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Electronic medical records-based comparison of glycemic control efficacy between sulfonylureas and dipeptidyl peptidase-4 inhibitors added on to metformin monotherapy in patients with type 2 diabetes

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ABSTRACT

Sulfonylurea (SU) and dipeptidyl peptidase-4 (DPP-4) inhibitors are most common secondary agents that are added to metformin monotherapy. Real-world studies have become increasingly important in providing evidence of treatment effectiveness in clinical practice and real-world data could help appropriate therapeutic information. Therefore, this study aims to compare the glycemic effectiveness of SU and DPP-4 inhibitors, which are added to metformin monotherapy in real clinical practice using electronic medical record (EMR) data. EMR data of type 2 diabetes patients treated at Seoul National University Hospital from December 2002 to December 2012 were retrieved and analyzed. The patients were divided into three groups: patients who maintained metformin monotherapy (M), and patients who added SU (MS) or DPP-4 inhibitors (MD) to metformin monotherapy. The mean change in HbA1c level, the proportion of patients achieving the HbA1c target < 7.0%, proportion of patients with treatment failure, and probability of treatment failure occurrence and changes in prescription were evaluated to compare glycemic control efficacy between SU and DPP-4 inhibitors. The MS showed significantly greater reduction in the Hb1Ac level than MD. The proportion of patients achieving HbA1c < 7.0% is higher in MD, whereas the proportion of patients with treatment failure was greater in MS. The probability of the treatment failure and probability of changes in the prescription were lower in MD than MS with hazard ratio of 0.499 and 0.579, respectively. In conclusion, this real-world study suggested that DPP-4 inhibitors are expected to show more durable glycemic control efficacy than SU in long-term use.

Keywords: Real-World Data; Type 2 Diabetes; Sulfonylureas; DPP-4 Inhibitors; Glycemic Control

INTRODUCTION

Type 2 diabetes mellitus (T2D) is a chronic metabolic disorder and the number of T2D patients has been increasing constantly across the world [1]. In type 2 diabetes optimal

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glycemic control is the basis of managing symptoms and essential to reduce the risk of long-term diabetes complications such as cardiovascular disease, retinopathy, nephropathy, and neuropathy [2,3]. According to standards of medical care in diabetes, the target of HbA1c < 7% is recommended in many non-pregnant adults and HbA1c < 6.5% can be suggested in a selected individual patient in the case of the patient achieving the target without hypoglycemia or other adverse effects [4].

Metformin monotherapy is accepted as the most preferred first-line treatment in type 2 diabetic patients. However, some patients end up with treatment failure due to an insufficient control of glucose level. Therefore, for those who were not suitable for metformin monotherapy, secondary agents could be considered. Sulfonylurea (SU) and dipeptidyl peptidase-4 (DPP-4) inhibitors are the most common secondary agents that are added to metformin monotherapy. SU was introduced to the market in the 1950s [5]. SU mainly increases insulin concentration in plasma by binding to SU receptors on β -pancreatic cells [6]. SU was widely used due to its general safety, cost efficiency, and predictability but the use of SU was limited by hypoglycemia and weight gain [7]. On the other hand, DPP-4 inhibitors are a glucose-lowering agent that has a different mechanism from previous oral hypoglycemic agents. Gastrointestinal tract secreted glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP), which is called incretin, are produced when food is ingested. Incretins are hormones that can modulate insulin and glucagon secretion but disassemble shortly by an enzyme named DPP-4 [8]. DPP-4 inhibitors suppressed DPP-4 enzyme to increase incretin concentration [9,10].

Real-world studies have become increasingly important in providing evidence of treatment effectiveness in clinical practice as the effectiveness could be different between real-world data and clinical trials [11]. Furthermore, this real-world data could help appropriate therapeutic information. The aim of this study is to compare the glycemic effectiveness of SU and DPP-4 inhibitors, which are added to metformin monotherapy in real clinical practice using electronic medical record (EMR) data.

