Doctoral Thesis in

Failure of monotherapy in patients with type 2 diabetes: The Korean National Diabetes Program

Ajou University Graduate School

Department of Medical Sciences

Major in Medicine

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Failure of monotherapy in patients with type 2 diabetes: The Korean National Diabetes Program

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I submit this thesis as the Doctoral thesis in Medicine.

February, 2019

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The Doctoral thesis of Ja Young Jeon in Medicine is hereby approved.

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Ajou University Graduate School

December, 24, 2018

- ABSTRACT -

Failure of monotherapy in patients with type 2 diabetes: The Korean National Diabetes Program

Aims: We investigated the failure of monotherapy in patients with type 2 DM in real practice settings.

Methods: The Korea National Diabetes Program was a prospective, multicenter observational cohort study of type 2 DM patients in Korea. Of the 3,950 patients enrolled in the study, we studied 998 who were continuously maintained on monotherapy for at least 90 days at six participating centers. To balance the baseline characteristics of patients in each group, we employed propensity-matching at a 1:1 ratio (metformin vs. sulfonylureas) and 4:1 ratios (metformin vs. meglitinides and metformin vs. alpha-glucosidase inhibitors [aGIs]). The hazard ratios of treatments (compared with metformin) were determined via Cox's proportional hazards regression modeling.

Results: The median follow-up time was 56 months and monotherapy failed in 45% of all patients. The annual incidences of failure were 15.6%, 21.3%, 27%, and 9.6% in the metformin, sulfonylurea, meglitinide, and aGI groups. Compared with metformin, sulfonylureas and meglitinides were associated with higher risks of monotherapy failure (HR 1.39, CI 1.08–1.80; HR 1.92, CI 1.13–3.27) and aGIs with risk similar to that of metformin (HR 0.80, CI 0.44–1.45). When analyzed by failure type, sulfonylureas, meglitinides and aGIs were associated with a higher risk of a switch to other agents (HR 4.43, CI 2.14–9.17; HR 18.80, CI 6.21–56.93; HR 4.25 CI 1.49–12.13) and aGIs with a lower risk of prescription of add-on second agents (HR 0.16, CI 0.04–0.64).

Conclusions: Metformin was associated with a lower failure risk than were sulfonylureas and meglitinides, but a comparable aGI failure rate.

Keywords: cohort study, monotherapy failure, type 2 diabetes

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I. Introduction

The fundamental goal of type 2 diabetes mellitus (DM) treatment is to attain and maintain near-normal glucose levels to prevent the development of various diabetic complications. Current clinical guidelines recommend that the glycemic target in most patients be an HbA1c < 7% [1]. Currently, metformin is the preferred initial treatment, in combination with lifestyle management in combination with lifestyle management [2]. However, some patients are intolerant of and/or are not candidates for metformin therapy; other anti-diabetic drugs must thus be considered for them. Recently, individualized therapy has become popular, based on individual patient characteristics. Therefore, it is essential to compare the performances of various anti-hyperglycemic agents. It is important to define treatment durabilities; DM exhibits a chronic, progressive natural course during which blood glucose concentrations rise gradually over time [3,4]. Both features present early in the natural course of disease [6]. However, some differences in the pathophysiological contributions to DM development or course may exist among various populations or ethnic groups [7-12]. In particular, East Asians have limited β-cell function and are thus susceptible to type 2 DM [7, 8, 10, 11].

Although the pathophysiology of type 2 DM is complex, declines in insulin secretion and peripheral insulin resistance are the principal problems [5]. In patients who have been recently diagnosed or in whom the disease is of short duration, anti-hyperglycemic agents differing in terms of their mechanisms of action may show different treatment responses in various populations.

The UKPDS trial enrolling patients newly diagnosed with type 2 DM found that monotherapy failure increased over time [3]. Additional therapy was required by approximately 50% of patients by 3 years and 75% by 9 years. The representative Diabetes Outcome Progression Trial (ADOPT) explored the durabilities of three monotherapies [13]; rosiglitazone (thiazolidinedione) was the most durable therapy and

metformin (a biguanide) therapy was more durable than that with glyburide (a sulfonylurea). However, little data on monotherapy durabilities are available. Furthermore, data from Asian populations, and those obtained in real clinical practice, are very limited.

Therefore, we investigated monotherapy failure rates (including that of metformin) during a multicenter, observational cohort study performed in South Korea; we used propensity-score matching to compare durabilities.

II. Methods

A. Ethics statement

Our study protocol was approved by the institutional review boards of all participating hospitals and conformed to the ethical guidelines of the Declaration of Helsinki. All participants gave written informed consent.

B. Study design and participants

The Korea National Diabetes Program (KNDP) cohort study has been described previously [14]. In brief, the KNDP was a prospective, multicenter, observational cohort study enrolling patients with type 2 DM and those at risk of DM in South Korea. All patients were enrolled between May 2006 and December 2012 and followed up to December 2013. The type 2 DM cohort included patients ≥ 20 years of age who satisfied the 2004 diagnostic criteria of the American Diabetes Association. Of the 3,950 patients enrolled in the KNDP, the present study population consisted of 998 patients receiving continuous oral hypoglycemic agent monotherapy for at least 90 days in six KNDP centers. The index date was that of monotherapy commencement. The monotherapies were restricted to metformin, sulfonylureas, meglitinides and alpha-glucosidase inhibitors (aGIs). Patients prescribed thiazolidinedione or dipeptidyl peptidase-4 inhibitor monotherapies were excluded; their numbers were too small. Patients prescribed metformin, sulfonylureas, aGIs, and meglitinides numbered 666, 249, 49, and 34, respectively. The sulfonylureas were glimepiride and gliclazide (58% and 42%); the aGIs were voglibose and acarbose (65% and 35%); and the meglitinides were nateglinide, repaglinide, and mitiglinide (68%, 24%, and 9%). We used propensity-score matching to balance baseline characteristics (age, gender, body mass index, DM duration, glycated hemoglobin [HbA1c] level, and estimated glomerular filtration rate [eGFR]) among groups at a 1:1 ratio (metformin vs. sulfonylureas) and 4:1 ratios (metformin vs. meglitinides and metformin vs. aGIs).

C. Baseline variables

The baseline variables were based on the last values of the index dates. We recorded age, DM duration, body mass index, smoking status, systolic/diastolic blood pressure, diabetic complications, and comorbidities. After 12-h overnight fasts, the HbA1c, plasma glucose, serum creatinine, lipid, and insulin levels were measured at baseline and at every 3- or 6-month visits. Diabetic retinopathy was diagnosed by ophthalmologists, or via a history of photocoagulation or vitrectomy. Subjects with hypertension, as diagnosed by a physician or those taking anti-hypertensive medications, were classified as patients with hypertension. Similarly, dyslipidemia was defined as cases of having a history of dyslipidemia or taking lipid-lowering medications. Cardiovascular disease included any history of myocardial infarction, angina, heart failure, or an intervention triggered by coronary artery obstructive disease. Cerebrovascular disease included any history of ischemic or hemorrhagic stroke, or a transient ischemic attack. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation [15]. The homeostatic indices of insulin resistance (HOMA-IR) and β-cell function (HOMA-β) were also calculated [16]. The medication possession ratio (MPR) was the percentage of sum of days supply divided by the number of days in the evaluation period. An MPR >100% was scored as 100%.

