ORIGINAL ARTICLE

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

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ABSTRACT

Aims/Introduction: We investigated the failure of monotherapy in patients with type 2 diabetes mellitus in real practice settings.

Materials and Methods: The Korean National Diabetes Program was a prospective, multicenter observational cohort study of type 2 diabetes mellitus 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 used propensity matching at a 1:1 ratio (metformin vs sulfonylureas) and 4:1 ratio (metformin vs meglitinides and metformin vs alpha-glucosidase inhibitors [aGIs]). The hazard ratios (HRs) of treatments (compared with metformin) were determined by 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, 95% confidence interval [CI] 1.08–1.80; HR 1.92, 95% CI 1.13–3.27), and aGIs with risks similar to that of metformin (HR 0.80, 95% 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, 95% CI 2.14–9.17; HR 18.80, 95% CI 6.21–56.93; HR 4.25, 95% CI 1.49–12.13), and aGIs with a lower risk of prescription of add-on second agents (HR 0.16, 95% 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.

INTRODUCTION

The fundamental goal of type 2 diabetes mellitus treatment is to attain and maintain near-normal glucose levels to prevent the development of various diabetic complications. The current clinical guidelines recommend that the glycemic target in most patients be a glycated hemoglobin (HbA1c) level <7%[1]. Currently, metformin is the preferred initial treatment, in combination with lifestyle management[2]. However, some patients are intolerant of and/or are not candidates for metformin therapy;

other antidiabetic 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 antihyperglycemic agents. It is important to define treatment durabilities; type 2 diabetes mellitus shows a chronic, progressive natural course, during which blood glucose concentrations rise gradually over time[3,4].

Although the pathophysiology of type 2 diabetes mellitus is complex, declines in insulin secretion and peripheral insulin resistance are the principal problems[5]. Both features present early in the natural course of the disease[6]. However, some

differences in the pathophysiological contributions to diabetes mellitus development or course might 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 diabetes mellitus[7,8,10,11]. In patients who have been recently diagnosed or in whom the disease is of short duration, antihyperglycemic agents differing in terms of their mechanisms of action might show different treatment responses in various populations.

The UK Prospective Diabetes Study, which enrolled patients newly diagnosed with type 2 diabetes mellitus, 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 carried out in Korea; we used propensity score matching to compare durabilities.

METHODS

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.

Study design and participants
The Korean 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 diabetes mellitus and those at risk of diabetes mellitus in Korea. All patients were enrolled between May 2006 and December 2012, and followed up to December 2013. The type 2 diabetes mellitus cohort included patients aged ≥20 years 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, sex, body mass index, diabetes mellitus duration, HbA1c level and estimated glomerular filtration rate) among groups at a 1:1 ratio (metformin vs sulfonylureas) and 4:1 ratio (metformin vs meglitinides and metformin vs aGIs).

Baseline variables
The baseline variables were based on the last values of the index dates. We recorded age, diabetes mellitus 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 visit. Diabetic retinopathy was diagnosed by ophthalmologists, or through a history of photocoagulation or vitrectomy. Participants with hypertension, as diagnosed by a physician or those taking antihypertensive medications, were classified as patients with hypertension. Similarly, dyslipidemia was defined as patients 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 estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation[15]. The homeostatic model assessment of insulin resistance (HOMA-IR) and β-cell function (HOMA-β) were also calculated[16]. The medication possession ratio (MPR) was the percentage of the sum of days' supply divided by the number of days in the evaluation period. An MPR >100% was scored as 100%.

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

Statistical analysis
Continuous variables are presented as mean ± standard deviation; Student's t-test was used for comparisons. Categorical variables are presented as numbers with percentages; the χ^2-test 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 by propensity score matching using a 1:1 ratio for metformin to sulfonylureas, and a 4:1 ratio of metformin to both aGIs and meglitinides, before survival analysis. We matched age, sex, body mass index, diabetes mellitus duration, HbA1c level and estimated glomerular filtration rate. We next ensured that that the covariates were balanced using the χ^2-test

or Fisher's exact test for categorical variables, and Student's *t*-test for continuous variables. Monotherapy failure curves were plotted using the Kaplan–Meier method and compared using the log–rank test. We carried out 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.