METHODS

Patient population

T2D outpatients treated at Seoul National University Hospital (SNUH) from December 2002 to December 2012 were included in this study. During this period, patients who had a history of malignant tumor or a hemoglobin level < 10 g/dL, were excluded as it might affect the HbA1c goal or the HbA1c measurement. Patients who had history of steroid therapy that might interfere with glycemic control, were also excluded. There were a total of 2,000 T2D patients who had metformin monotherapy as their first prescription among the 12,315 T2D patients retrieved from the SNUH EMR database. The demographics (i.e., sex and age), prescription (i.e., prescribed drug, prescription date, and number of days), laboratory (i.e., date of HbA1c measurement and HbA1c levels) information of 2,000 T2D patients were collected and used for this study. The T2D patients who did not have prescription or laboratory test information, were excluded in the analysis. Data collection and analysis were conducted after the protocol had been approved by the Institutional Review Board of Seoul National University Hospital.

Data analysis

In this study, the T2D patients were divided into three groups (Fig. 1). In group M, the patients who maintained the newly prescribed metformin monotherapy during observation, were included. The T2D patients who added SU to metformin monotherapy, were classified as MS whereas patients who added DPP-4 inhibitors to metformin monotherapy, were classified as MD. In addition, patients who received the newly prescribed metformin monotherapy in MS and MD, were sub-classified into MS1 and MD1 while patients who had pre-existing metformin monotherapy in MS and MD, were sub-classified into MS2 and MD2. The newly prescribed metformin monotherapy was assumed when the HbA1c level measurement existed during more than the third quarter without any prescription for diabetes one year before the first metformin monotherapy. Patient data showing other prescribed medications were excluded from the analysis.

To calculate mean HbA1c levels, the HbA1c levels were collected by the following time intervals: 0 to 3, 3 to 6, 6 to 9, 9 to 12, 12 to 16, 16 to 20, 20 to 24, 24 to 30, and 30 to 36 months before and after prescription in all patients (30 days were regarded as 1 month). In the case of several HbA1c measurements during a single interval, the measurement closest to the prescription was selected to reduce the possibility of bias due to oversampling. Since HbA1c indicates the three-month average plasma glucose concentration, the measurement within the first 3 months after the prescription were not included to allow time for physiologic adjustment and dosage titration.