D. Primary endpoint

The primary outcome was the time to monotherapy failure, defined as an HbA1c level ≥ 7.5%, a switch to another anti-DM agent, or add-on of another agent.

E. Statistical analyses

Continuous variables are presented as means ± standard deviations (SDs); Student's *t*-test was used for comparisons. Categorical variables are presented

as numbers with percentages; the chi-squared (χ^2) or Fisher's exact test was used to compare the two groups. Monotherapy failure rates were calculated as the ratios of incident case numbers to the person-years of the entire study population. To minimize bias, group baseline characteristics were balanced via propensity-scorematching using a 1:1 ratio for metformin to sulfonylureas, and 4:1 ratios of metformin to both aGIs and meglitinides, prior to survival analysis. We matched age, sex, body mass index, DM duration, HbA1c level, and eGFR. We next ensured that that the covariates were balanced using the chi-squared or Fisher's exact test for categorical variables and Student's *t*-test for continuous variables. Monotherapy failure curves were plotted employing the Kaplan-Meier method and compared using the log-rank test. We performed Cox's proportional hazard regression (after propensity-score matching) to derive hazard ratios for monotherapy failure. A two-sided p-value < 0.05 was considered to reflect statistical significance. All data were analyzed using SPSS (version 23.0; SPSS Inc., Chicago, IL, USA) and R (R version 3.3.2; R Foundation for Statistical Computing; Vienna, Austria; http://www.R-project.org/) software packages.

III. Results

A. Baseline patient characteristics

The median (interquartile range [IQR]) follow-up duration was 56.1 (34.4–70.2) months for all patients, of whom approximately 45% (454/998) exhibited monotherapy failure (17% per year; Table 1 and Table 2). The annual monotherapy failure rates were 15.6%, 21.3%, 27%, and 9.6% for metformin, sulfonylureas, meglitinides, and aGIs, respectively (HR 1.35 [95% CI, 1.10–1.66], HR 1.64 [95% CI, 1.04–2.58], and HR 0.61 [0.35–1.06] when sulfonylureas, meglitinides, and aGIs were compared with metformin, respectively). The mean (SD) age and DM duration were 55.6 (9.8) years and 5.4 (5.1) years, respectively. The mean baseline HbA1c level was 6.9% (0.9) and the MPR 88.5%. Figure 1 and table 3 showed mean HbA1c levels during follow-up period. About 5% of all patients had histories of diabetic retinopathy and 4.5% and 5.7% had previously been diagnosed with coronary artery disease and cerebrovascular disease, respectively.

Table 1. Demographic data and baseline characteristics of all study patients.

	Total (n=998)
Age (years)	55.6±9.8
Female/male, n (%)	411/587 (41/59)
Weight (kg)	67.6±10.6
Body mass index (kg/m^2)	25.3±3.0
Duration of diabetes (years)	5.4±5.1
Smoking (current/past/never, %)	18/31/52
Systolic BP (mmHg)	125±15
Diastolic BP (mmHg)	78±10
HbA1c (%)	6.9±0.9
Glucose (mg/dL)	132±28
Creatinine (mg/dL)	0.9±0.3
eGFR (mL/min/1.73 m^2)	80±20.0
Total cholesterol (mg/dL)	181±37
Triglyceride (mg/dL)	162±103
HDL cholesterol (mg/dL)	50±12
LDL cholesterol (mg/dL)	101±30
Insulin (μIU/mL)	9.4±7.2
Medication use rate (%)	88.5
Comorbidities	
Hypertension (%)	47
Dyslipidemia (%)	41
Retinopathy (%)	4.9
Coronary artery disease (%)	4.5

Cerebrovascular disease (%)	5.7
Total failure (%, 100 person-years)	45.4/17.0

Values are presented as means ± standard deviations or as numbers (with %).

Table 2. Demographic data and baseline characteristics of all study patients by monotherapy groups.

	MET	SU	aGI	GLI	p-value
n	666	249	49	34	
Subtype (%)		58/42/0	65/35	68/24/9	
Age (yrs)	54.1±9.4	58.9±9.4*	56.7±10.0	59.8±11.8*	<0.001¶
Female (n, %)	41.3	42.2	34.7	41.2	0.812‡
Weight (kg)	68.5±10.9	66.7±9.9	62.3±7.5*	64.2±9.9	<0.001¶
Body mass index (kg/m^2)	25.5±3.0	25.0±2.9	23.5±2.3*	24.8±2.7	<0.001¶
Duration of DM (yrs)	4.6±4.8	7.4±5.5*	5.9±4.6	6.0±5.9	<0.001¶
Smoking (current/past/never, %)	19/31/50	15/28/57	20/35/46	19/25/56	0.547‡
Systolic BP (mmHg)	124.7±14.5	124.6±15.0	123.0±14.7	123.1±14.8	0.816¶
Diastolic BP (mmHg)	78.3±9.3	78.3±10.2	78.2±9.6	77.1±11.0	0.919¶
HbA1c	6.9±1.0	6.9±0.9	6.5±0.6*	6.8±0.7	<0.001¶
Glucose (mg/dL)	131.4±27.1	132.6±33.4	130.0±22.3	137.0±24.7	0.588¶
Creatinine (mg/dL)	0.9±0.3	1.0±0.2*	0.9±0.2	1.2±0.8	0.001¶
eGFR (mL/min/1.73 m^2)	82.8±18.8	73.9±21.1*	79.5±18.6	70.5±21.8*	<0.001¶
Total cholesterol (mg/dL)	183.9±37.3	176.5±35.4*	169.9±38.3	179.3±40.6	0.007¶

Triglyceride (mg/dL)	163.2±106.2	161.2±84.9	139.2±125.1	190.6±121.6	0.165¶
HDL cholesterol (mg/dL)	49.1±11.1	52.6±12.4*	55.3±13.5*	48.0±12.6	<0.001¶
LDL cholesterol (mg/dL)	101.9±30.7	98.9±28.4	91.9±29.4	105.3±26.6	0.077¶
Insulin (uIU/ml)	9.8±7.8	8.9±5.0	8.6±8.5	8.2±5.0	0.266¶
HOMA-IR	3.2±2.7	2.9±1.8	2.8±2.5	3.0±2.0	0.499¶
HOMA-B	59.1±55.1	56.0±41.7	53.2±73.6	45.0±25.0	0.481¶
Medication use rate (%)	88.0±17.8	93.7±16.4*	86.9±20.4	94.9±13.2*	<0.001¶
Complications					
Retinopathy (%)	3.2	8.4	4.1	14.7	0.001†
Nephropathy (%)	0.2	1.6	2.0	2.9	0.008†
Comorbidities					
Hypertension (n, %)	44.6	54.6	40.8	52.9	0.036‡
Dyslipidemia (%)	40.5	44.6	40.8	23.5	0.129‡
Coronary artery disease (%)	3.8	7.2	4.1	0.0	0.098†
Cerebrovascular disease (%)	4.7	8.8	2.0	8.8	0.048†

Values are presented as means ± standard deviations or as numbers (with %). Subtype means; SUs are composed of glimepiride, gliclazide, and glipizide (%), aGIs are composed of voglibose and acarbose (%), and GLIs are composed of

nateglinide, repaglinide, and mitiglinide (%).¶, ‡, and † performed ANOVA test, Chi-squared test, and Fisher's exact test, respectively. * $p<0.05$ vs. MET.

