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Comparison of baseline characteristics and clinical course in Japanese patients with type 2 diabetes among whom different types of oral hypoglycemic agents were chosen by diabetes specialists as initial monotherapy (JDDM 42)

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Abstract

Little is known about the relationships between patient factors and the antihyperglycemic agents that have been prescribed as initial therapy by diabetes specialists for patients with type 2 diabetes. Moreover, there has been little clarification of the subsequent usage patterns and related factors that influenced the continuation or discontinuation of the drug or the addition of another drug. To provide information on these issues, we evaluated the clinical characteristics of Japanese patients with type 2 diabetes for whom different types of oral hypoglycemic agents (i.e., either sulfonylureas, biguanides, or DPP-4 inhibitors (DPP-4Is)) were chosen as initial monotherapy by diabetes specialists and evaluated subsequent usage patterns.

Prescription data on 3 different antidiabetic agents from December 2009 to March 2015 from diabetes specialists' patient registries were used to identify variables at baseline related to initial prescriptions; also, the addition of another hypoglycemic drug or discontinuation of the initial therapy was evaluated 1 year after the initial prescription. Analyzed were data on 2666 patients who received initial monotherapy with either a sulfonylurea (305 patients), biguanide (951 patients), or DPP-4I (1410 patients). Patients administered sulfonylureas were older, had a lower body mass index (BMI), longer duration of diabetes, and worse glycemic control than recipients of biguanides. Use of biguanides was related to younger age, short duration of diabetes, and obesity but was negatively associated with poor glycemic control. Older age but neither obesity nor poor glycemic control was associated with DPP-4Is. In all 3 groups a high HbA1c value was related to adding another hypoglycemic agent to the initial therapy. Moreover, adding another drug to a DPP-4I was related to a younger age and higher BMI.

Patients' age, duration of diabetes, obesity, and glycemic control at baseline influenced the choice of hypoglycemic agents. Selection of a biguanide differs greatly from that of a sulfonylurea or DPP-4I with regard to age and obesity.

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Abbreviations: ADA = American Diabetes Association, BMI = body mass index, DPP-4I = dipeptidyl peptidase-4 inhibitors, EASD = European Association for the Study of Diabetes, JDDM = The Japan Diabetes Clinical Data Management Study Group, T2DM = type 2 diabetes mellitus.

Keywords: diabetes specialists, hypoglycemic prescription, initial therapy, patterns of usage

1. Introduction

Metformin was recommended as a first-line treatment option for type 2 diabetes mellitus (T2DM) in the consensus statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), but ~40% of patients received an initial oral antidiabetic drug other than metformin in the United States and Italy.[1–3] These observations suggest that physicians consider other factors (e.g., age, glycemic control, duration of diabetes before the initial prescription of an antidiabetic drug, obesity, complications, risk of hypoglycemia, comorbidities, and life expectancy) when choosing an initial antidiabetic drug.

The choice of medication should depend on individual patient factors while strictly adhering to clinical guidelines.[4,5] Physicians, especially diabetes specialists, can be expected to choose hypoglycemic medications in consideration of factors that influence the overall health and clinical outcome of each patient, with particular concern regarding cardiovascular diseases. However, little is known about the relationship between patient factors identified at the time of the initial therapy (i.e., baseline data) and the initial monotherapies prescribed by diabetes specialists or about the continuation of an initially prescribed hypoglycemic agent over a prolonged period, its possible discontinuation, and the prescription of an additional agent.

Japan's universal health coverage allows doctors to prescribe hypoglycemic medications within a combination of 3 types of hypoglycemic agents.[6] The choice of a hypoglycemic agent has depended on individual physicians' considerations of the patient's background in relation to diabetes since there are no specific guidelines in Japan on the appropriate use of these agents.[5] The first drug of choice has dramatically changed in Japan, since several new drugs, as represented by dipeptidyl peptidase-4 inhibitors (DPP-4I), have been developed during the last decade.[7–9] In fact, a recent study revealed that the top three initially prescribed hypoglycemic agents in Japan were DPP-4I, biguanides, and sulfonylureas in that order.[9]

The Japan Diabetes Clinical Data Management Study Group (JDDM) is one of the largest cohorts of Japanese diabetes specialists consisting of more than 120 leading clinical diabetologists in 98 facilities and has provided information on characteristics of patients with T2DM as well as hypoglycemic prescriptions in Japan.[7,8,10,11] Therefore, using JDDM data we sought to determine the factors that influence the choice of each of 3 hypoglycemic agents prescribed as initial monotherapy by specialists as well as the patients' factors that influenced the continuation or discontinuation of the drug or the addition of another drug over a 1-year period. Such information would be helpful in guiding the treatment of patients with T2DM by diabetes specialists and physicians in general practice in clinical settings.

