Clinical features and sulfonylurea usage among outpatients with diabetes aged ≥90 years in an urban diabetes clinic in Tokyo

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Keywords
Elderly diabetes patient, Nonagenarian, Reverse clinical inertia, Sulfonylurea

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J Diabetes Investig 2022; 13: 2010–2017
doi: 10.1111/jdi.13901

ABSTRACT
Aims/Introduction: Aging of society is accelerating in many countries. The purpose of this study was to describe the clinical features and sulfonylurea usage among diabetes outpatients aged ≥90 years (nonagenarians).

Materials and Methods: This study was a retrospective observational study. The study population consisted of 69 nonagenarian diabetes outpatients and 857 diabetes outpatients aged <90 years. Patients were classified into four groups: group 1, <65 years; group 2, 65–74 years; group 3, 75–89 years; and group 4, ≥90 years. The presence of hypoglycemic episodes was defined as having self-reported symptoms, or self-monitored or clinically measured blood glucose level <70 mg/dL.

Results: The median glycated hemoglobin (HbA1c) in group 1 and group 4 was 7.0% and 7.2%, respectively (P = 0.506). The proportion of sulfonylurea treatment in group 4 was 45.5%, which is significantly higher compared with the other three groups (20.0–27.8%, P < 0.001). In group 4, there was no difference between patients with or without sulfonylurea in age, sex, body mass index, HbA1c and number of antihyperglycemic agents. Five out of 25 nonagenarian sulfonylurea-treated patients had hypoglycemic episodes within the last 2 years, their HbA1c were all 7.0 ≤ HbA1c < 8.0, and sulfonylurea or insulin was tapered in all cases after confirming hypoglycemia. Tapering dosage was attempted in all 25 sulfonylurea-treated nonagenarian patients, but 15 needed to continue sulfonylurea for glycemic control, and 10 continued sulfonylurea with unknown reasons from their medical records.

Conclusions: Although tapering the dosage of sulfonylurea was attempted in nonagenarian patients, sulfonylurea was widely continued for glycemic control. Reverse clinical inertia may exist in some sulfonylurea-treated nonagenarian patients.

INTRODUCTION
According to a report in 2021, the Japanese society is increasingly aging, and the proportion of people aged ≥65 years in Japan is 29.3%, ≥75 years is 15.0% and ≥85 years old is 5.2%. Aging of the population is accelerating not only in Japan, but also in many countries, and the focus is shifting to "healthy life expectancy" rather than just longevity.

In Japan and many other countries, elderly people are defined as individuals aged ≥65 years. However, there is no medical or biological evidence to support this definition. As there are many people aged ≥65 years who are socially and physically active, the definition is being questioned in Japan. In 2017, “the Joint Committee of Japan Gerontological Society and the Japan Geriatrics Society on the definition and classification of the elderly people” analyzed various data from different perspectives, such as physical function, psychological health, incidence rate of diseases, mortality rate and public recognition.
of classification of the older people among Japanese people, and proposed a classification of people aged ≥65 years as follows: "pre-old age", 65–74 years; "old age", ≥75 years; and "oldest-old" or "super-old", ≥90 years.² Six

There are only a few reports focused on patients with diabetes aged ≥90 years²–⁶. In terms of treating elderly patients with diabetes, the Japan Diabetes Society recommend that sulfonylureas is a risk factor for hypoglycemia in elderly patients with diabetes and should be titrated appropriately.⁶ However, in a multicentered cross-sectional study of clinical characteristics and treatment of patients with type 2 diabetes aged ≥60 years old in Japan, it was reported that the ratio of sulfonylurea treatment in patients aged ≥90 years was higher than the rest of the age groups.⁶ Although clinical characteristics and treatment of each generation were described, no further data regarding sulfonylurea and age groups was shown. Furthermore, hypoglycemic episodes and reasons for continuing sulfonylurea in elderly patients with diabetes were not investigated.

Therefore, we focused on patients with diabetes aged ≥90 years who were able to visit our clinic regularly, and investigated those treated with sulfonylurea. The purpose of the present study was to describe the clinical features of outpatients with diabetes aged ≥90 years, especially those treated with sulfonylurea, in an urban diabetes clinic, the Institute of Medical Science, Asahi Life Foundation, in Tokyo, Japan.

MATERIALS AND METHODS

The present study was a retrospective observational study. The protocol was approved by the Committee of Ethics in the Institute of Medical Science, Asahi Life Foundation (approval number 12605). Informed consent was obtained in the form of opt-out on our website. Investigations were carried out in accordance with the principals of Declaration of Helsinki.