MET, metformin; SU, sulfonylurea; aGI, alpha-glucosidase inhibitor; GLI, meglitinide; eGFR, estimated glomerular filtration rate; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-B, homeostasis model assessment of β-cell function.

Table 3. Mean HbA1c levels in total population during follow-up period

	MET	SU	aGI	GLI
Hba1c_bs	6.90±0.91	6.88±0.95	6.47±0.56	6.83±0.69
Hba1c_yr1	6.83±0.79	6.89±0.89	6.48±0.55	6.65±0.62
Hba1c_yr2	6.86±0.77	6.86±0.88	6.50±0.62	6.63±0.74
Hba1c_yr3	6.91±0.80	6.94±0.78	6.62±0.75	6.71±0.68

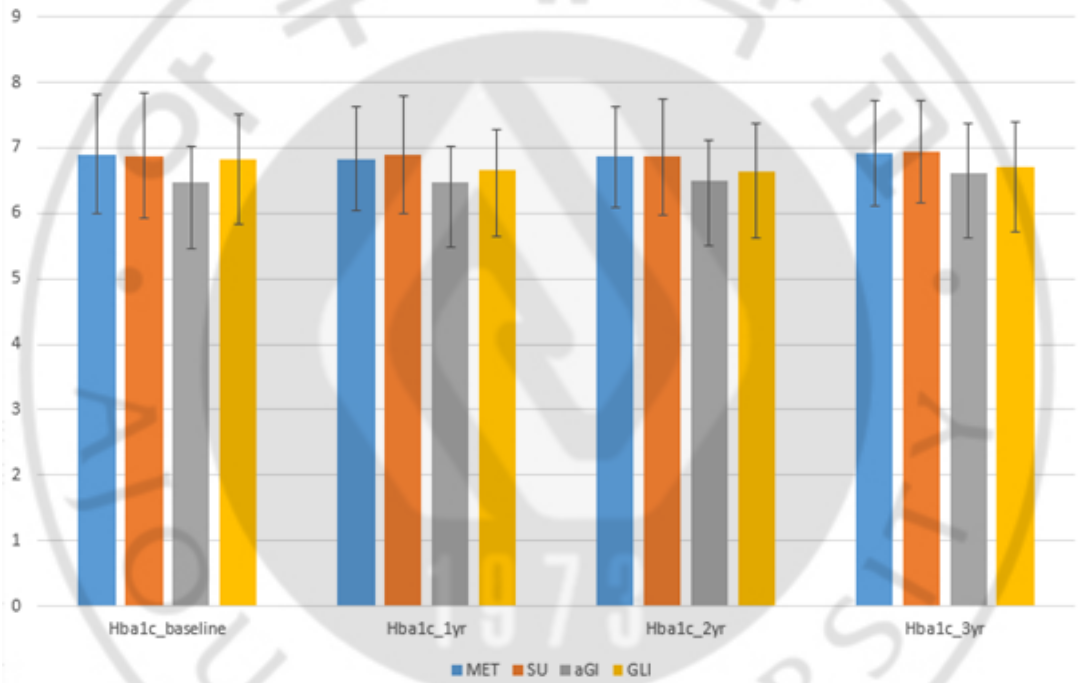

Figure 1. Mean HbA1c levels in total population during follow-up period

After 1:1 propensity-score matching of patients taking metformin and sulfonylureas (247:247); and 4:1 matching of those taking metformin and meglitinides (128:32) and metformin and aGIs (196:49), most baseline characteristics were balanced (Table 3), although the sulfonylurea group had higher fasting glucose and HDL levels; and the meglitinide group had a higher MPR, a lower HOMA-B score, and fewer diagnoses of dyslipidemia; aGI groups had lower total cholesterol and higher HDL levels, compared with the metformin group. Figure 2, 3, and 4 (Table 4, 5, and 6) showed mean HbA1c levels between propensity-score matching groups during follow-up period.

Table 4. Mean HbA1c levels in patients taking metformin and sulfonylureas after propensity-score matching during follow-up period

	MET	SU
Hba1c_bs	6.80±0.96	6.89±0.95
Hba1c_yr1	6.73±0.78	6.89±0.89
Hba1c_yr2	6.79±0.77	6.86±0.88
Hba1c_yr3	6.80±0.72	6.94±0.79

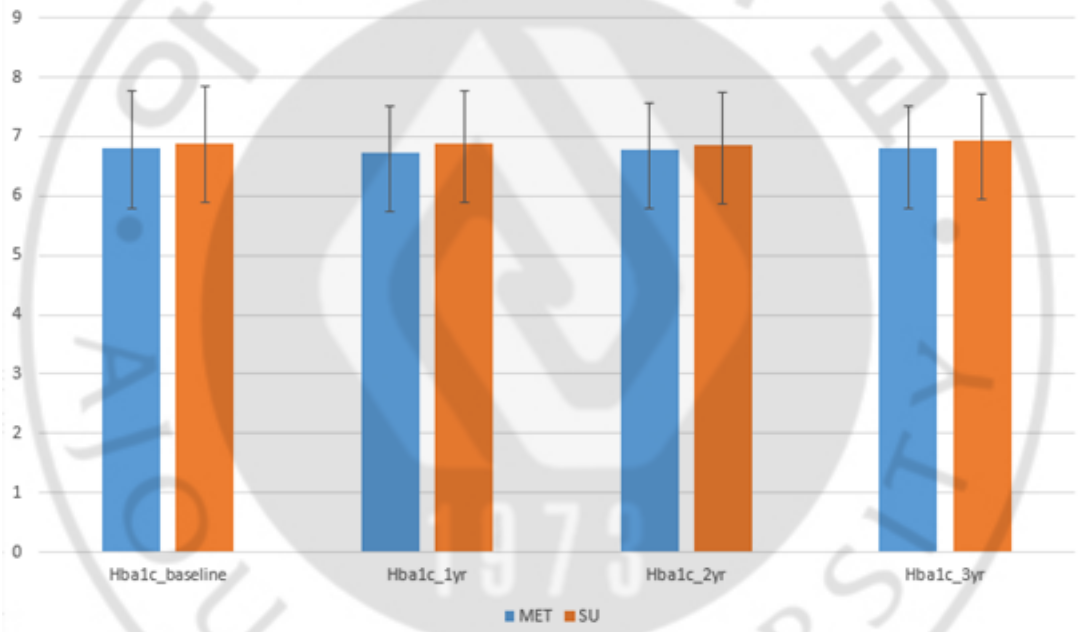

Figure 2. Mean HbA1c levels in patients taking metformin and sulfonylureas after propensity-score matching during follow-up period

