4i. Accordingly, we investigated the risk of DR progression associated with DPP4i use based on real-world population-cohort study.

METHODS

Study design and participants
The study protocol was reviewed and approved by the Institutional Review Board of Severance Hospital at Yonsei University College of Medicine (IRB No. 4-2016-1005) and informed consent was waived because of the anonymous nature of the data. Data of approximately 50 million of Korean patients covered by the mandatory social National Health Insurance Service (NHIS) was investigated. The NHIS involves claim database including demographic information, diagnoses, prescriptions, and procedures. Diagnoses are coded using the International Classification of Diseases, 10th revision (ICD-10). The NHIS also requires all insured employees and self-employed individuals aged ≥40 years as well as their family dependents for general medical examination regularly every 2 years. This health screening data include body size, blood pressure, blood chemistry data including lipid profile, health behaviors, and

personal and family histories of diseases. We used the NHIS database for primary analysis, and secondary analysis implied the health screening data of NHIS.

This study used NHIS data (NHIS-2017-1-054) made by NHIS of Korea. We first extracted patients with type 2 diabetes mellitus (E11 to E14, ICD-10 codes) who had received metformin monotherapy for at least 90 days between January 2009 and December 2012. The second line antidiabetic medications implied DPP4i, SU, or thiazolidinedione (TZD), and those initiated second line antidiabetic therapy from January 2013 to December 2015 were included. Patients treated with above mentioned medications for more than 90 consecutive days were included, while those with insulin treatment were excluded. Further inclusion and exclusion criteria are summarized in Fig. 1.

Outcomes and covariates
The presence of DR was determined on the diagnostic code of DR (H36.0, ICD-10 code). Among the patients already diagnosed with DR, the progression of DR was defined by (1) the procedure code of panretinal photocoagulation (S5160), intravitreal injection (S5070) or vitrectomy (S5160 and S5121-22); or (2) the addition of diagnostic code of vitreous hemorrhage (H43.1 and H45.0, ICD-10 codes), retinal detachment (H33.0, H33.4, and H33.5, ICD-10 codes), or neovascular glaucoma (H40.5 and H40.88, ICD-10 codes). The definition of DR progression was based on the protocol of the Diabetic Retinopathy Clinical Research Network [18].

Following covariates were subjected to serial statistical adjustments to minimize confounding effects: age, sex, duration of metformin therapy, hypertension, dyslipidemia, atrial fibrillation, chronic kidney disease, microvascular complications of diabetes (neuropathy, or nephropathy), the Charlson comorbidity score, intravitreal injections, and calendar index year. The Charlson comorbidity score is a weighted index that implies the number and the seriousness of comorbid disease, used to predict survival in patients with multiple comorbidities [19]. The calendar index year was used to adjust selection bias associated with calendar time for cohort studies [20].