RESULTS

Baseline patient characteristics

The median (interquartile range) follow-up duration was 56.1 months (34.4–70.2 months) for all patients, of whom approximately 45% (454/998) showed monotherapy failure (17% per year; Table 1). The annual monotherapy failure rates were 15.6, 21.3, 27 and 9.6% for metformin, sulfonylureas, meglitinides and aGIs, respectively (hazard ratio [HR] 1.35, 95% confidence interval [CI] 1.10–1.66; HR 1.64, 95% CI 1.04–2.58; and HR 0.61, 95% CI 0.35–1.06 when sulfonylureas, meglitinides and aGIs were compared with metformin, respectively). The mean (standard deviation) age and diabetes mellitus duration were 55.6 years (9.8 years) and 5.4 years (5.1 years), respectively. The mean baseline HbA1c level was 6.9% (0.9) and the MPR 88.5%. Approximately 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.

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 2), although the sulfonylurea group had higher fasting glucose and high-density lipoprotein levels; and the meglitinide group had a higher MPR, a lower HOMA-β score, and fewer diagnoses of dyslipidemia; aGI groups had lower total cholesterol and higher high-density lipoprotein levels, compared with the metformin group.

Monotherapy failures in each treatment group

When monotherapy failure rates were compared after propensity score matching, the sulfonylurea and meglitinide groups had higher failure rates, and the aGI group had a similar failure rate compared with the metformin group (Figure 1; *P* = 0.011, *P* = 0.014 and *P* = 0.465, respectively). The monotherapy failure rates of the sulfonylurea and meglitinide groups did not differ significantly (data not shown).

Monotherapy failure was defined as attainment of an HbA1c level ≥7.5%, a switch to another antidiabetic agent and/or add-on treatment. By failure subtype, sulfonylurea failures often switched to other antidiabetic agents compared with the metformin group (Table 3; HR 4.43, 95% CI 2.14–9.17). As was true of the sulfonylurea group, meglitinide patients were

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/m²)	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 m²)	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 mean ± standard deviation or as numbers (with %). BP, blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

switched more often to other antidiabetic 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 antidiabetic agents are described in Table S1.

DISCUSSION

The KNDP was a prospective, multicenter, observational, Korean cohort study. Of these, the present study patients had been recently diagnosed with type 2 diabetes mellitus, were obese (body mass index ≥25 kg/m²) and showed 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 Korea. The failure rate was somewhat lower than that of the UK Prospective Diabetes Study trial[17], which used 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

Table 2 | Demographic data and baseline characteristics of all patients after propensity score matching

	MET vs SU			MET vs GLI			MET vs aGI		
	MET	SU	P-value	MET	GLI	P-value	MET	aGI	P-value
n	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)	127.2 ± 24.2	132.8 ± 33.5	0.039	126.1 ± 27.9	135.0 ± 22.7	0.112	123.5 ± 24.2	130.0 ± 22.3	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)	179.3 ± 34.6	176.4 ± 35.5	0.363	186.0 ± 36.8	180.3 ± 41.6	0.456	182.2 ± 37.1	169.9 ± 38.3	0.040
Triglyceride (mg/dL)	156.8 ± 103.5	161.4 ± 85.2	0.590	177.8 ± 124.8	195.4 ± 123.8	0.475	152.0 ± 98.0	139.2 ± 125.1	0.441
HDL cholesterol (mg/dL)	49.7 ± 11.2	52.6 ± 12.4	0.016	48.4 ± 10.3	48.8 ± 12.3	0.889	48.6 ± 11.6	55.3 ± 13.5	0.001
LDL cholesterol (mg/dL)	100.3 ± 29.7	98.9 ± 28.5	0.622	99.0 ± 28.1	104.5 ± 27.2	0.324	101.3 ± 30.1	91.9 ± 29.4	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-β	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
Comorbidities									
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 mean ± standard deviation or as numbers (with %). aGI, alpha-glucosidase inhibitor; BP, blood pressure; eGFR, estimated glomerular filtration rate; GLI, meglitinide; HbA1c, glycated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β-cell function; MET, metformin; SU, sulfonylurea.