Table 5. Mean HbA1c levels in patients taking metformin and meglitinides after propensity-score matching during follow-up period

	MET	GLI
Hba1c_bs	6.72±0.80	6.83±0.69
Hba1c_yr1	6.69±0.68	6.65±0.62
Hba1c_yr2	6.79±0.69	6.63±0.74
Hba1c_yr3	6.76±0.67	6.71±0.68

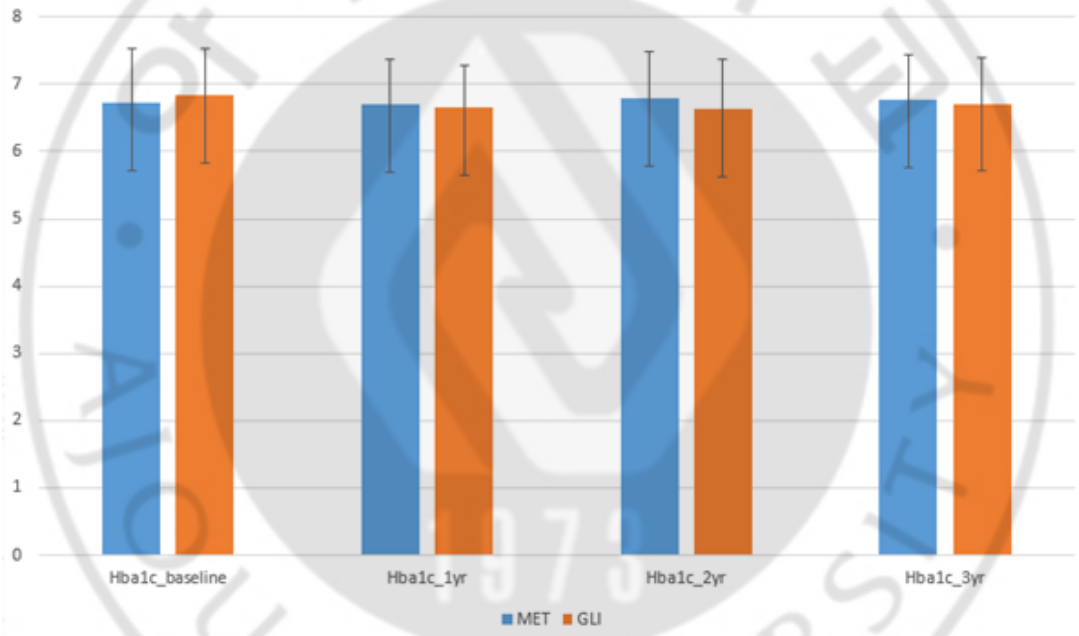

Figure 3. Mean HbA1c levels in patients taking metformin and meglitinides after propensity-score matching during follow-up period

Table 6. Mean HbA1c levels in patients taking metformin and alpha-glucosidase inhibitors after propensity-score matching during follow-up period

	MET	aGI
Hba1c_bs	6.80±0.96	6.47±0.56
Hba1c_yr1	6.70±0.75	6.48±0.55
Hba1c_yr2	6.74±0.81	6.50±0.62
Hba1c_yr3	6.73±0.67	6.62±0.75

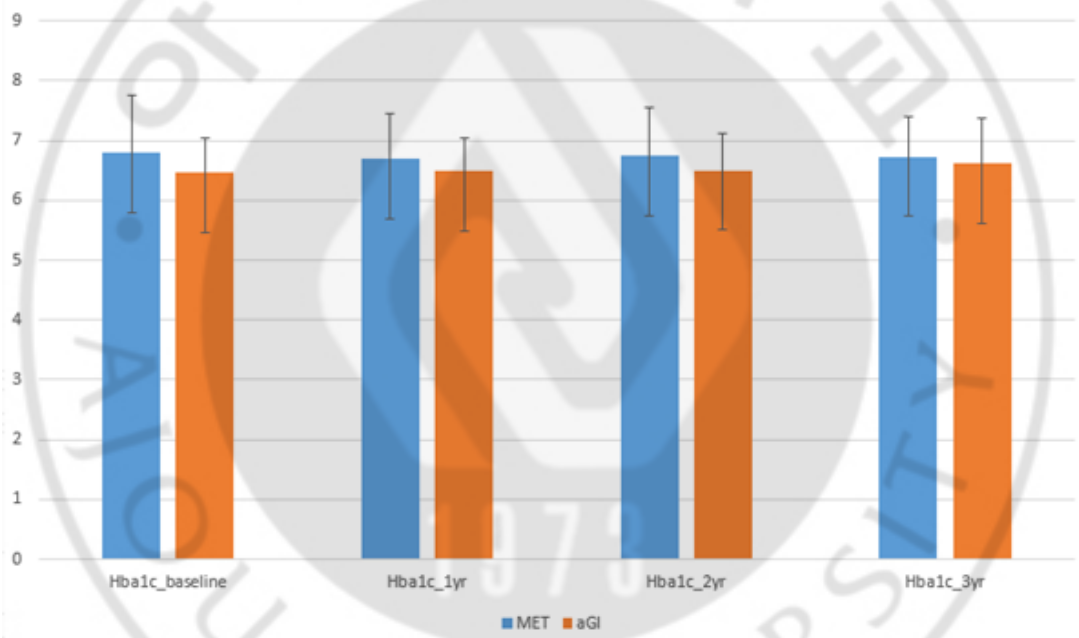

Figure 4. Mean HbA1c levels in patients taking metformin and alpha-glucosidase inhibitors after propensity-score matching during follow-up period

Table 7. Demographic data and baseline characteristics of all patients after propensity-score matching.