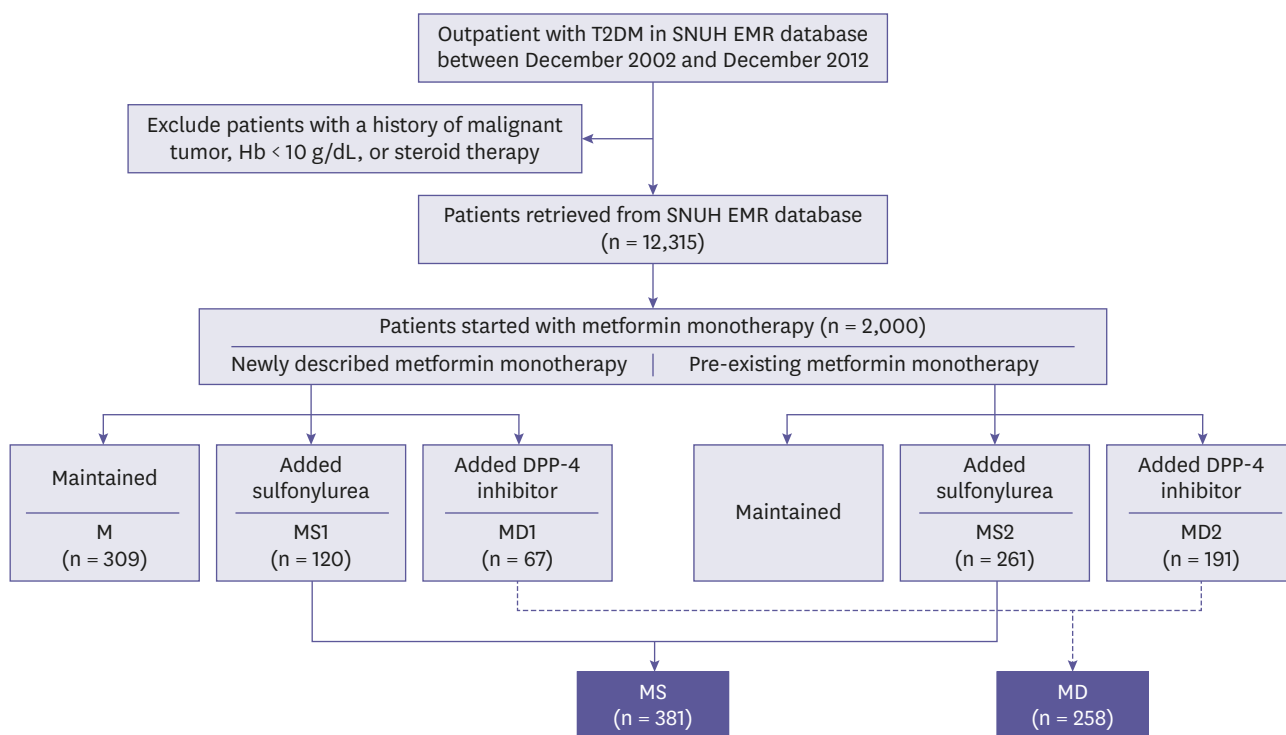


Figure 1. Flow chart of the patients retrieved in this study. T2DM, type 2 diabetes mellitus; SNUH, Seoul National University Hospital; EMR, electronic medical record; M, patients with metformin monotherapy only which is newly prescribed; MS, patients with addition of sulfonylurea to metformin monotherapy; MD, patients with addition of DPP-4 inhibitor to metformin monotherapy; MS1 and MS2, subgroups of MS with newly prescribed and pre-existing metformin monotherapy, respectively; MD1 and MD2, subgroups of MD with newly prescribed and pre-existing metformin monotherapy, respectively.

Evaluation variables

To evaluate the efficacy of the treatment, the following five variables are evaluated: the mean change in the HbA1c level before and after prescription of metformin monotherapy, and SU or DPP-4 inhibitors, which is added to metformin monotherapy; the proportion of patients achieving the HbA1c target < 7.0%; the proportion of patients with treatment failure, which is defined as HbA1c ≥ 8.0% during 3–6 months after treatment; the probability of treatment failure occurrence; and the probability of treatment change in prescription.

Statistical analysis

IBM SPSS Statistics software version 22.0 (IBM, Armonk, NY, USA) was used for all statistical analysis. Comparing the mean change of the HbA1c level between groups were performed using Student's t-test, and changes in prescription and treatment failure occurrence were assessed using Cox's proportional hazard model.

RESULTS

Baseline characteristics

A total of 961 patients were included in this study (Table 1). The proportion of females remained at about 40 percent. In the MS and MD group, the average age at the start of metformin monotherapy and at adding the secondary agent was similar, which is the mid-fifties. Before starting metformin monotherapy (i.e., treatment naïve period), the mean HbA1c level was steadily increased until -90d and dramatically elevated for 3 months shortly before prescription (Fig. 2A). After the metformin monotherapy, T2D patients in M was maintained around 6.7% of the HbA1c level on average. However, the mean HbA1c levels in MS and MD was comparatively higher, which is around 7.0% or above (Fig. 2A).

Change in the HbA1c level before and after adding the secondary agent

Three months before adding the secondary agent (SU and DPP-4 inhibitors for MS and MD, respectively), the mean HbA1c level was dramatically increased (Fig. 2B). After the patients started the secondary agent, the mean HbA1c level was significantly reduced around 7.0% or less and the glyceic control was maintained for 2 years in both group (Fig. 2B). After approximately 2.5 years, the HbA1c level tended to increase in the MS group while the MD group maintained the HbA1c level (Fig. 2B). The mean HbA1c level before and after adding SU or DPP-4 inhibitors was significantly different between MS and MD (Table 2). The average change in HbA1c levels before and after the prescription was significantly greater in MS than in MD (Table 2). The proportion of patients achieving HbA1c < 7.0% within 3–6 months was lower in MS than MD but there are no statistical differences between the two groups (Table 3). When compared after the patients were classified into two groups according to the HbA1c levels before adding SU or DPP-4 inhibitors (Table 3), the proportion of patients achieving < 7.0% had no significant differences