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, might be somewhat less rigid than those of the present study (HbA1c level >7.5%), monotherapy failure, reflected in a switch to or addition of other antidiabetic agents, can 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 showed a somewhat longer diabetes mellitus duration than those of the ADOPT trial, for which the time since diabetes mellitus diagnosis was <2 years in most participants. This difference might increase the incidence of monotherapy failure in the present 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 healthcare databases in the USA showed that the annual metformin monotherapy failure rate was 17%[19]. The results of both studies were comparable with our findings.

The present study consisted of patients taking one oral hypoglycemic agent for ≥90 days. Therefore, this study included non-responders who did not show an initial good response or did not tolerate a specific monotherapy. These patients were
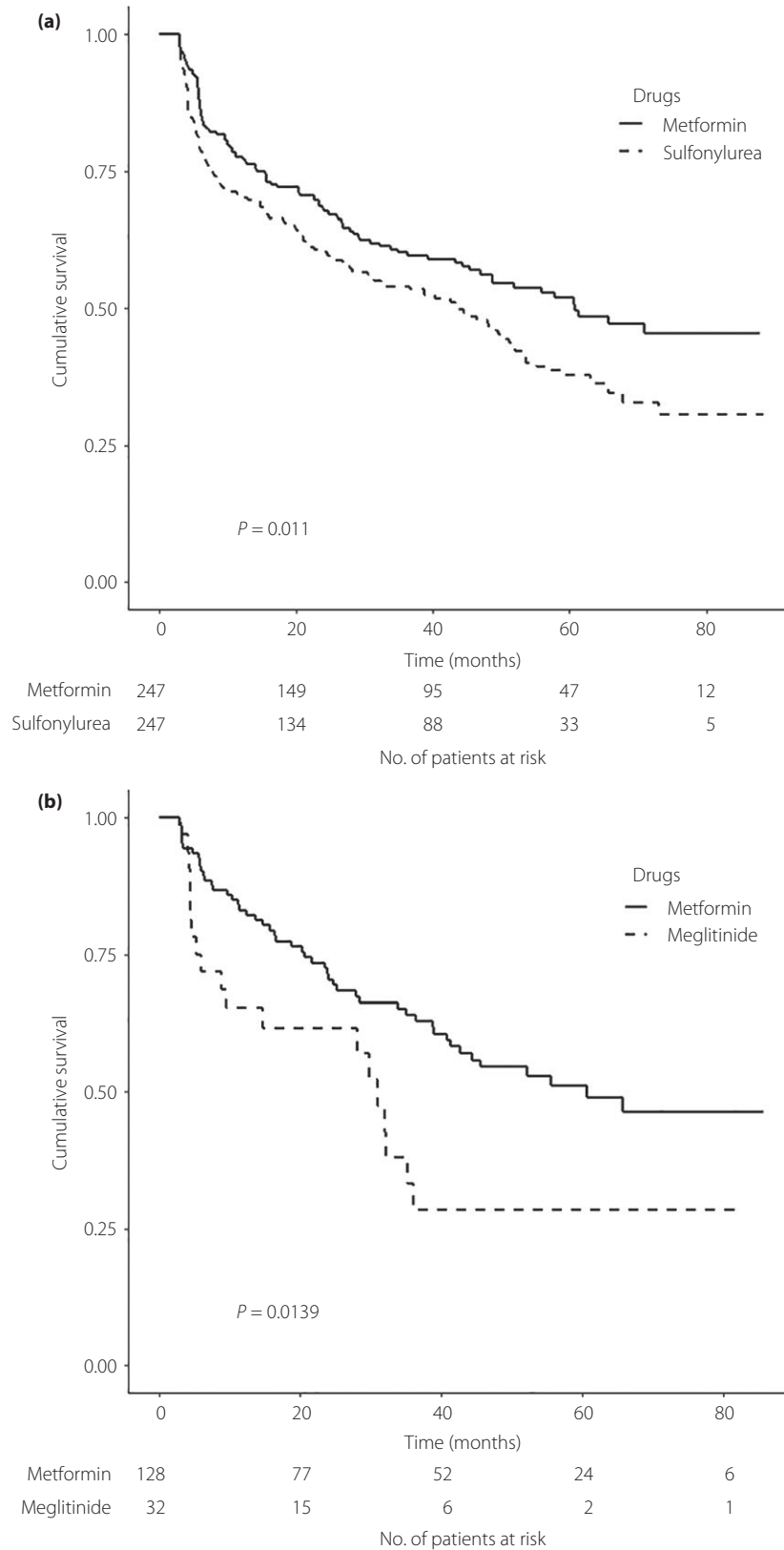
Figure 1 | Kaplan–Meier curve of monotherapy failure after propensity score matching. (a) Metformin vs sulfonylureas, (b) metformin vs meglitinides and (c) metformin vs alpha-glucosidase inhibitors (aGI).
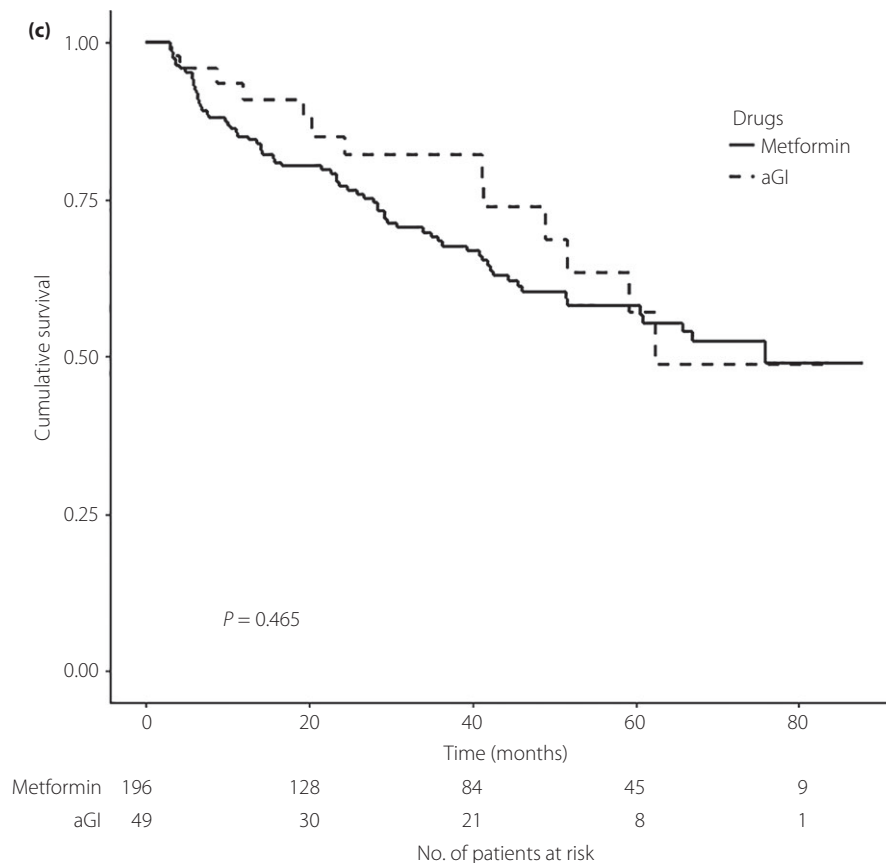
Figure 1 | (Continued).

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 the metformin and sulfonylurea group, early non-responders with a monotherapy duration of <6 months had longer diabetes duration and higher baseline HbA1c levels than responders (data not shown). In comparison between the metformin and meglitinide group, early non-responders in the 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 factors for choice of antihyperglycemic agents[19,20].