The study population was 69 patients with diabetes aged ≥90 years who visited our clinic regularly at least twice a year, and took a blood test at least once between January 2015 and September 2020, and 857 patients aged in their 30s and took a blood test at least once between January 2015 and September 2020, and 857 patients aged in their 30s and took a blood test at least once during the same period. Patients were classified into the following four groups: group 1, <65 years; group 2, 65–74 years; group 3, 75–89 years; and group 4, ≥90 years.

We defined the “visit” as the latest visit with a blood and urine test. Age, blood pressure, body mass index (BMI), prescription and duration of diabetes at the latest “visit” were used for the analysis. Other data collected were sex, type of diabetes, age of onset of diabetes and past medical history. Furthermore, in patients with diabetes aged ≥90 years, hypoglycemic episodes were collected from their clinical records. The presence of hypoglycemic episodes was defined by either self-reported symptoms or blood glucose level <70 mg/dL, either self-monitored or measured at a clinic visit. Also, to investigate the reasons for continuing sulfonylurea in 25 patients with diabetes aged ≥90 years, we defined “tapering dosage” as reducing dosage of sulfonylurea during the past 2 years. Furthermore, we evaluated the reasons for continuing sulfonylurea as unknown when we were unable to find any reasons or plans of sulfonylurea treatment in the patients’ clinical record.

We assessed normality of continuous variables by histogram, quantile-quantile plot and Shapiro-Wilk test. The t-test was used to compare parametric continuous variables, and the Wilcoxon rank sum test was used to compare non-parametric continuous variables. Pearson’s χ²-test or Fisher’s exact test was used to compare categorical variables as appropriate. To compare continuous variables of the four groups, the Steel–Dwass test was carried out after Kruskal–Wallis analysis of variance, because they were all non-parametric variables. The threshold of statistical significance was two-tailed P < 0.05.

Statistical analyses were carried out using JMP version 16.0.0 (SAS Institute Inc., Cary, NC, USA).

RESULTS

The characteristics of the 69 outpatients with diabetes aged ≥90 years are shown in Table 1. Among patients aged ≥90 years, female patients were significantly older than male patients, whereas there was no significant difference in BMI, glycated hemoglobin (HbA1c), duration of diabetes, blood pressure, lipid control, liver and kidney function, and history of cerebral cardiovascular disease or malignancy between male and female patients. Furthermore, there was no significant difference in renin–angiotensin system inhibitor treatment, statin treatment, and diabetes medication between male and female patients.

Next, we compared the four generation groups based on the classification of people aged ≥65 years proposed in 2017 by the Joint Committee of Japan Gerontological Society and the Japan Geriatrics Society: group 1, <65 years; group 2, 65–74 years; group 3, 75–89 years; and group 4, ≥90 years (Table 2). The older the generation was, the significantly higher the female ratio was and significantly lower the BMI was (P < 0.005, all pairs of groups). However, HbA1c did not show a significant difference between group 1 and group 4 (P = 0.506). In contrast, the systolic blood pressure of group 3 and group 4 were significantly higher than group 1 (P = 0.008 and 0.019, respectively). Diastolic blood pressure was significantly lower as the generation was older (P < 0.001, in all pairs of groups except for group 3 vs group 4; P = 0.248). Although there was a significant difference between group 4 and group 1 in systolic and diastolic blood pressure, there was no significant difference in the rate of patients achieving the goal of <130/80 mmHg between the four groups (P = 0.441). As for kidney function, the estimated glomerular filtration rate was significantly lower in older generations (P < 0.004, in all pairs of groups), and the proportion of patients with proteinuria was significantly higher in group 4 compared with the other three groups (P = 0.002, 0.011 and 0.020; group 4 vs group 1, group 4 vs group 2 and group 4 vs group 3, respectively). As for lipid control,
significant difference was seen between group 4 and the other three groups; total cholesterol ($P = 0.989, 0.205$ and $0.324$; group 4 vs group 1, group 4 vs group 2 and group 4 vs group 3, respectively), low-density lipoprotein cholesterol ($P = 0.784, 0.551$ and $0.466$), high-density lipoprotein cholesterol ($P = 0.938, 0.911$ and $0.458$) and non-high-density lipoprotein cholesterol ($P = 0.999, 0.100$ and $0.103$). Furthermore, the older generation had a significantly higher age of onset of diabetes ($P < 0.001$, in all pairs of groups). There was significantly higher proportion of non-medication among the patients with diabetes aged $\geq 90$ years compared with other generations.