Table 1. Demographic characteristics of the patients included in this study

Variables	M	MS	MD
Total number of patients	309	381	258
Proportion of female (%)	46.3	41.5	40.3
Age at start of metformin monotherapy (yr)*	59.8 [22–87]	55.2 [12–84]	55.1 [17–81]
Age at adding secondary agent (yr)*	N/A	56.8 [12–86]	57.2 [21–83]

M, patients with metformin monotherapy only which is newly prescribed; MS, patients with addition of sulfonylurea to metformin monotherapy; MD, patients with addition of DPP-4 inhibitor to metformin monotherapy; N/A: not applicable.

*Mean [minimum–maximum].

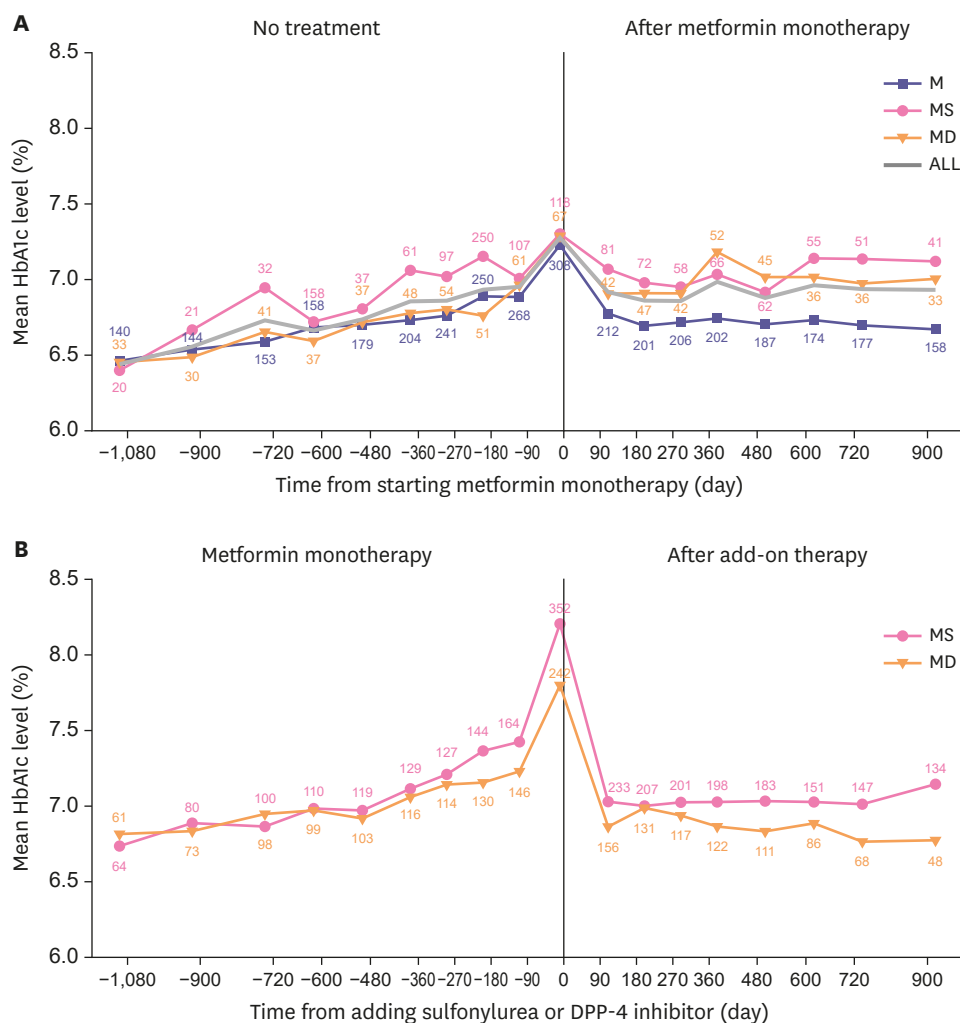


Figure 2. Mean HbA1c profiles before and after (A) starting metformin monotherapy and (B) adding sulfonylurea or DPP-4 inhibitor to metformin monotherapy. Numbers on the graph represent the number of HbA1c measurements used in the mean HbA1c level calculation.