2. Methods

Data were extracted by software (CoDiC) from the JDDM on patients prescribed hypoglycemic agents from December 2009 to March 2015. Details on the JDDM and CoDiC were described elsewhere.[7,8,10,11] We included as participants individuals who were aged 20 years or older who started medical treatment (sulfonylureas, biguanides, or DPP-4Is) in outpatient clinics for T2DM. Of the 3555 participants who received initial monotherapy during the above period, including a 1-year follow-up after the first prescription, we excluded 889 individuals because of prescription of another antidiabetic medicine including insulin as initial therapy or missing data. Thus, data on 2666 patients who were prescribed sulfonylureas, biguanides, or DPP-4Is as the initial medical treatment were analyzed. Of these, sulfonylureas, biguanides, and DPP-4Is were administered to 305, 951, and 1410 patients, respectively. The present study was approved by the ethics committee of the JDDM. Informed consent was obtained from all patients at each participating institute in accordance with the Guidelines for Epidemiological Studies of the Ministry of Health, Labor and Welfare of Japan.

HbA1c was converted from the Japanese Diabetes Society values into National Glycohemoglobin Standardization Program equivalent values.[12] Hypertension was defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg or the current use of antihypertensive agents.

2.1. Statistical analysis

Categorical variables were expressed as numerals and percentages and were compared with χ^2 tests. Continuous variables were expressed as mean ± SD and were compared using the Kruskal–Wallis test for comparisons in each group. Multinomial logistic regression analysis and logistic regression analyses were performed to identify variables related to each hypoglycemic agent prescribed for initial monotherapy. Logistic regression analyses were also performed to identify variables related to the addition of another drug to each initial therapy or the discontinuation of each initial hypoglycemic monotherapy based on data obtained 1 year after the initial prescription. Covariates simultaneously included continuous variables or categories: age (<50, 50–64, and ≥65 years), sex, duration of diabetes at the beginning of the first treatment (<10 and ≥10 years), body mass index (BMI) (<25.0 and ≥25.0 kg/m^2), hypertension, HbA1c (<8.0 and ≥8.0% (64 mmol/mol)), and clinics. All statistical analyses were performed by SPSS (version 19.0, Chicago, IL), and statistical significance was considered for $P < 0.05$.

3. Results

Table 1 shows participants' baseline characteristics according to each of the 3 hypoglycemic medications prescribed as initial monotherapy. Except for the value of diastolic blood pressure, there were significant differences among the 3 groups. Participants who were prescribed sulfonylureas were older, had a lower BMI, a longer duration of diabetes, and worse glycemic control than those who were prescribed biguanides. In comparison with patients prescribed a sulfonylurea or DPP-4I, participants who were administered biguanides were younger, had a higher BMI, and a shorter duration of diabetes. Participants who were prescribed DPP-4Is were older, had a lower BMI, and a longer duration of diabetes in comparison with those prescribed

Table 1

Characteristics of study participants according prescription of each of 3 hypoglycemic drugs.

Characteristic	SU	BG	DPP-4I	*P*
Number of patients, n	305	951	1410	
Age, y	62±12	56±11	64±11	<0.001
Age <50 y, %	32 (10)	244 (26)	147 (10)	<0.001
Age 50–64 y, %	108 (35)	487 (51)	540 (38)	
Age ≥65 y, %	165 (54)	220 (23)	723 (51)	
Male/female	178/127	641/310	890/520	0.009
Body mass index, kg/m^2	24.8±4.6	27.3±4.5	24.7±3.7	<0.001
Duration of diabetes, y	10.1±10.2	5.4±5.8	7.7±7.6	<0.001
Hypertension, n (%)	166 (54)	442 (47)	727 (52)	0.018
Systolic blood pressure, mm Hg	130±18	128±14	130±16	<0.001
Diastolic blood pressure, mm Hg	74±12	76±11	75±11	0.232
HbA1c, % (NGSP)	7.8±1.4	7.0±1.0	7.4±1.0	<0.001
HbA1c, mmol/mol (IFCC)	62±15	59±11	58±11	

BG = biguanides, DPP41 = DPP4 inhibitor, IFCC = International Federation of Clinical Chemistry, NGSP = National Glycohemoglobin Standardization Program, SU = sulfonylureas.