	MET versus SU			MET versus GLI			MET versus aGI		
	MET	SU	p-value	MET	GLI	p-value	MET	aGI	p-value
Number	247	247		128	32		196	49	
Age (years)	59.1±8.1	58.9±9.4	0.786	59.5±8.7	59.7±11.9	0.901	57.1±8.9	56.7±10.0	0.791
Female (n, %)	40.9	42.1	0.784	45.3	40.6	0.633	36.2	34.7	0.842
Weight (kg)	65.7±9.9	66.7±9.9	0.234	66.2±10.9	64.6±9.9	0.447	63.3±9.7	62.3±7.5	0.431
Body mass index (kg/m^2)	24.9±2.9	25.1±2.9	0.644	25.0±2.7	24.9±2.6	0.849	23.6±2.4	23.5±2.3	0.808
Duration of diabetes (years)	6.8±5.5	7.4±5.5	0.230	5.3±6.2	5.7±5.7	0.736	5.9±5.9	5.9±4.6	0.989
Smoking (current/past/never, %)	12/36/52	15/28/57	0.185	17/36/48	19/25/56	0.516	18/36/46	20/35/46	0.968
Systolic BP (mmHg)	126±15	125±15	0.291	124±13	123±15	0.726	125±15	123±15	0.499
Diastolic BP (mmHg)	78±9	78±10	0.654	78±10	77±11	0.681	77±9	78±10	0.454
HbA1c (%)	6.9±0.9	6.9±0.9	0.867	6.8±0.9	6.8±0.7	0.717	6.5±0.6	6.5±0.6	0.670
Glucose (mg/dL)	127±24	133±34	0.039	126±28	135±23	0.112	124±24	130±22	0.095

Creatinine (mg/dL)	0.9±0.2	1.0±0.2	0.093	1.0±0.3	1.1±0.8	0.367	0.9±0.2	0.9±0.2	0.959
eGFR (mL/min/1.73 m^2)	75.9±17.3	73.9±21.1	0.259	72.8±15.7	72.0±20.2	0.815	79.3±17.7	79.5±18.6	0.961
Total cholesterol (mg/dL)	179±35	176±36	0.363	186±37	180±42	0.456	182±37	170±38	0.040
Triglyceride (mg/dL)	157±104	161±85	0.590	178±125	195±124	0.475	152±98	139±125	0.441
HDL cholesterol (mg/dL)	50±11	53±12	0.016	48±10	49±12	0.889	49±12	55±14	0.001
LDL cholesterol (mg/dL)	100±30	99±29	0.622	99±28	105±27	0.324	101±30	92±29	0.051
Insulin (μIU/mL)	9.2±6.6	8.9±5.0	0.642	10.5±7.0	7.9±4.8	0.059	8.0±5.6	8.6±8.5	0.601
HOMA-IR	2.9±2.3	2.9±1.8	0.991	3.4±2.7	2.8±1.8	0.276	2.5±2.0	2.8±2.5	0.359
HOMA-B	58.2±48.3	56.1±41.8	0.637	66.8±48.1	45.1±25.5	0.002	53.5±38.1	53.2±73.6	0.971
Medication use rate (%)	88.7±16.1	91.6±13.0	0.032	89.3±15.9	93.9±9.9	0.045	89.1±16.2	85.9±19.1	0.225
Hypertension (%)	52.2	54.7	0.588	53.1	50.0	0.752	42.9	40.8	0.796
Dyslipidemia (%)	39.7	44.9	0.236	48.4	21.9	0.007	34.2	40.8	0.386
Retinopathy (%)	4.5	8.5	0.068	3.9	12.5	0.080	3.1	4.1	0.662
Coronary artery disease (%)	4.5	7.3	0.180	5.5	0.0	0.346	3.1	4.1	0.662
Cerebrovascular disease (%)	6.1	8.9	0.232	4.7	9.4	0.385	3.6	2.0	>0.999

Values are presented as means ± standard deviations or as numbers (with %).

MET, metformin; SU, sulfonylurea; aGI, alpha-glucosidase inhibitor; GLI, meglitinide; eGFR, estimated glomerular filtration rate; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-B, homeostasis model assessment of β-cell function

B. Monotherapy failures in each treatment group

When monotherapy failure rates were compared after propensity-score matching (Table 7), the sulfonylurea and meglitinide groups had higher failure rates and the aGI group had a similar failure rate compared with the metformin group (Figure 5; $p = 0.011$, Figure 6; $p = 0.014$, and Figure 7; $p = 0.465$, respectively). The monotherapy failure rates of the sulfonylurea and meglitinide groups did not differ significantly.

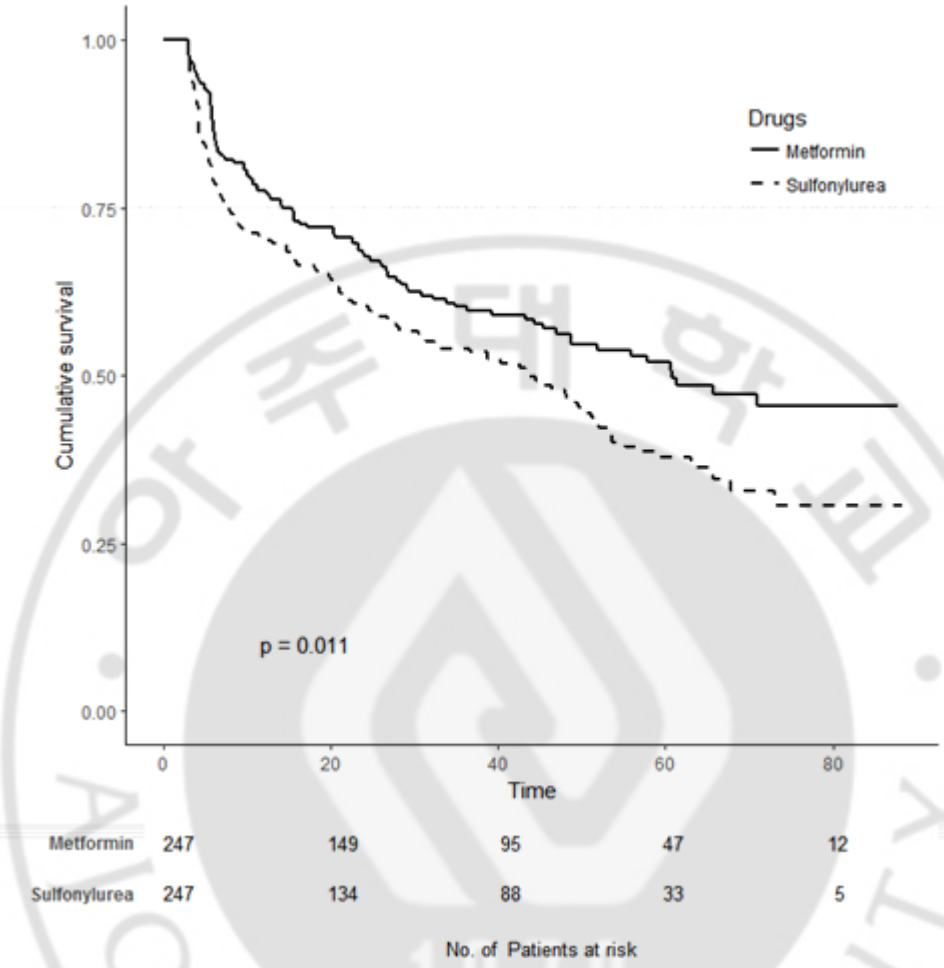

Figure 5. Kaplan-Meier curve of monotherapy failure after propensity-score matching (metformin vs. sulfonylureas)