Metformin was associated with a lower incidence of monotherapy failure than were either sulfonylureas or meglitinides when both the 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 diabetes mellitus of shorter duration and fewer comorbidities than those prescribed sulfonylureas or meglitinides (data not shown). 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, might 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-β than the metformin group. This might 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 might 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, whereas sulfonylureas did not[21–23]. East Asians show lower β-cell function than do other ethnic groups, and lack the ability to induce

Table 3 | 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 (1.08–1.80)	0.011
	Switch	15.0 vs 3.6	4.43 (2.14–9.17)	<0.001
	Add-on	36.4 vs 32.8	1.23 (0.91–1.66)	0.177
	HbA1c >7.5%	20.6 vs 15.0	1.48 (0.97–2.26)	0.069
GLI vs MET	Overall	59.4 vs 39.8	1.92 (1.13–3.27)	0.015
	Switch	46.9 vs 3.1	18.80 (6.21–56.93)	<0.001
	Add-on	0.9 vs 33.6	0.37 (0.11–1.20)	0.096
	HbA1c >7.5%	21.9 vs 10.9	2.16 (0.87–5.37)	0.096
aGI vs MET	Overall	26.5 vs 35.7	0.80 (0.44–1.45)	0.467
	Switch	14.3 vs 3.6	4.25 (1.49–12.13)	0.007
	Add-on	4.1 vs 28.6	0.16 (0.04–0.64)	0.010
	HbA1c >7.5%	10.2 vs 8.7	1.17 (0.43–3.18)	0.752

[†]Hazard ratio (HR) for monotherapy failure of a sulfonylurea (SU), alpha-glucosidase inhibitor (aGI), or meglitinide (GLI) compared with metformin (MET). CI, confidence interval; HbA1c, glycated hemoglobin.

early-stage compensatory hyperinsulinemia during diabetes mellitus 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 antidiabetic drugs are prioritized, monotherapy using insulin secretagogues might fail more rapidly in Koreans with type 2 diabetes mellitus than in Western populations. Comparison studies in East Asians showed that sulfonylureas rapidly and effectively lowered HbA1c levels more than did metformin, but only for several months[25,26]. However, the HR for monotherapy failure of insulin secretagogues in Koreans was no higher than that of the Swedish cohort.

Clinicians have to determine the next steps, such as change or the adding of antihyperglycemic agents, after monotherapy failure due to the progressive nature of the disease. To view cases with monotherapy failure in our data, especially focused on metformin or sulfonylurea treatment groups, the major further treatment option was combination therapy by adding another antihyperglycemic agent or switching to dual therapy. According to the current guidelines, there are several options of dual therapy when monotherapy fails[2,27]. In the present data, metformin plus sulfonylurea and metformin plus dipeptidyl peptidase-4 (DPP-4) inhibitor were most common. This reflects prescription trends of antihyperglycemic 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 might be solid. Sulfonylureas are still commonly used due to a comparatively higher efficacy and lower cost, although sulfonylureas show a short time to failure, high risk of hypoglycemia and weight gain. Otherwise, DPP-4 inhibitors have become a widespread antihyperglycemic agent due to favorable safety profiles. However, the ideal combination therapy can differ according to the patient's

factors; thus, the pros and cons of antihyperglycemic drugs should be well considered. Most current guidelines recommend individualized therapy in patients with diabetes.

To the best of our knowledge, this is the first report on aGI monotherapy failure in clinical practice. In the present study, the 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 diabetes mellitus treatment for 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 diabetes mellitus[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 a significantly lower add-on failure rate than did metformin, although overall monotherapy failure was comparable.

Unfortunately, we can offer no data on monotherapies using DPP-4 inhibitors or thiazolidinediones, as patient numbers were too small. DPP-4 inhibitors were introduced in Korea only in 2011, and thiazolidinedione prescriptions have fallen rapidly in number since 2007.

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

In conclusion, the annual overall monotherapy failure rate was 17% in Koreans with type 2 diabetes mellitus 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 diabetes mellitus.

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DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1 | Medications switched or added from original monotherapy.