Statistical analysis
All analysis were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA). Baseline characteristics were compared among DPP4i users, SU users, and TZD users as second line medication. Cox proportional hazards regres-
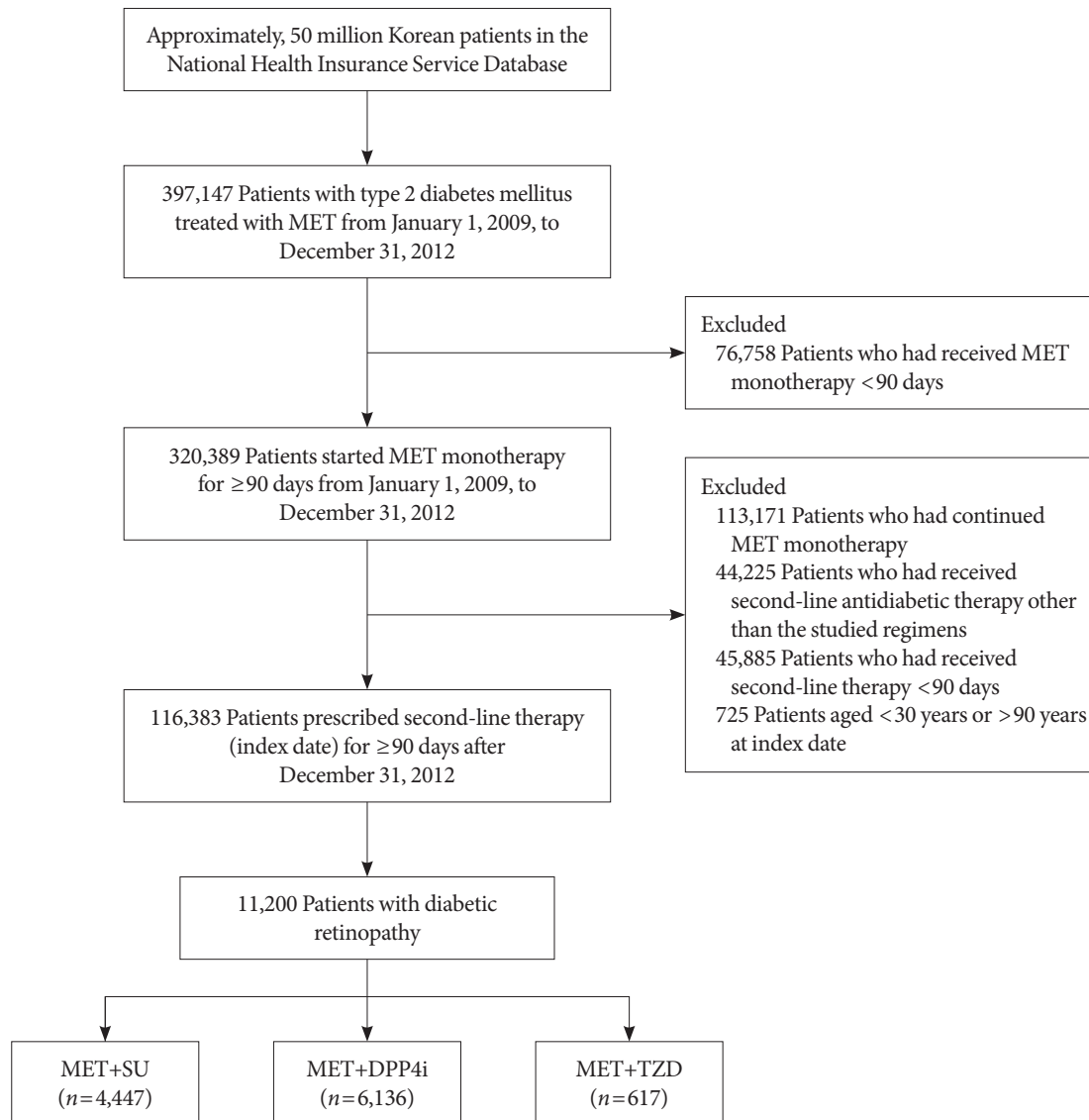
Approximately, 50 million Korean patients in the
National Health Insurance Service Database

↓

397,147 Patients with type 2 diabetes mellitus
treated with MET from January 1, 2009, to
December 31, 2012

→ Excluded
76,758 Patients who had received MET
monotherapy <90 days

↓

320,389 Patients started MET monotherapy
for ≥90 days from January 1, 2009, to
December 31, 2012

→ Excluded
113,171 Patients who had continued
MET monotherapy
44,225 Patients who had received
second-line antidiabetic therapy other
than the studied regimens
45,885 Patients who had received
second-line therapy <90 days
725 Patients aged <30 years or >90 years
at index date

↓

116,383 Patients prescribed second-line therapy
(index date) for ≥90 days after
December 31, 2012