biguanides. Age and BMI were similar in participants who were prescribed a sulfonylurea or DPP-4I, whereas the duration of diabetes and HbA1c values were higher in those prescribed a sulfonylurea than a DPP-4I. Supplemental Tables 1 and 2, http://links.lww.com/MD/B565 show the results of logistic regression analyses of odds ratios for variables according to the hypoglycemic medications selected as monotherapy. Prescribing sulfonylureas was associated with older age, long duration of diabetes, and an elevated level of HbA1c, but was negatively associated with obesity. Prescribing biguanides was related to younger age, short duration of diabetes, and obesity but was negatively associated with an elevated HbA1c. The use of DPP-4Is was related to older age, but was negatively associated with obesity and an elevated HbA1c. Significant interactions were observed for variables according to the agent prescribed. For sulfonylureas, interactions between age and BMI and age and HbA1c were observed while for biguanides an interaction between BMI and HbA1c was observed. With DPP-4Is we found interactions between the duration of diabetes and BMI and the duration of diabetes and HbA1c. Table 2 shows the results of the multinomial logistic regression analysis of odds ratios for biguanides and DPP-4I according to variables using sulfonylureas as the reference. Patients who received biguanides as initial therapy had lower odds ratios for age, duration of diabetes, hypertension, and an elevated HbA1c compared with those started on sulfonylureas, whereas the odds ratio for BMI was higher. Patients who received

Table 2

Odds ratios for explanatory variables by multinomial logistic regression analysis for selected diabetes drug therapies.

	BG		DPP-4I	
N	951	*P*	1410	*P*
Age, y	0.95 (0.94–0.96)	<0.01	0.99 (0.98–1.01)	0.26
Sex, male	1.32 (0.99–1.77)	0.06	1.30 (1.00–1.69)	0.048
Duration of diabetes	0.94 (0.92–0.96)	<0.01	0.96 (0.95–0.97)	<0.01
Body mass index, kg/m^2	1.19 (1.14–1.24)	<0.01	1.03 (0.99–1.07)	0.09
Hypertension	0.67 (0.50–0.90)	<0.01	0.90 (0.69–1.18)	0.46
HbA1c, %	0.65 (0.57–0.73)	<0.01	0.68 (0.61–0.76)	<0.01

Reference category: sulfonylureas. Odds ratios were adjusted by clinics.
BG = biguanides, DPP-4I = DPP-4 inhibitor, hypertension = SBP ≥140 and/or DBP ≥90 or treatment.

DPP-4Is as initial therapy had lower odds ratios for the duration of diabetes and an elevated HbA1c compared with those started on sulfonylureas. Figure 1 shows results of the evaluation of patterns of use of antidiabetic agents 1 year after the initial prescription of 3 different drugs. The continuous use of sulfonylureas, biguanides, and DPP-4Is occurred in 164 (54%), 625 (66%), and 1042 (74%) participants, respectively, while 17 (6%), 13 (7%), and 74 (5%) of the participants discontinued sulfonylureas, biguanides, and DPP-4Is, respectively. An additional drug was added to sulfonylureas, biguanides, and DPP-4Is in 77 (25%), 192 (20%), and 231 (16%) participants, respectively. Table 3 and Supplemental Table 3, http://links.lww.com/MD/B565 show the results of logistic regression analyses for odds ratios of explanatory valiables related to the addition of another hypoglycemic medication to each initial hypoglycemic medication, indicating an intensified treatment strategy. In all 3 groups there was an association between the addition of another hypoglycemic medication and the baseline HbA1c values. Moreover, the addition of another drug to a DPP-4I was related to younger age and a higher BMI. Supplemental Tables 4 and 5, http://links.lww.com/MD/B565 show the results of logistic regression analyses of odds ratios for explanatory variables related to stopping each of the initially prescribed hypoglycemic medications. Stopping the initial biguanides therapy was associated with the degree of elevation of HbA1c values at baseline.

4. Discussion

As far as we know, this is the first large-scale study to investigate the relationships between patient factors and initial monotherapy