Next, we analyzed the details of diabetes medication of each generation (Table 3). There was no difference in the proportion of insulin treatment among the four groups. The proportion of glucagon-like peptide-1 analog, biguanide and sodium–glucose cotransporter 2 inhibitor treatment were significantly smaller as the group became older. In contrast, the proportion of sulfonylurea treatment was markedly higher in patients with diabetes aged $\geq 90$ years compared with the other three groups.

Therefore, we compared patients with diabetes aged $\geq 90$ years treated with sulfonylurea with patients medicated without sulfonylurea (Table 4). There was no difference between patients with or without sulfonylurea in age, sex, BMI, HbA1c, estimated glomerular filtration rate and proteinuria. Similarly, there was no significant difference in the number of antihyperglycemic agents between patients with or without sulfonylurea. Regarding concomitant diabetes drugs, although the proportion of insulin usage was significantly lower in patients treated with sulfonylurea, there was no significant difference in the proportion of usage of other drugs between with and without sulfonylurea treatment.

Next, we investigated the characteristics of the 25 patients with diabetes aged $\geq 90$ years treated with sulfonylurea. Details

- **Table 1 | Characteristics of outpatients with diabetes aged $\geq 90$ years**

| Characteristics of outpatients with diabetes aged $\geq 90$ years | Total, $n = 69$ (100) | Male, $n = 43$ (62.3) | Female, $n = 26$ (37.7) | $P$-value |
|---|---|---|---|---|
| Age (years) | 91 (90, 93) | 91 (90, 92) | 93 (91, 94) | 0.007 |
| BMI (kg/m$^2$) | 21.3 (18.7, 23.8) | 21.3 (19.1, 24.2) | 209 (18.2, 23.4) | 0.399 |
| HbA1c (%) | 7.2 (6.6, 7.8) | 7.2 (6.6, 7.6) | 7.3 (6.6, 8.0) | 0.633 |
| Type 1 diabetes | 1 (1.5) | 0 (0) | 1 (3.9) | 0.195 |
| Duration of diabetes (years) | 32 (23, 40) | 32 (23, 40) | 31 (22, 39) | 0.628 |
| Systolic blood pressure (mmHg) | 135 (123, 147) | 131 (121, 147) | 140 (125, 147) | 0.304 |
| Diastolic blood pressure (mmHg) | 68 (61, 74) | 68 (61, 74) | 67 (59, 74) | 0.850 |
| T-Chol (mg/dL) | 188 (172, 212) | 191 (177, 214) | 182 (166, 209) | 0.475 |
| LDL-C (mg/dL) | 107 (85, 123) | 110 (87, 125) | 105 (83, 118) | 0.126 |
| HDL-C (mg/dL) | 57 (44, 67) | 55 (43, 63) | 58 (45, 71) | 0.423 |
| Non-HDL (mg/dL) | 133 (112, 150) | 133 (113, 153) | 133 (109, 144) | 0.202 |
| AST (U/L) | 21 (18, 26) | 20 (18, 26) | 21 (19, 27) | 0.537 |
| ALT (U/L) | 15 (11, 21) | 15 (12, 22) | 15 (10, 20) | 0.381 |
| eGFR (mL/min/1.73 m$^2$) | 53.9 (42.8, 66.3) | 54.0 (40.9, 63.5) | 53.8 (43.4, 73.4) | 0.667 |
| Proteinuria | 17 (24.6) | 12 (27.9) | 5 (19.2) | 0.418 |
| History of coronary artery disease | 18 (26.1) | 13 (30.2) | 5 (19.2) | 0.313 |
| History of cerebrovascular disease | 12 (17.4) | 6 (14.0) | 6 (23.1) | 0.333 |
| History of malignancy | 16 (23.2) | 11 (25.6) | 5 (19.2) | 0.545 |
| ACE inhibitor, ARB or DRI treatment | 24 (34.8) | 16 (37.2) | 8 (30.8) | 0.586 |
| Statin treatment | 24 (34.8) | 14 (32.6) | 10 (38.5) | 0.618 |
| Diabetes medication | 55 (79.7) | 34 (79.1) | 21 (80.8) | 0.865 |
| DPP-4 inhibitor | 33 (60.0) | 21 (61.8) | 12 (57.1) | 0.734 |
| Sulfonylurea | 25 (45.5) | 15 (44.1) | 10 (47.6) | 0.800 |
| Insulin | 22 (40.0) | 12 (35.3) | 10 (47.6) | 0.365 |
| Biguanide | 11 (20.0) | 7 (20.6) | 4 (19.1) | 0.890 |
| Glinide | 6 (10.9) | 5 (14.7) | 1 (4.8) | 0.251 |
| Alpha-glucosidase inhibitor | 5 (9.1) | 2 (5.9) | 3 (14.3) | 0.292 |
| GLP-1 receptor agonist | 2 (3.6) | 2 (5.9) | 0 (0) | 0.258 |
| Thiazolidinedione | 1 (1.8) | 1 (2.9) | 0 (0) | 0.428 |
| SGLT-2 inhibitor | 0 (0) | 0 (0) | 0 (0) | – |