↓

11,200 Patients with diabetic
retinopathy

↓

| MET+SU | MET+DPP4i | MET+TZD |
| (n=4,447) | (n=6,136) | (n=617) |

Fig. 1. Flow chart of the study design. MET, metformin; SU, sulfonylurea; DPP4i, dipeptidyl peptidase-4 inhibitor; TZD, thiazoli-dinedione.

sion models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for DR progression. Potential confounders were sequentially adjusted in two statistical models as follows: model 1, age and sex; model 2, age, sex, duration of metformin therapy, the Charlson comorbidity score, intravitreal injections, calendar index year, and comorbidities (hypertension, dyslipidemia, atrial fibrillation, chronic kidney disease, and microvascular complications of diabetes).

For the analysis of the subgroup with health screening data, model 2 was adjusted for age, sex, duration of metformin therapy, body mass index, waist circumference, systolic blood pres-

sure, total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, triglycerides, fasting glucose, serum creatinine level, smoking status, family history of stroke and heart disease, the Charlson comorbidity score, intravitreal injections, and calendar index year.

RESULTS

Among patients with DR who used second line drug along with metformin, those using DPP4i finally implied 4,447 patients, those with SU were 6,136 patients, and those with TZD

Table 1. Baseline characteristics by type of second-line antidiabetic medication

Variable	MET+SU (n=4,447)	MET+DPP4i (n=6,136)	MET+TZD (n=617)	P value
Age, yr	61.1±10.6	58.1±10.5	58.1±10.5	<0.001
Men, sex	2,064 (46.4)	2,927 (47.7)	323 (52.4)	0.018
Duration of MET monotherapy, mo	10.1±3.5	10.3±3.6	10.2±3.6	0.002
Duration of second line therapy, mo	20.3±17.2	19.7±15.7	18.6±16.5	<0.001
Comorbidities				
Hypertension	3,166 (71.2)	4,124 (67.2)	410 (66.5)	<0.001
Dyslipidemia	3,155 (71.0)	5,029 (82.0)	482 (78.1)	<0.001
Atrial fibrillation	67 (1.5)	108 (1.8)	10 (1.6)	0.599
Chronic kidney disease	59 (1.3)	65 (1.1)	6 (1.0)	0.405
Diabetic neuropathy	652 (14.7)	877 (14.3)	69 (11.2)	0.068
Diabetic nephropathy	328 (7.4)	662 (10.8)	72 (11.7)	<0.001
Charlson score, unit	3.3±1.8	3.2±1.7	3.2±1.7	0.072
Intravitreal injection	46 (1.0)	60 (1.0)	3 (0.5)	0.429
Inclusion year				<0.001
2009	2,120 (47.7)	3,079 (50.2)	355 (57.5)	
2010	1,113 (25.0)	1,547 (25.2)	128 (20.8)	
2011	685 (15.4)	899 (14.7)	84 (13.6)	
2012	529 (11.9)	611 (10.0)	50 (8.1)	

Values are presented as mean±standard deviation or number (%).
MET, metformin; SU, sulfonylurea; DPP4i, dipeptidyl peptidase-4 inhibitor; TZD, thiazolidinedione.

Table 2. Hazard ratios for aggravation of diabetic retinopathy by type of second-line antidiabetic medication

Drugs	PY	No. of cases	Event rate, /100,000 PY	Adjusted 1[a]		Adjusted 2[b]	
				HR (95% CI)	P value	HR (95% CI)	P value
MET+SU	7,087	3,271	46,154	1.00		1.00	
MET+DPP4i	7,835	4,217	53,823	0.74 (0.62–0.89)	0.001	0.80 (0.66–0.97)	0.024
MET+TZD	948	399	42,089	0.45 (0.27–0.76)	0.003	0.50 (0.29–0.84)	0.009

PY, person-years; HR, hazard ratio; CI, confidence interval; MET, metformin; SU, sulfonylurea; DPP4i, dipeptidyl peptidase-4 inhibitor; TZD, thiazolidinedione.
[a]Adjusted for sex and age, [b]Adjusted for sex, age, duration of metformin therapy, hypertension, dyslipidemia, atrial fibrillation, chronic kidney disease, microvascular complications of diabetes (neuropathy, or nephropathy), the Charlson comorbidity score, intravitreal injections, and calendar index year.

were 617 patients (Fig. 1). The mean age of the study population was 59.3±10.6 years, and 47.4% were male. Baseline characteristics of these patients are presented in Table 1.