M, patients with metformin monotherapy only which is newly prescribed; MS, patients with addition of sulfonylurea to metformin monotherapy; MD, patients with addition of DPP-4 inhibitor to metformin monotherapy; ALL, average of M, MS, and MD.

Table 2. Mean HbA1c levels before and after prescription (i.e., adding sulfonylurea or DPP-4 inhibitor to metformin monotherapy)

Variables	MS	MD	p-value*
Number of patients	219	149	
HbA1c level before prescription (within 3 mon)	8.2 ± 1.0	7.7 ± 0.8	< 0.001
HbA1c level after prescription (3–6 mon)	7.0 ± 0.8	6.9 ± 0.6	0.025
Change in HbA1c level (%points)	-1.2 ± 1.1	-0.9 ± 0.8	< 0.001

Data were presented as mean ± standard deviation.

MS, patients with addition of sulfonylurea to metformin monotherapy; MD, patients with addition of DPP-4 inhibitor to metformin monotherapy.

*p-value from t-test.

between the two groups in the patients whose HbA1c level was < 8% and ≥ 8.0% before adding the secondary agent. However, the proportion of patients achieving HbA1c < 7.0% within 3–6 months after adding SU or DPP-4 inhibitors to metformin monotherapy was significantly higher in the patients whose HbA1c level was < 8%, no matter of the treatment. For treatment

Table 3. Proportions of patients achieving an HbA1c level < 7% or with treatment failure after adding sulfonylurea or DPP-4 inhibitor to metformin monotherapy

Variables	MS	MD	p-value	HbA1c level < 8% before prescription		p-value	HbA1c level ≥ 8% before prescription		p-value*
				MS	MD		MS	MD	
				Number of patients	219		149		
Proportion of patients achieving: HbA1c level < 7.0% (%) [†]	53.9	61.7	0.163	63.5	71.9	0.194	45.2 [‡]	28.6 [§]	0.116
Proportion of patients with treatment failure (%) ^{b†}	13.2	4.0	0.003	6.7	1.8	0.090	19.1 [§]	11.4 [‡]	0.325

MS, patients with addition of sulfonylurea to metformin monotherapy; MD, patients with addition of DPP-4 inhibitor to metformin monotherapy. *p-value from Fisher's exact test; [†]during 3–6 months after prescription; [‡]p < 0.05, [§]p < 0.01 in comparison with the corresponding group with HbA1c level < 8% before prescription.

Table 4. Predicted Hazard ratio for treatment failure occurrence and changes in prescription based on cox proportional hazard model

Variables	Hazard ratio	95% confidence interval	p-value
Probability of treatment failure after adding sulfonylurea or DPP-4 inhibitor to metformin monotherapy			
MS (= reference)			
MD	0.665	0.470–0.942	0.022
Age	0.98	0.970–0.993	0.002
HbA1c level ≥ 8% before prescription	2.309	1.745–3.056	< 0.001
Probability of changes in prescription after adding sulfonylurea or DPP-4 inhibitor to metformin monotherapy			
MS (= reference)			
MD	0.581	0.440–0.767	< 0.001
Sex (female)	1.303	1.029–1.650	0.031
Age	0.987	0.976–0.997	0.012

MS, patients with addition of sulfonylurea to metformin monotherapy; MD, patients with addition of DPP-4 inhibitor to metformin monotherapy.

failure, MS showed a greater proportion of patients with treatment failure than MD within 3–6 months and there were significant differences between the two groups (**Table 3**). However, as with the proportion of patients achieving < 7.0%, there were no notable differences between MD and MS when compared based on glucose status but there were significant differences according to glucose status in the treatment groups.