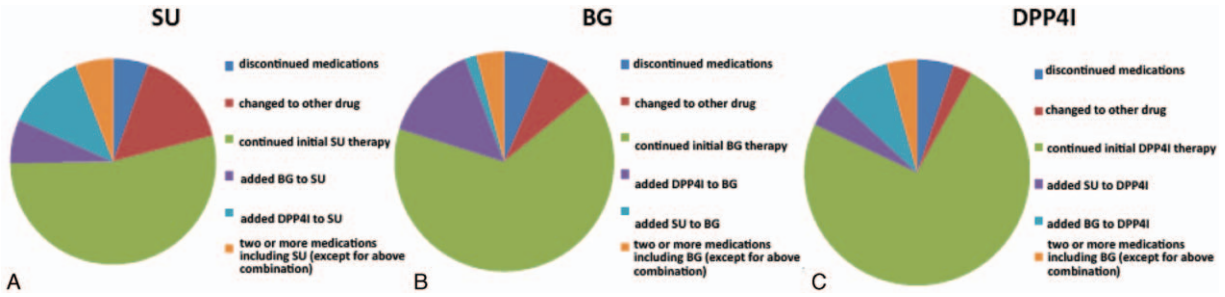

Figure 1. Results of evaluation of patterns of usage of 3 antidiabetic agents 1 year after initial prescription. (A) Sulfonylureas, (B) biguanides, and (C) DPP-4Is as monotherapy. BG = biguanides, DPP-4Is = dipeptidyl peptidase-4 inhibitors, SU = sulfonylureas.

Table 3

Odds ratios for explanatory variables by logistic regression analysis for the addition of another diabetes drug.

	SU	BG	DPP-4I
n	77	192	231
Age, y	0.99 (0.96–1.01)	0.99 (0.97–1.00)	0.98 (0.96–0.99)
Sex, male	0.98 (0.54–1.78)	1.30 (0.89–1.90)	1.02 (0.75–1.37)
Duration of diabetes	1.00 (0.96–1.01)	0.98 (0.94–1.01)	0.98 (0.96–1.00)
Body mass index, kg/m^2	1.00 (0.92–1.08)	1.00 (0.96–1.05)	1.05 (1.01–1.10)
Hypertension	0.90 (0.50–1.61)	0.96 (0.67–1.38)	1.04 (0.76–1.41)
HbA1c, %	1.27 (1.01–1.61)	1.65 (1.41–1.95)	1.69 (1.48–1.92)

BG = biguanides, DPP-4I = DPP-4 inhibitor, hypertension = SBP ≥140 and/or DBP ≥90 or treatment, SU = sulfonylureas.

by 1 of 3 specific hypoglycemic agents provided by diabetes specialists for T2DM in Japan. The choice of each hypoglycemic agent was influenced by patients' age, duration of diabetes, obesity, and glycemic control at baseline. Moreover, the choice of biguanides differs greatly from the choice of a sulfonylurea or DPP-4I with regard to age and obesity, which might reflect specialists' consideration of insulin resistance, insulin secretion, or side effects. These findings might partially reflect the consensus of specialists as to what agents would be most suitable as initial therapy for patients with particular characteristics, which is not specified in the current consensus recommendations but is valuable in clinical settings. Intensifying therapy through the addition of one or more agents to a DPP-4I was related to younger age and a higher BMI at baseline. This information would provide guidance for pharmacotherapy based on specialists' prescriptions as individualized therapy for T2DM, which was emphasized in ADA/EASD consensus recommendations.[4]

The role of the initial therapy over the long term could be important in the treatment of diabetes when key elements such as continuation of the initially prescribed drug, discontinuation of that drug, or the addition of another drug are considered. Although metformin was recommended as first-line therapy in the ADA/EASD consensus recommendations, ~40% of patients initiating oral hypoglycemic medications did not receive the recommended initial therapy with metformin.[1–3] Moreover, it has not been clarified whether these recommendations were applicable to Asians, including Japanese, whose T2DM tends to be characterized more by impaired insulin secretion than by increased insulin resistance compared with Caucasians.[13–15] Our study is the first to show differences in factors that influence the choice of each of 3 hypoglycemic medications by Japanese diabetes specialists in a real world setting. These findings reflect their opinions on the suitability of specific agents for specific patients.

We found that prescribing sulfonylureas was related to older age, a long duration of diabetes, and poor glycemic control, but not obesity. Impaired insulin secretion had a greater impact on the background of T2DM compared to insulin resistance in a Japanese population.[13–15] In fact, Asians typically have a lower mean BMI but a higher prevalence of diabetes compared with Caucasians at similar BMI levels.[16] Our findings might reflect the consensus of diabetes specialists that sulfonylureas could be used to increase insulin secretion in Japanese T2DM patients. Patients who received sulfonylureas as initial therapy had a lower BMI and a long duration of diabetes at baseline compared with those started on biguanides, indicating that the need for sulfonylureas was more closely associated with impaired insulin secretion than in those prescribed biguanides as initial monotherapy who required another hypoglycemic agent to achieve glycemic control. No clinical characteristics were revealed to be related to discontinuation of sulfonylureas as initial therapy. However, we could not analyze separately participants who stopped taking sulfonylureas due to hypoglycemia or whose glycemic control had improved. Therefore, these results should be interpreted with caution.