The age and sex-adjusted HR of DR progression was 0.74 (95% CI, 0.62 to 0.89; P=0.001) for DPP4i add-on group compared with SU add-on group (Table 2). This lower risk of DR progression remained significant after additional adjustments for comorbidities, duration of metformin therapy, intravitreal injections and calendar index year (HR, 0.80; 95% CI, 0.66 to

0.97; P=0.024).

To adjust other confounding risk factors, we performed a subgroup analysis with additional adjustment for variables investigated at the health screening data of NHIS including fasting glucose level. Baseline characteristics of this subgroup are summarized in Supplementary Table 1. DPP4i add-on therapy was still associated with lower risk of DR progression although not statistically significant (HR, 0.89; 95% CI, 0.64 to 1.24; P= 0.493) (Table 3).

Table 3. Hazard ratios for aggravation of diabetic retinopathy by type of second-line antidiabetic medication in a subgroup with available health screening data

Drugs	PY	No. of cases	Event rate, /100,000 PY	Adjusted 1[a]		Adjusted 2[b]	
				HR (95% CI)	P value	HR (95% CI)	P value
MET+SU	2,436	1,106	45,402	1.00		1.00	
MET+DPP4i	3,065	1,630	53,181	0.89 (0.64–1.24)	0.493	0.92 (0.64–1.32)	0.646
MET+TZD	315	146	46,349	0.36 (0.11–1.13)	0.079	0.38 (0.12–1.22)	0.103

PY, person-years; HR, hazard ratio; CI, confidence interval; MET, metformin; SU, sulfonylurea; DPP4i, dipeptidyl peptidase-4 inhibitor; TZD, thiazolidinedione.

[a]Adjusted for sex and age, [b]Adjusted for sex, age, duration of metformin therapy, body mass index, waist circumference, systolic blood pressure, total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, triglycerides, fasting glucose, serum creatinine level, smoking status, and family history of stroke and heart disease, the Charlson comorbidity score, intravitreal injections, and calendar index year.

DISCUSSION

In this study, less patients with DPP4i revealed DR progression than those with SU as add-on therapy. We previously reported a retrospective pilot study showing the protective effect of DPP4i on DR progression based on Early Treatment Diabetic Retinopathy Study (ETDRS) severity scale, which was independent of glycemic control [14,21]. This study showed similar protective tendency, while the determination of DR progression was based on procedures required to treat complications or diagnoses associated with proliferative stage [18], not by the ETDRS severity scale. As the codes for procedures are mandatorily submitted in NHIS, less requirement of procedure codes with DPP4i use might reflect benefits for patients by less costs and saved time for treatment.

However, this protective effect of DPP4i was not evident in the subgroup analysis performed with those with available health screening data. The lower HR of DR progression with DPP4i was not statistically significant after adjusting variables including fasting glucose levels. It should be noted that the fasting glucose level was slightly higher in SU add-on group in Supplementary Table 1. Based on these data, there is a possibility that the benefit using DPP4i over SU in DR progression as shown in Table 1 might be due to better glycemic control since the glycemic control is important in DR progression [22]. A recent cohort study revealed that DPP4i did not increased overall risk of DR while a risk existed at early treatment phase, comparing ever-use and never-use cases of DPP4i [23]. Similarly, a cohort study with United States population aged 65 years or older reported that DPP4i use did not increase the risk of DR requiring treatments [24]. Taken together, it is reasonable to conclude that the use of DPP4i may not increase the

risk of DR progression, compared to SU as add-on medication to metformin. DPP4i can be considered as second-line therapy in patient with type 2 diabetes mellitus, in safety from DR progression.