Treatment failure and changes in prescription

There are significant differences in probability of patients with treatment failure between MS and MD after adding SU and DPP-4 inhibitors to metformin monotherapy. MD showed a lower treatment failure risk than MS with the hazard ratio of treatment failure for MS to MD of 0.665 [0.450–0.942] (**Table 4**). Patients who had an HbA1c level ≥ 8.0% before prescription had a higher treatment failure risk with a hazard ratio of 2.309 [1.745–3.056]. For probability of changes in prescription after adding SU or DPP-4 inhibitors to metformin monotherapy, MD showed a lower relative risk with a hazard ratio of 0.579 [0.440–0.763], which indicated that DPP-4 inhibitors added to metformin monotherapy maintained longer than SU (**Table 4**). The study also identified that sex and age were factors that influence the probability of changes in prescription and/or the probability of treatment failure after adding SU or DPP-4 inhibitors to metformin monotherapy.

DISCUSSION

This study analyzed the mean change in the HbA1c level, the proportion of patients achieving the HbA1c target < 7.0%, the proportion of patients with treatment failure, and the probability of treatment failure occurrence and changes in prescription using EMR data to compare the glycemic control efficacy of SU and DPP-4 inhibitors as the add-on therapy in patients with type 2 diabetes.

The HbA1c level tended to increase dramatically three months prior to starting therapy and similar aspects were reported in a previous study [12]. This indicated that continuous monitoring is required and the time of add-on therapy should be determined rapidly. Patients who were not sufficiently controlled by metformin monotherapy, received a second therapy, and MS showed a relatively higher HbA1c level before adding SU when compared to MD. The reason for adding SU in MS when the HbA1c level was higher than MD are as follows. SU was used to treat T2D since the 1950s whereas DPP-4 inhibitors were approved in 2006 [6,13]. The current guideline recommends that the treatment should be intensified if the HbA1c level is still above the goal after three months of treatment while the intensification of treatment occurred when the HbA1c level was $> 8\%$ before 2004 [4,14,15].

Adding SU as an add-on therapy showed an appreciably greater reduction in the HbA1c level than DPP-4 inhibitors. This may be due to MS having a higher HbA1c level than MD before starting the add-on therapy as the higher HbA1c baseline had a greater effect of reduction after treatment [16]. The proportion of patients achieving HbA1c $< 7.0\%$ was not different between SU and DPP-4 inhibitors and the target rate was considerably high among the drugs when HbA1c was low prior to the add-on therapy. Additionally, it was revealed that there are no significant differences between SU and DPP-4 inhibitors in the HbA1c level change from the baseline at 52 weeks in the meta-analysis [17]. In Cox's proportional hazards model, the probability of treatment failure was higher in the patients with an HbA1c level $\geq 8\%$. This indicates that the add-on therapy needs to be conducted when HbA1c is not too high. Overall, the short-term glycemic control effect would not be much different between the two drugs.

The probability of treatment failure was lower in MD. DPP-4 inhibitors not only increase beta cell insulin secretion, but also reduce metabolic stress [18]. DPP-4 inhibitors promote insulin secretion to increase beta cell mass and promote glucose dependent insulin secretion. Thus, DPP-4 inhibitors can reduce the insulin requirement through glucagon suppression [18]. On the other hand, long term use of SU can lead progressive dysfunction and insulin secretion to deteriorate due to SU directly acting on β -cell. Therefore, diabetes could be worsening in the long term despite improved glycemic control in the short term when using SU as the secondary agent [6].

The probability of changes in prescription was lower in MD because SU might induce weight gain while DPP-4 inhibitors have the ability of weight loss as managing body weight assists to improve glycemic control, which is important in type 2 diabetes [19,20]. Furthermore, while SU is linked with cardiovascular disease, DPP-4 inhibitors can reduced risk of cardiovascular disease when compared to SU [19] and the meta-analysis demonstrated that DPP-4 inhibitors do not increase the risk of heart failure, myocardial infarction, cardiovascular death and stroke [20]. Hence, DPP-4 inhibitors can be used for long-term stability.

Females had a higher probability of changes in prescription than males, which might be due to females poorly achieved optimal glycemic control after one year of treatment [21] and a 50% higher risk of cardiovascular disease than males [22]. There is a cross-sectional study about sex differences that correlate to poor glycemic control in T2D patients. This study revealed that females poorly controlled the glycemic level than males, which is possibly due to glucose homeostasis differences, treatment response, and psychological factors [23].