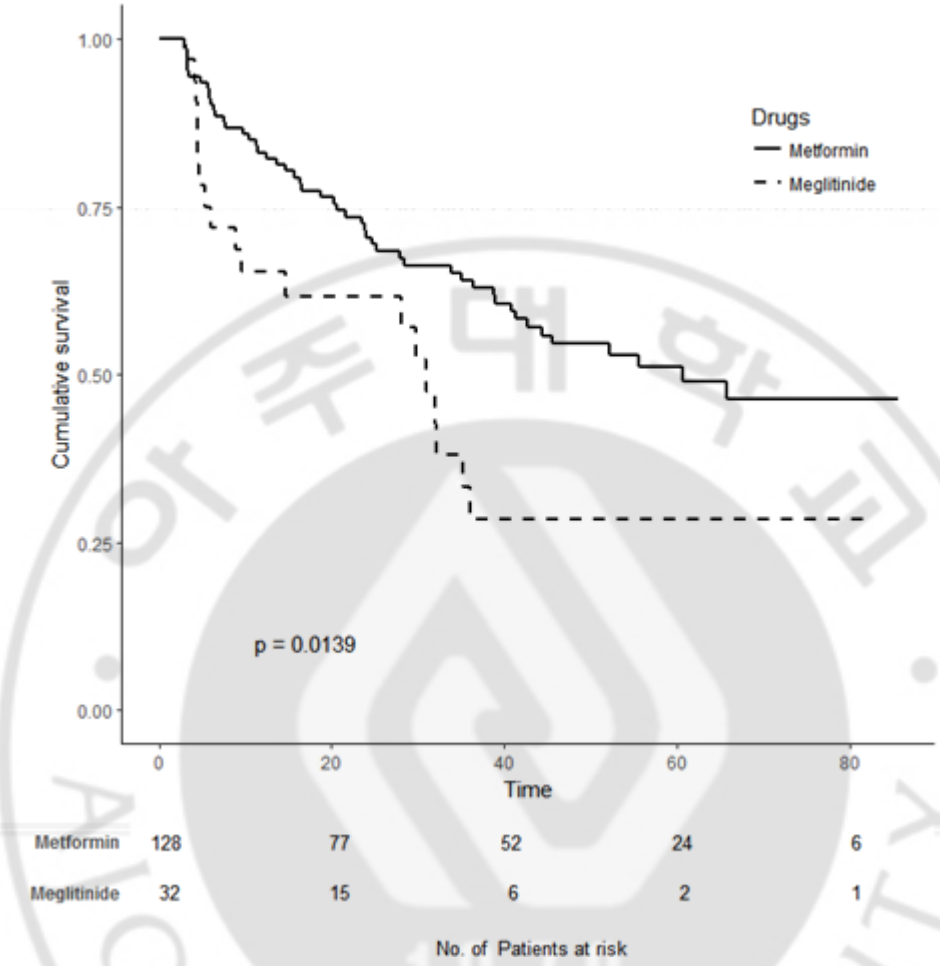

Figure 6. Kaplan-Meier curve of monotherapy failure after propensity-score matching (metformin vs. meglitinides)

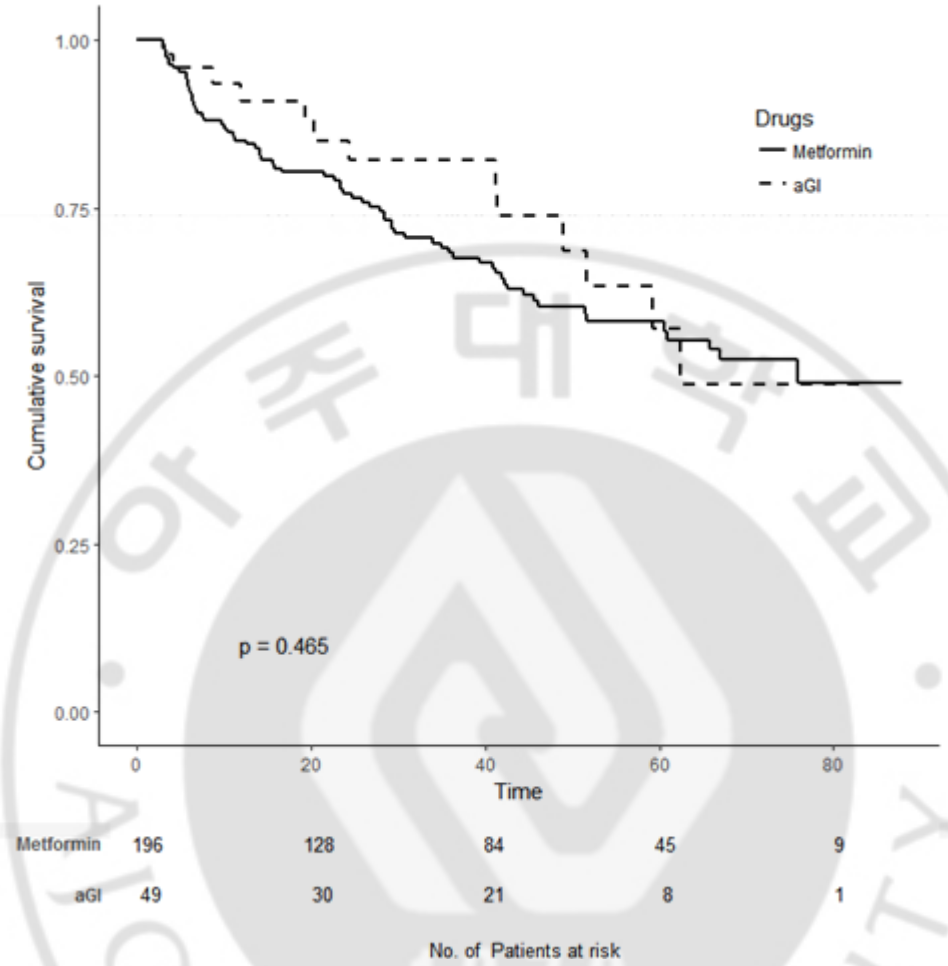

Figure 7. Kaplan-Meier curve of monotherapy failure after propensity-score matching (metformin vs. alpha-glucosidase inhibitors)

Monotherapy failure was defined as attainment of an HbA1c level ≥ 7.5%, a switch to another anti-diabetic agent, and/or add-on treatment. By failure subtype, sulfonylurea failures often switched to other anti-diabetic agents compared with the metformin group (Table 8; HR 4.43 [95% CI, 2.14–9.17]). As was true of the sulfonylurea group, meglitinide patients were switched more often to other anti-diabetic agents than were metformin patients (HR 18.8 [95% CI, 6.21–56.93]).
Add-on treatment failure was less common in the aGI than in the metformin group, although overall failure in the aGI group did not differ significantly from that in the metformin group (HR 0.16 [95% CI, 0.04–0.64]). After monotherapy failure, switched or added anti-diabetic agents are described in Table 9.