DR is one of major causes of visual impairment resulting in an important burden on health care systems [25-27], so that protective factors other than glycemic control need to be considered in clinical practice. Retinopathy and nephropathy share common pathogenesis as microvascular complications of diabetes [12]. Renoprotective effect of DPP4i has been reported [28-30], while there are few clinical studies on the effect of retinopathy [14]. Experimental studies on DR and DPP4i have revealed conflicting results. One study using linagliptin reported that loss of pericytes and retinal ganglion cells were prevented with the medication [16], while another study with sitagliptin also reported inhibition of blood-retinal barrier breakdown as well as decreased retinal inflammation and neuronal apoptosis [31]. Topical administration of DPP4i showed also protective effect by preventing neurodegeneration as well as vascular leakage in experimental diabetic retina [32]. However, there is still a study reporting increased vascular leakage with DPP4i suggesting possibility of DR progression [15].

Relatively small number of patients with TZD were included in this study compared to those with DPP4i or SU, which might be associated with low rate of TZD prescription in Korea [6]. Anti-angiogenic and anti-inflammatory effects of TZD in ischemic retina have been reported in experimental studies [33,34], while a recent cohort study revealed no consistent evidence of DR progression in patients with TZD suggesting no association [35]. The low HR of DR aggravation in patients with TZD shown in this study was not further discussed here to avoid misinterpretation of the results, which need to be in-

vestigated with larger sample size of patients with TZD.

There are several limitations in this study. First, the presence of DR was defined by the presence of diagnostic code from NHIS database. Although the diagnostic code is mandatory for any patient, the accuracy of diagnoses are not adjudicated by medical records or laboratory tests. Second, bevacizumab is one of the widely used treatment for diabetic macular edema or complications of proliferative DR [36,37], but intravitreal injection of bevacizumab was not identified in this analysis as this procedure is not covered by NHIS due to its off-label use in Korea. However, the ratio of patients treated intravitreally with other medications (ranibizumab, aflibercept, triamcinolone, or dexamethasone implants) were not different between groups, so that intravitreal bevacizumab injections may be also similar between groups as this may not be one-sided. Third, lack of glycemic control data is also critical, as intensive glycemia treatment and intensive combination treatment of dyslipidemia are well known to reduce the rate of DR aggravation [22]. We tried to overcome this limitation by adjusting fasting glucose levels instead in our subgroup analysis, although insufficient to reflect the whole study population. Lastly, follow-up period for DR aggravation was relatively short to compare the effect for second-line antidiabetic medications. However, above mentioned limitations might affect both DPP4i group and SU group, so that one-sided application might be prevented. Further study with larger sample size of patients with blood chemistry data would be helpful, so that more criteria would be available for the choice of second-line antidiabetic medications.

In conclusion, this population-based cohort study demonstrated that the use of DPP4i as second line medication did not increase the risk of DR progression compared with SU in patients with DR. This suggests that DPP4i can be considered as second line antidiabetic medication safely in patients with DR.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2018.0137.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conception or design: H.C.K., K.L., D.J.K.
Acquisition, analysis, or interpretation of data: K.H.H., S.J.P.
Drafting the work or revising: Y.R.C.
Final approval of the manuscript: K.L., D.J.K.