Data are $n$ (%) or median (interquartile range). ARB, angiotensin receptor blocker; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DPP-4, dipeptidyl peptidase-4; DRI, direct renin inhibitor; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SGLT-2, sodium–glucose cotransporter 2; T-Chol, total cholesterol.
of sulfonylureas prescribed to these 25 patients with diabetes are shown in Table 5. Hypoglycemic episodes were observed even though prescribed sulfonylurea was not of a high dosage in some patients aged ≥90 years (Table 5). Of 25 patients aged ≥90 years treated with sulfonylurea, 16 were 7.0 ≤ HbA1c < 8.0 (Table 6). Five out of 25 patients had hypoglycemic episodes during the past 2 years, and their HbA1c levels were all 7.0 ≤ HbA1c < 8.0 (Table 6). It should be noted that doctors tapered sulfonylurea or insulin in all cases after they confirmed hypoglycemic episodes. Furthermore, we investigated the reasons for continuing sulfonylurea in patients with diabetes aged ≥90 years (Table 6). We grouped the patients aged ≥90 years by HbA1c level: 6.0 ≤ HbA1c < 7.0, 7.0 ≤ HbA1c < 8.0 and 8.0 ≤ HbA1c < 9.0, and found that in all groups, tapering dosage or withdrawal of sulfonylurea were attempted. However, 15 out of 25 patients aged ≥90 years treated with sulfonylurea needed to continue sulfonylurea for glycemc control. Out of seven patients who resumed sulfonylurea after changing to another medication, four patients resumed sulfonylurea, because they were unable to inject insulin or weekly glucagon-like peptide-1 analog appropriately. In contrast, the reasons of continuing sulfonylurea in some patients were unknown from their medical records (Table 6).
DISCUSSION

The present retrospective study observed the clinical features of outpatients with diabetes aged ≥90 years in an urban diabetes clinic in Tokyo.

Our results showed there was no difference in HbA1c between male and female patients with diabetes aged ≥90 years. This is consistent with a previous population-based cross-sectional study of 11,645 Spanish type 2 diabetes patients aged ≥90 years, which also showed a similar glycemic control between male and female patients.7

Comparing each generation, there was no significant difference in HbA1c between patients aged <65 years and ≥90 years in the present study. However, a previous study based on a German large real-world database reported that HbA1c levels were much lower in type 2 diabetes patients aged ≥90 years than those aged in their 50s and 60s8. The difference between

| Table 4 | Comparison between patients treated with or without sulfonylurea in medicated patients with diabetes aged ≥90 years |
|---------|---------------------------------------------------------------------------------------------------------------|
| Age (years) | 91 (90, 93) | 92 (90, 94) | 0.808 |
| Sex (male) | 19 (63.3) | 15 (60.0) | 0.800 |
| BMI (kg/m²) | 21.3 (19.4, 24.3) | 21.6 (19.7, 23.5) | 0.905 |
| HbA1c (%) | 7.3 (6.8, 8.2) | 7.3 (7.0, 7.8) | 1.000 |
| eGFR (mL/min/1.73m²) | 52.9 (38.5, 64.2) | 55.8 (45.8, 70.6) | 0.398 |
| Proteinuria | 8 (26.7) | 6 (24.0) | 1.000 |

No. antihyperglycemic agents

| | Sulfonylurea (−), n = 30 | Sulfonylurea (+), n = 25 | P-value |
|---|---|---|---|
| 1 | 13 (43.3) | 7 (28.0) | 0.375 |
| 2 | 11 (36.7) | 10 (40.0) | 0.605 |
| 3 | 5 (16.7) | 8 (32.0) | 0.109 |
| 4 | 1 (3.3) | 0 | 0.001 |