Table 8. Subtype failure of Monotherapy failure after propensity-score matching.

Drugs	Type of failure	Events (%)	HR (95% CI)*	p-value
SU vs. MET	Overall	53.4 vs. 42.1	1.39 (1.08 to 1.80)	0.011
	Switch	15.0 vs. 3.6	4.43 (2.14 to 9.17)	<0.001
	Add-on	36.4 vs. 32.8	1.23 (0.91 to 1.66)	0.177
	HbA1c >7.5%	20.6 vs. 15.0	1.48 (0.97 to 2.26)	0.069
GLI vs. MET	Overall	59.4 vs. 39.8	1.92 (1.13 to 3.27)	0.015
	Switch	46.9 vs. 3.1	18.80 (6.21 to 56.93)	<0.001
	Add-on	0.9 vs. 33.6	0.37 (0.11 to 1.20)	0.096
	HbA1c >7.5%	21.9 vs. 10.9	2.16 (0.87 to 5.37)	0.096
aGI vs. MET	Overall	26.5 vs. 35.7	0.80 (0.44 to 1.45)	0.467
	Switch	14.3 vs. 3.6	4.25 (1.49 to 12.13)	0.007
	Add-on	4.1 vs. 28.6	0.16 (0.04 to 0.64)	0.010
	HbA1c >7.5%	10.2 vs. 8.7	1.17 (0.43 to 3.18)	0.752

HR, hazard ratio; CI, confidence interval; SU, sulfonylurea; MET, metformin; GLI, meglitinide; aGI, alpha glucosidase inhibitor

* Hazard ratio for monotherapy failure of an SU, aGI, or GLI compared with MET.

Table 9. Medications switched or added from original monotherapy

Drugs	Type of failure	Events (%)	Switching (adding) drugs	Events (%)
MET	Switch	3.9	insulin	2.6
			others	1.3
	Add-on	34.7	DPPIV inhibitor	19.4
			SU	11.1
			others	4.2
SU	Switch	14.9	MET + DPPIV inhibitor	4.8
			insulin	4
			DPPIV inhibitor	3.2
			others	2.8
	Add-on	36.5	MET	17.1
			aGI	12
			others	7.4
GLI	Switch	47.1	SU + MET	17.6
			MET + DPPIV inhibitor	8.8
			SU	8.8
			others	11.9
	Add-on	8.8	MET	8.8
aGI	Switch	14.3	DPPIV inhibitor	6.1
			SU	4.1
			others	4.1
	Add-on	4.1	SU	4.1

MET, metformin; SU, sulfonylurea; aGI, alpha glucosidase inhibitor; GLI, meglitinide

IV. Discussion

The KNDP was a prospective, multicenter, observational, South Korean cohort study. Of these, our study patients had been recently diagnosed with type 2 DM, were obese (BMI ≥25 kg/m^2), and exhibited good MPRs; a few patients had diabetic complications. Overall, the annual monotherapy failure rate was 17%; attaining 40% at 3 years and 60% at 6 years. To the best of our knowledge, this is the first report of monotherapy failure in South Korea. The failure rate was somewhat lower than that of the UKPDS trial [17], which employed stricter failure cut-offs (an HbA1c level > 7% or a fasting plasma glucose level > 140 mg/dL). Compared with the ADOPT trial, the annual monotherapy failure rates of our present study were threefold higher (15.6% vs. 4.3% in the metformin group; 21.3% vs. 7.5% in the sulfonylurea group) [13]. The study designs differed significantly. Although the primary ADOPT cut-off levels, determined by reference to consecutive fasting plasma glucose levels > 180 mg/dL, may be somewhat less rigid than ours (an HbA1c level > 7.5%), monotherapy failure, reflected in a switch to or addition of other anti-diabetic agents, may develop before the fasting plasma glucose level attains 180 mg/dL, to afford better glycemic control. In the ADOPT trial, most withdrawals (12%–15%) were attributable to adverse drug events and were included in the analysis, but this was not counted as the monotherapy failure. As the ADOPT was a clinical trial, the participants would have been better motivated than those of our observational cohort study reflecting real clinical practice. Our patients exhibited a somewhat longer DM duration than those of the ADOPT trial which the time since DM diagnosis was < 2 years in most participants. This difference may increase the incidence of monotherapy failure in our study. An observational Swedish study of monotherapy durability reported that failure of sulfonylurea, meglitinide, and metformin monotherapies rose to almost 50% by 5.5 years [18]. Analysis of health care

databases in the United States revealed that the annual, metformin, monotherapy failure rate was 17% [19]. The results of both studies were comparable to our findings.

This study consisted of patients taking one oral hypoglycemic agent for 90 days or longer. So, this study included non-responders who did not show an initial good response or did not tolerate a specific monotherapy. These patients were presented as rapid initial failure of the Kaplan-Meier curve in the metformin vs. sulfonylurea group and the metformin vs. meglitinide group. In comparison between metformin and sulfonylurea group, early non-responders with a monotherapy duration of less than 6 months had longer diabetes duration and higher baseline HbA1c levels than responders (data not shown). In comparison between metformin and meglitinide group, early non-responders in meglitinide group also showed higher baseline HbA1c levels than responders (data not shown). These, such as long diabetes duration and high HbA1c levels might be predictive factors for long-term durability and considerable factor for choice of anti-hyperglycemic agents [19, 20].

Metformin was associated with a lower incidence of monotherapy failure than were either sulfonylureas or meglitinides when both total cohort and propensity score-matched data were analyzed. As we expected, those prescribed metformin among all 998 study patients were younger, more obese, had DM of shorter duration, and fewer comorbidities, than those prescribed sulfonylureas or meglitinides. When baseline characteristics were balanced using propensity-score matching, the risks of monotherapy failure in those given sulfonylureas and meglitinides were 40%–90% higher than that of the metformin group. Switching from one drug to another drug does not always mean poor glucose-lowering effects of the original drug. Monotherapy subtype failure (indicated by a switch to other agents) was significantly higher in both the sulfonylurea and the meglitinide groups than in the metformin group, consistent with the data of a previous report [18]. In the sulfonylurea group, switching to another monotherapy rather than combination treatment or insulin treatment was more common compared with the metformin group. That is, adverse

drug reactions of sulfonylurea, such as hypoglycemia and weight gain, may be a considerable factor of high rate of switching failure. Lower β cell function is related to treatment failure [17]. In comparison between the metformin and meglitinide group, the meglitinide group had lower HOMA-B than the metformin group. This may be a confounding factor and influence the high rate of monotherapy failure in the meglitinide group. Progressive glycemic deterioration is associated with loss of β-cell function [13]. Metformin may retard β-cell dysfunction; pharmacologically, metformin increases insulin sensitivity and reduces the workload imposed on pancreatic β cells. *In vitro*, metformin protected pancreatic β cells, while sulfonylureas did not [21-23]. East Asians exhibit lower β-cell function than do other ethnic groups, and lack the ability to induce early-stage compensatory hyperinsulinemia during DM development [8, 24]. To overcome β-cell dysfunction, insulin secretagogues, such as sulfonylureas and meglitinides, can be the preferred drugs for East Asians. However, when the preservation of β-cell function and the durability of anti-diabetic drugs are prioritized, monotherapy using insulin secretagogues may fail more rapidly in South Koreans with type 2 DM than in Western populations. Comparison studies in East Asians showed that sulfonylureas rapidly and effectively lowered HbA1c levels more than did than metformin, but only for several months [25, 26]. However, the HR for monotherapy failure of insulin secretagogues in South Koreans was no higher than that of the Swedish cohort.