ORCID

Yoo-Ri Chung https://orcid.org/0000-0002-6871-6721
Kihwang Lee https://orcid.org/0000-0003-0478-8758
Dae Jung Kim https://orcid.org/0000-0003-1025-2044

ACKNOWLEDGMENTS

REFERENCES

1. Stitt AW, Lois N, Medina RJ, Adamson P, Curtis TM. Advances in our understanding of diabetic retinopathy. Clin Sci (Lond) 2013;125:1-17.
2. Bandello F, Lattanzio R, Zucchiatti I, Del Turco C. Pathophysiology and treatment of diabetic retinopathy. Acta Diabetol 2013;50:1-20.
3. Pearson PA, Comstock TL, Ip M, Callanan D, Morse LS, Ashton P, Levy B, Mann ES, Eliott D. Fluocinolone acetonide intravitreal implant for diabetic macular edema: a 3-year multicenter, randomized, controlled clinical trial. Ophthalmology 2011;118:1580-7.
4. Sivaprasad S, Crosby-Nwaobi R, Heng LZ, Peto T, Michaelides M, Hykin P. Injection frequency and response to bevacizumab monotherapy for diabetic macular oedema (BOLT Report 5). Br J Ophthalmol 2013;97:1177-80.
5. Ip MS, Domalpally A, Sun JK, Ehrlich JS. Long-term effects of therapy with ranibizumab on diabetic retinopathy severity and baseline risk factors for worsening retinopathy. Ophthalmolo-

gy 2015;122:367-74.

6. Ko SH, Kim DJ, Park JH, Park CY, Jung CH, Kwon HS, Park JY, Song KH, Han K, Lee KU, Ko KS; Task Force Team for Diabetes Fact Sheet of the Korean Diabetes Association. Trends of antidiabetic drug use in adult type 2 diabetes in Korea in 2002-2013: nationwide population-based cohort study. Medicine (Baltimore) 2016;95:e4018.

7. Hampp C, Borders-Hemphill V, Moeny DG, Wysowski DK. Use of antidiabetic drugs in the U.S., 2003-2012. Diabetes Care 2014;37:1367-74.

8. Ko SH, Han K, Lee YH, Noh J, Park CY, Kim DJ, Jung CH, Lee KU, Ko KS. Past and current status of adult type 2 diabetes mellitus management in Korea: a National Health Insurance Service database analysis. Diabetes Metab J 2018;42:93-100.

9. 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.

10. Mishriky BM, Cummings DM, Tanenberg RJ. The efficacy and safety of DPP4 inhibitors compared to sulfonylureas as add-on therapy to metformin in patients with type 2 diabetes: a systematic review and meta-analysis. Diabetes Res Clin Pract 2015;109:378-88.

11. 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.

12. Avogaro A, Fadini GP. The effects of dipeptidyl peptidase-4 inhibition on microvascular diabetes complications. Diabetes Care 2014;37:2884-94.

13. Patil HR, Al Badarin FJ, Al Shami HA, Bhatti SK, Lavie CJ, Bell DS, O'Keefe JH. Meta-analysis of effect of dipeptidyl peptidase-4 inhibitors on cardiovascular risk in type 2 diabetes mellitus. Am J Cardiol 2012;110:826-33.

14. Chung YR, Park SW, Kim JW, Kim JH, Lee K. Protective effects of dipeptidyl peptidase-4 inhibitors on progression of diabetic retinopathy in patients with type 2 diabetes. Retina 2016;36:2357-63.

15. 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.

16. Dietrich N, Kolibabka M, Busch S, Bugert P, Kaiser U, Lin J, Fleming T, Morcos M, Klein T, Schlotterer A, Hammes HP. The DPP4 inhibitor linagliptin protects from experimental diabetic retinopathy. PLoS One 2016;11:e0167853.

17. Fadini GP, Avogaro A. How to interpret the role of SDF-1α on diabetic complications during therapy with DPP-4 inhibitors. Cardiovasc Diabetol 2018;17:22.

18. Bressler SB, Liu D, Glassman AR, Blodi BA, Castellarin AA, Jampol LM, Kaufman PL, Melia M, Singh H, Wells JA; Diabetic Retinopathy Clinical Research Network. Change in diabetic retinopathy through 2 years: secondary analysis of a randomized clinical trial comparing aflibercept, bevacizumab, and ranibizumab. JAMA Ophthalmol 2017;135:558-68.

19. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-83.

20. Törner A, Duberg AS, Dickman P, Svensson A. A proposed method to adjust for selection bias in cohort studies. Am J Epidemiol 2010;171:602-8.

21. Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs: an extension of the modified Airlie House classification. ETDRS report number 10. Ophthalmology 1991;98(5 Suppl):786-806.

22. ACCORD Study Group; ACCORD Eye Study Group, Chew EY, Ambrosius WT, Davis MD, Danis RP, Gangaputra S, Greven CM, Hubbard L, Esser BA, Lovato JF, Perdue LH, Goff DC Jr, Cushman WC, Ginsberg HN, Elam MB, Genuth S, Gerstein HC, Schubart U, Fine LJ. Effects of medical therapies on retinopathy progression in type 2 diabetes. N Engl J Med 2010;363:233-44.

23. Kim NH, Choi J, Kim NH, Choi KM, Baik SH, Lee J, Kim SG. Dipeptidyl peptidase-4 inhibitor use and risk of diabetic retinopathy: a population-based study. Diabetes Metab 2018;44:361-7.

24. Wang T, Hong JL, Gower EW, Pate V, Garg S, Buse JB, Sturmer T. Incretin-based therapies and diabetic retinopathy: real-world evidence in older U.S. adults. Diabetes Care 2018;41:1998-2009.

25. Ross EL, Hutton DW, Stein JD, Bressler NM, Jampol LM, Glassman AR; Diabetic Retinopathy Clinical Research Network. Cost-effectiveness of aflibercept, bevacizumab, and ranibizumab for diabetic macular edema treatment: analysis from the diabetic retinopathy clinical research network comparative effectiveness trial. JAMA Ophthalmol 2016;134:888-96.

26. Kusuhara S, Fukushima Y, Ogura S, Inoue N, Uemura A. Pathophysiology of diabetic retinopathy: the old and the new. Diabetes Metab J 2018;42:364-76.

dmj

27. Ghaem H, Daneshi N, Riahi S, Dianatinasab M. The prevalence and risk factors for diabetic retinopathy in Shiraz, Southern Iran. Diabetes Metab J 2018;42:538-43.

28. Kim YG, Byun J, Yoon D, Jeon JY, Han SJ, Kim DJ, Lee KW, Park RW, Kim HJ. Renal protective effect of DPP-4 inhibitors in type 2 diabetes mellitus patients: a cohort study. J Diabetes Res 2016;2016: 1423191.

29. Esaki H, Tachi T, Goto C, Sugita I, Kanematsu Y, Yoshida A, Saito K, Noguchi Y, Ohno Y, Aoyama S, Yasuda M, Mizui T, Yamamura M, Teramachi H. Renoprotective effect of dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes mellitus. Front Pharmacol 2017;8:835.

30. Mega C, Teixeira-de-Lemos E, Fernandes R, Reis F. Renoprotective effects of the dipeptidyl peptidase-4 inhibitor sitagliptin: a review in type 2 diabetes. J Diabetes Res 2017;2017:5164292.

31. Goncalves A, Marques C, Leal E, Ribeiro CF, Reis F, Ambrosio AF, Fernandes R. Dipeptidyl peptidase-IV inhibition prevents blood-retinal barrier breakdown, inflammation and neuronal cell death in the retina of type 1 diabetic rats. Biochim Biophys Acta 2014;1842:1454-63.

32. Hernandez C, Bogdanov P, Sola-Adell C, Sampedro J, Valeri M, Genis X, Simo-Servat O, Garcia-Ramirez M, Simo R. Topical administration of DPP-IV inhibitors prevents retinal neurodegeneration in experimental diabetes. Diabetologia 2017;60: 2285-98.