Real-world evidence (RWE) aims to include patient populations that more represent an unselected population than randomized controlled trials (RCT), and usually have big data

that can provide therapeutic information about specific populations that are usually excluded from RCTs [24]. RWE is likely to provide realistic data and to suggest appropriate therapeutic information. The strength of the study results was derived using real world data to reflect a real clinical practice that could not be identified in limited situations like RCT.

There are several limitations in this study. First, only the HbA1c level was evaluated and there is no other diabetes biomarker such as insulin or C-peptide and safety evaluation index such as weigh gain and cardiac disease. However, the data is still considerable due to the HbA1c level mainly used to predict T2D patients in clinical practice. Second, the prescription times were different between the two drugs, which may have affected the changes in the prescription due to the treatment period including the time of the changed prescription guidelines. In addition, SU had longer-term data and the DPP-4 inhibitors had relatively shorter-term data. To correct for this difference, the data are analyzed based on the time of prescription, and pre-HbA1c was also analyzed as an influence factor. Third, the number of patients who were on metformin monotherapy was relatively small when compared to the base population. This is due to the tertiary-care teaching hospital nature of our institution, in which there are relatively few numbers of treatment-naïve patients. Consequently, further meta-analysis is needed to confirm these results.

This study was analyzed using old data and there might not be new findings from the previous studies. However, this study is still meaningful in that the results are consistent with contents reflected in the guidelines by using well-refined and analyzed large-scale RWE. In addition, it is worthwhile that the concept of RWE was applied and analyzed for the South Korean population. Although there are studies on the safety of T2D patients through RWE of the South Korean population, this study focused on glyceic control using the HbA1c level. Therefore, this real-world database study suggested that starting the add-on therapy at a low HbA1c level is better for glyceic control and that DPP-4 inhibitors may result in longer and more stable glyceic control.

REFERENCES

1. Olokoba AB, Obateru OA, Olokoba LB. Type 2 diabetes mellitus: a review of current trends. *Oman Med J* 2012;27:269-273.
[PUBMED](#) | [CROSSREF](#)
2. Afroz A, Ali L, Karim MN, Alramadan MJ, Alam K, Magliano DJ, et al. Glycaemic control for people with type 2 diabetes mellitus in Bangladesh: an urgent need for optimization of management plan. *Sci Rep* 2019;9:10248.
[PUBMED](#) | [CROSSREF](#)
3. Haghghatpanah M, Nejad AS, Haghghatpanah M, Thunga G, Mallayasamy S. Factors that correlate with poor glyceic control in type 2 diabetes mellitus patients with complications. *Osong Public Health Res Perspect* 2018;9:167-174.
[PUBMED](#) | [CROSSREF](#)
4. American Diabetes Association. 6. Glyceic targets: standards of medical care in diabetes-2020. *Diabetes Care* 2020;43 Suppl 1:S66-S76.
[PUBMED](#) | [CROSSREF](#)
5. Quianzon CC, Cheikh IE. History of current non-insulin medications for diabetes mellitus. *J Community Hosp Intern Med Perspect* 2012;2:19081.
[PUBMED](#) | [CROSSREF](#)
6. Sola D, Rossi L, Schianca GP, Maffioli P, Bigliocca M, Mella R, et al. Sulfonylureas and their use in clinical practice. *Arch Med Sci* 2015;11:840-848.
[PUBMED](#) | [CROSSREF](#)