Prescribing biguanides was associated with a younger age, short duration of diabetes, and obesity, but not poor glycemic control or the presence of hypertension. Although biguanides are not defined as first-line hypoglycemic agents in Japan, these results are consistent with a previous study[17] and also with the consensus statement of the ADA/EASD.[4] It is generally considered that chronic biguanide use is weight-neutral[18] and does not increase the risk of hypoglycemia.[19] Biguanides can cause lactic acidosis, and avoiding their use is advised in patients at risk for this side effect, such as older patients and those with advanced renal insufficiency.[20] Our study results might support the opinion that Japanese diabetes specialists considered a wide range of indications for biguanides. Unfortunately, we could not obtain information on renal failure among participants; therefore, future studies are needed to assess these issues. Prescribing an additional hypoglycemic agent to biguanides was related to a higher baseline HbA1c level and the rate of prescribing an additional drug was lower in patients ≥50 years old compared to those <50 years of age. Discontinuing biguanides as initial therapy was related to a lower HbA1c value, suggesting that an improvement in glycemic control by diet and exercise therapy in the initial phase might have led to discontinuing biguanides.

The DPP-4I is a key drug in Asians, who are more likely to have impaired insulin secretion compared with Caucasians. The DPP-4I prescription rate has dramatically increased in Japan in recent years.[8,9] In our study, prescribing a DPP-4I was associated with older age, but was negatively related to obesity. In a previous study, we found no association between DPP-4I prescription and older age since our sample size was insufficient and we could not analyze separately participants newly prescribed a hypoglycemic agent or only participants whose prescriptions had been changed during outpatient care.[7] A recent study from United States showed that prescribing DPP-4Is was associated with older age.[21] The mechanism of DPP-4Is is to increase incretin levels, leading to increased insulin secretion.[22] Thus, clinicians expect the choice of a DPP-4I to lead to improvement of impaired insulin secretion as well as reduced glucagon levels. Moreover, DPP-4Is cause little hypoglycemia or weight gain.[23] Our study results could support the opinion that Japanese diabetes specialists expect a low risk of side effects from the choice of a DPP-4I. The reason for the higher rate of continuous use of a DPP-4I compared sulfonylurea was the lower HbA1c level at baseline in the DPP-4I group than in the sulfonylurea group. Adding another drug to a DPP-4I was related to a higher HbA1c value, younger age, and higher BMI at baseline. A recent meta-analysis indicated that DPP-4Is exhibited better glucose-lowering efficacy in studies consisting of ≥50% Asians compared with studies having <50% Asians,[24] which is consistent with our findings. No clinical characteristic was shown for discontinuing initial therapy with a DPP-4I, suggesting the possibility of good tolerance of a DPP-4I as first-line therapy for T2DM in Asians. However, further studies are needed to evaluate the effectiveness and safety of DPP-4Is as initial therapy over a long period of time, including evaluation of cardiovascular outcome.

Several limitations must be addressed regarding this study. First, we could not obtain information on the presence or absence of diabetes complications, dementia, renal failure, psychiatric factors, social factors, and comorbidities because of the incomplete data in the CoDiC database. Moreover, we could not separately analyze random glucose and postprandial glucose. Therefore, further studies are necessary to clarify the relationships between the prescription of each hypoglycemic medication and characteristics of patients that require consideration of those important factors. Second, our study revealed the associations between baseline patient factors and the initial monotherapies and in principle could not prove causality. Third, the rate of use of hypoglycemic agents other than sulfonylureas, biguanides, or DPP-4I was too small to assess a relationship between each available hypoglycemic agent and clinical characteristics. Moreover, the prescription periods were too short to assess a relationship between the prescription of SGLT-2 inhibitors and characteristics of participants. Further studies are needed to clarify these points with an adequate number of patients. Fourth, the results may be limited to an ethnic Japanese population with T2DM.

In conclusion, as far as we know, this is the first study to investigate the relationships between patient factors and initial prescriptions of 3 different hypoglycemic agents provided by diabetes specialists for patients with T2DM in Japan. Our results revealed sharp differences in characteristics among patients who were prescribed 3 hypoglycemic medications by diabetes specialists. The choice of each hypoglycemic agent was influenced by 4 factors determined at baseline: patients' age, duration of diabetes, obesity, and glycemic control. The choice of a biguanide differs greatly from the choice of a sulfonylurea and DPP-4I with regard to age and obesity, which suggests that the consideration of factors by diabetes specialists is related to insulin secretion, insulin resistance, or side effects. Intensified therapy by the addition of one or more agents to a DPP-4I was related to a younger age and a higher BMI at baseline. This information would provide guidance for pharmacotherapy based on specialists' prescriptions for T2DM as individualized therapy.

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