33. Higuchi A, Ohashi K, Shibata R, Sono-Romanelli S, Walsh K, Ouchi N. Thiazolidinediones reduce pathological neovascularization in ischemic retina via an adiponectin-dependent mechanism. Arterioscler Thromb Vasc Biol 2010;30:46-53.

34. Murata T, Hata Y, Ishibashi T, Kim S, Hsueh WA, Law RE, Hinton DR. Response of experimental retinal neovascularization to thiazolidinediones. Arch Ophthalmol 2001;119:709-17.

35. Gower EW, Lovato JF, Ambrosius WT, Chew EY, Danis RP, Davis MD, Goff DC Jr, Greven CM; ACCORD Study Group. Lack of longitudinal association between thiazolidinediones and incidence and progression of diabetic eye disease: the ACCORD eye study. Am J Ophthalmol 2018;187:138-47.

36. Stewart MW. Treatment of diabetic retinopathy: recent advances and unresolved challenges. World J Diabetes 2016;7:333-41.

37. Virgili G, Parravano M, Evans JR, Gordon I, Lucenteforte E. Anti-vascular endothelial growth factor for diabetic macular oedema: a network meta-analysis. Cochrane Database Syst Rev 2017;6:CD007419.

Supplementary Table 1. Baseline characteristics of second-line drugs in a subgroup with available health screening data

Variable	MET+SU (n=1,504)	MET+DPP4i (n=2,384)	MET+TZD (n=224)	P value
Age, yr	59.9±10.0	57.0±9.7	57.3±9.5	<0.001
Men, sex	736 (48.9)	1,198 (50.3)	123 (54.9)	0.234
Duration of MET treatment, mo	10.1±3.5	10.3±3.5	10.0±3.5	0.104
Duration of second line therapy, mo	20.4±16.8	20.2±16.0	19.3±16.9	0.040
Body mass index, kg/m^2	25.0±3.3	24.9±3.1	24.7±3.0	0.401
Waist circumference, cm	84.9±8.5	84.2±8.4	83.6±8.1	0.012
Systolic blood pressure, mm Hg	128.6±14.7	126.1±14.5	127.2±14.8	<0.001
Total cholesterol, mg/dL	186.7±39.4	177.8±36.1	177.7±35.2	<0.001
Triglyceride, mg/dL	134.5 (98.0–189.0)	124.0 (90.0–176.0)	132.0 (92.5–187.0)	0.001
HDL-C, mg/dL	51.4±20.9	51.4±23.0	50.0±12.2	0.645
LDL-C, mg/dL	106.0±50.1	99.9±57.6	97.6±31.6	0.001
Fasting glucose, mg/dL	132.0 (115.0–152.5)	126.0 (113.0–142.0)	123.5 (112.0–142.0)	<0.001
Creatinine, mg/dL	1.01±1.01	0.98±0.99	1.04±1.07	0.528
Smoking status				0.383
Never	978 (65.0)	1,550 (65.0)	137 (61.2)	
Former	322 (21.4)	517 (21.7)	61 (27.2)	
Current	204 (13.6)	317 (13.3)	26 (11.6)	
Family history				
Stroke	125 (8.3)	262 (11.0)	24 (10.7)	0.024
Heart disease	69 (4.6)	143 (6.0)	11 (4.9)	0.157
Charlson score, unit	3.1±1.7	3.1±1.6	3.1±1.7	0.851
Intravitreal injection	13 (0.9)	20 (0.8)	0 (0.0)	0.382
Inclusion year				<0.001
2009	665 (44.2)	1,181 (49.5)	133 (59.4)	
2010	390 (25.9)	631 (26.5)	46 (20.5)	
2011	265 (17.6)	349 (14.6)	33 (14.7)	
2012	184 (12.2)	223 (9.4)	12 (5.4)	

Values are presented as mean±standard deviation, number (%), or median (interquartile range).
MET, metformin; SU, sulfonylurea; DPP4i, dipeptidyl peptidase-4 inhibitor; TZD, thiazolidinedione; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.