Clinicians have to determine the next steps, such as change or the adding of anti-hyperglycemic agents, after monotherapy failure due to progressive nature of the disease. To view cases with monotherapy failure in our data, especially focused on metformin or sulfonyluea treatment groups, major further treatment option was combination therapy by adding another anti-hyperglycemic agent or switching to dual therapy. According to current guidelines, there are several options of dual therapy when monotherapy failed [2, 27]. In our data, metformin plus sulfonylurea and metformin plus DPPIV inhibitor were most common. These are reflecting

prescription trends of anti-hyperglycemic agents in Korea [28]. Metformin plus sulfonylurea is the traditional combination therapy. Metformin's position as a first-line treatment and cornerstone of combination therapy may be solid. Sulfonylureas are still commonly used due to a comparatively higher efficacy and lower cost, although sulfonylureas have a short time to failure, high risk of hypoglycaemia, and weight gain. Otherwise, DPPIV inhibitors become a widespread anti-hyperglycemic agent due to favorable safety profiles. However, the ideal combination therapy can differ according to patient's factors; thus, the pros and cons of anti-hyperglycemic drugs should be well considered. Most current guidelines recommend individualized therapy in patient with diabetes.

To the best of our knowledge, this is the first report on aGI monotherapy failure in clinical practice. In present study, aGI group had a similar failure rate compared with the metformin group. Although compliance with aGI regimens is poor (attributable to gastrointestinal side effects and the need for frequent doses), this class of drugs is optimal DM treatment for South Koreans who consume high levels of carbohydrates [29, 30]. AGIs reduce plasma glucose levels by delaying digestion and absorption of consumed carbohydrates; aGIs exert no direct effect on insulin secretion. Both metformin and acarbose delayed the progression from prediabetes to DM [31]. The similarity of durability in both drugs could be associated with the effects on preventing diabetes and mechanisms of action with no direct effects on insulin secretion. Additionally, we found that aGIs had significantly lower add-on failure rate than did metformin, although overall monotherapy failure was comparable.

Unfortunately, we can offer no data on monotherapies using DPPIV inhibitors or thiazolidinediones; patient numbers were too small. DPPIV inhibitors were introduced in South Korea only in 2011 and thiazolidinedione prescriptions have fallen rapidly in number since 2007.

Our study had certain limitations. The numbers of patients on aGI or meglitinide monotherapies were relatively small compared to the numbers given metformin or sulfonylureas, reflecting current prescription practices [28]. We did not explore within-class drug durabilities. Physicians prescribed each drug base on patient's characteristics; selection bias may have been in play. Although we matched several baseline characteristics, we may not have identified all possible confounding factors.

V. Conclusions

In conclusion, the annual overall monotherapy failure rate was 17% in South Koreans with type 2 DM enrolled in the KNDP cohort study. Using propensity-score matching, we found that metformin was associated with a lower risk of monotherapy failure than were sulfonylureas and meglitinides; the failure rates of metformin and aGIs were comparable. Our data will aid in the choice of appropriate treatment for patients with type 2 DM.

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- 국문요약 -

제2형 당뇨병 환자에서 경구혈당강하제 단독요법 실패율

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목적

본 연구는 실제 임상현장에서 2형 당뇨병 환자의 경구혈당강하제 단독요법의 실패율을 비교분석해 보고자 하였다.

방법

Korean National Diabetes Program (KNDP) 은 제2형 당뇨병 환자를 대상으로 시행된 전향적, 다기관 관찰연구이다. 본 연구는 KNDP 에 모집된 3950명의 환자 중에서 최소 90일 이상 단독요법을 지속적으로 시행받은 998명을 대상으로 하였다. 각각의 단독요법을 시행받은 군의 기본 특성을 맞추기 위하여 메트포르민 단독요법군과 설폰요소제 단독요법군은 1대1 비율로, 메트포르민 단독요법군과 메글리티나이드 단독요법군은 4대1 비율로, 메트포르민 단독요법군과 글루코시데이트 억제제 단독요법군은 4대 1의 비율로 성향점수 매칭(propensity-score matching)을 이용하였다. 각 단독요법군의 치료 실패율을 비교하기 위하여 Cox 비례위험모형을 이용하여 분석하였다.

결과

추적관찰 기간의 중앙값은 56개월이었고 대상환자의 45%에서 단독요법 실패를 경험하였다. 각 단독요법의 연간 치료 실패율은 메트포르민 단독요법군

에서는 15.6%, 설폰요소제 단독요법군에서는 21.3%, 메글리티나이드 단독요법군에서는 27%, 그리고 글루코시데이즈 억제제 단독요법군에서는 9.6% 를 보였다. 메트포르민 단독요법군과 비교시 설폰요소제 단독요법군과 메글리티나이드 단독요법군은 치료 실패율이 의미있게 높았고 (HR 1.39, 95% CI 1.08-1.80; HR 1.92, 95% CI 1.13-3.27) 글루코시데이즈 억제제 단독요법군의 치료 실패율은 비슷하였다 (HR 0.80, 95% CI 0.11-1.45). 치료 실패유형에 따라 구분하였을 때, 메트포르민 단독요법군에 비하여 설폰요소제 단독요법군, 메글리티나이트 단독요법군과 글루코시데이즈 억제제 단독요법군은 다른 약제로의 변경이 많았고 (HR 4.43, CI 2.14-9.17; HR 18.80, CI 6.21-56.93; HR 4.25 CI 1.49-12.13) 글루코시데이즈 억제제는 이차약제 추가하는 경우가 적었다 (HR 0.16, CI 0.04-0.64).

결론

메트포르민 단독요법은 설폰요소제 단독요법 및 메글리티나이트 단독요법에 비하여 치료 실패율이 낮았고 글루코시데이즈 억제제의 치료 실패율과는 유사하였다.

주제어: 코호트 연구, 경구혈당강하제 단독요법 실패율, 2형 당뇨병