7. White JR Jr. A brief history of the development of diabetes medications. *Diabetes Spectr* 2014;27:82-86.
[PUBMED](#) | [CROSSREF](#)
8. Kim W, Egan JM. The role of incretins in glucose homeostasis and diabetes treatment. *Pharmacol Rev* 2008;60:470-512.
[PUBMED](#) | [CROSSREF](#)
9. Drucker DJ. The role of gut hormones in glucose homeostasis. *J Clin Invest* 2007;117:24-32.
[PUBMED](#) | [CROSSREF](#)
10. Russell-Jones D, Gough S. Recent advances in incretin-based therapies. *Clin Endocrinol (Oxf)* 2012;77:489-499.
[PUBMED](#) | [CROSSREF](#)
11. Blonde L, Khunti K, Harris SB, Meizinger C, Skolnik NS. Interpretation and impact of real-world clinical data for the practicing clinician. *Adv Ther* 2018;35:1763-1774.
[PUBMED](#) | [CROSSREF](#)
12. Baxter M, Morimoto Y, Tamiwa M, Hattori M, Peng XV, Lubwama R, et al. A real-world observational study evaluating the probability of glycaemic control with basal insulin or glucagon-like peptide-1 receptor agonist in Japanese patients with type 2 diabetes. *Diabetes Ther* 2020;11:1481-1496.
[PUBMED](#) | [CROSSREF](#)
13. Dicker D. DPP-4 inhibitors: impact on glycaemic control and cardiovascular risk factors. *Diabetes Care* 2011;34 Suppl 2:S276-S278.
[PUBMED](#) | [CROSSREF](#)
14. Brown JB, Nichols GA. Slow response to loss of glycaemic control in type 2 diabetes mellitus. *Am J Manag Care* 2003;9:213-217.
[PUBMED](#)
15. Brown JB, Nichols GA, Perry A. The burden of treatment failure in type 2 diabetes. *Diabetes Care* 2004;27:1535-1540.
[PUBMED](#) | [CROSSREF](#)
16. DeFronzo RA, Stonehouse AH, Han J, Wintle ME. Relationship of baseline HbA1c and efficacy of current glucose-lowering therapies: a meta-analysis of randomized clinical trials. *Diabet Med* 2010;27:309-317.
[PUBMED](#) | [CROSSREF](#)
17. 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;109:378-388.
[PUBMED](#) | [CROSSREF](#)
18. Mu J, Woods J, Zhou YP, Roy RS, Li Z, Zycband E, et al. Chronic inhibition of dipeptidyl peptidase-4 with a sitagliptin analog preserves pancreatic beta-cell mass and function in a rodent model of type 2 diabetes. *Diabetes* 2006;55:1695-1704.
[PUBMED](#) | [CROSSREF](#)
19. Fadini GP, Avogaro A, Degli Esposti L, Russo P, Saragoni S, Buda S, et al. Risk of hospitalization for heart failure in patients with type 2 diabetes newly treated with DPP-4 inhibitors or other oral glucose-lowering medications: a retrospective registry study on 127,555 patients from the Nationwide OsMed Health-DB Database. *Eur Heart J* 2015;36:2454-2462.
[PUBMED](#) | [CROSSREF](#)
20. Elgendy IY, Mahmoud AN, Barakat AF, Elgendy AY, Saad M, Abuzaid A, et al. Cardiovascular Safety of dipeptidyl-peptidase iv inhibitors: a meta-analysis of placebo-controlled randomized trials. *Am J Cardiovasc Drugs* 2017;17:143-155.
[PUBMED](#) | [CROSSREF](#)
21. Choe SA, Kim JY, Ro YS, Cho SI. Women are less likely than men to achieve optimal glycaemic control after 1 year of treatment: a multi-level analysis of a Korean primary care cohort. *PLoS One* 2018;13:e0196719.
[PUBMED](#) | [CROSSREF](#)
22. Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. *BMJ* 2006;332:73-78.
[PUBMED](#) | [CROSSREF](#)
23. Duarte FG, da Silva Moreira S, Almeida MD, de Souza Teles CA, Andrade CS, Reingold AL, et al. Sex differences and correlates of poor glycaemic control in type 2 diabetes: a cross-sectional study in Brazil and Venezuela. *BMJ Open* 2019;9:e023401.
[PUBMED](#) | [CROSSREF](#)
24. Camm AJ, Fox KA. Strengths and weaknesses of 'real-world' studies involving non-vitamin K antagonist oral anticoagulants. *Open Heart* 2018;5:e000788.
[PUBMED](#) | [CROSSREF](#)