Concomitant drug

| Only sulfonylurea | – | 7 (28.0) | – |
| Biquanide | 21 (70.0) | 5 (20.0) | 0.109 |
| DPP-4 inhibitor | 18 (60.0) | 4 (16.0) | 0.001 |
| Insulin | 4 (13.3) | 2 (8.0) | 0.678 |
| SGLT-2 inhibitor | 0 (0) | 0 (0) | – |
| Alpha-glucosidase inhibitor | 0 (0) | 2 (8.0) | 0.001 |
| GLP-1 receptor agonist | 0 (0) | 0 (0) | – |
| Glimepiride | 4 (13.3) | 2 (8.0) | 0.678 |
| Thiazolidinedione | 0 (0) | 0 (0) | 1.000 |

Data are n (%) or median (interquartile range). BMI, body mass index; CI, confidence interval; DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin; SGLT-2, sodium–glucose cotransporter 2.

| Table 5 | Details of sulfonylurea prescribed for 25 patients with diabetes aged ≥90 years |
|---------|---------------------------------------------------------------------------------------------------------------|
| Amount of daily dose | No. patients | No. patients with hypoglycemic episodes on medical record within 2 years without change of medication |
| Gliclazide | 10 mg | 1 | 0 |
| | 20 mg | 5 | 0 |
| | 40 mg | 2 | 1 (Concomitant with linagliptin 5 mg/day and miglitol 25 mg/day) |
| | 80 mg | 2 | 0 |
| Glimepiride | 0.5 mg | 1 | 0 |
| | 1 mg | 6 | 3 (Concomitant with sitagliptin in one out of three patients, and with insulin in two out of three patients) |
| | 2 mg | 3 | 1 (Concomitant with sitagliptin 25 mg/day) |
| | 3 mg | 2 | 0 |
| Glibenclamide | 0.625 mg | 1 | 0 |
| | 5 mg | 2 | 0 |
| Total | 25 | 5 |

2014 J Diabetes Investig Vol. 13 No. 12 December 2022 © 2022 The Authors. Journal of Diabetes Investigation published by AASD and John Wiley & Sons Australia, Ltd
the present study and the previous study might be explained by the different proportion of insulin treatment among patients aged ≥90 years. There was no significant difference in the proportion of insulin treatment between group 1 and group 4 in the present study, although the proportion of insulin treatment was significantly higher in patients aged ≥90 years than those aged in their 50s in the previous study. Insulin treatment for elderly people is associated with a higher risk for hypoglycemia; therefore, a higher proportion of insulin treatment in patients aged ≥90 years might induce lower HbA1c in the previous study based on a German large real-world database.

As for blood pressure, in patients aged ≥90 years, systolic blood pressure was higher and diastolic blood pressure was lower than patients aged <65 years. This result was compatible with a previous multicenter cross-sectional study in Japan. However, there was no significant difference between the group aged ≥90 years and the other three groups in achieving blood pressure <130/80 mmHg, which is the blood pressure goal for patients with diabetes determined by the American College of Cardiology and American Heart Association and the Japanese Society of Hypertension. Thus, the present results suggested that glycemic control, blood pressure control and lipid control in patients with diabetes aged ≥90 years were as good as patients aged <65 years. In the present study, the proportion of patients aged ≥90 years that achieved <130/80 mmHg was 39.1%, whereas in the previous population-based, cross-sectional study of 11,645 persons aged ≥90 years with type 2 diabetes living in Madrid, the proportion that achieved <130/80 mmHg was 36.9%. The higher proportion of patients achieving <130/80 mmHg in the present study might be due to differences of the study population, which were patients visiting a specialist diabetes clinic compared with residents in Madrid in the previous study.

In the present study, the proportion of no diabetes medication and the proportion of sulfonylurea treatment was significantly higher among patients aged ≥90 years compared with other generations, whereas the proportion of insulin or glinide treatment was similar to other generations. Higher proportions of no diabetes medication and sulfonylurea treatment were compatible with the previous multicenter, cross-sectional study in Japan. However, in the previous study, patients aged ≥90 years were not treated with sulfonylurea, were not focused on. Furthermore, hypoglycemic episodes and reasons for continuing sulfonylurea were not investigated. Therefore, the present study has novelty in that we focused on Japanese patients aged ≥90 years, especially those treated with sulfonylurea, including the investigation of hypoglycemic episodes and reasons for continuing sulfonylurea.

The present study showed that patients aged ≥90 years treated with sulfonylurea tended to have combination therapy compared with patients not treated with sulfonylurea, although there was no statistically significant difference in the number of antihyperglycemic agents between these groups. Furthermore, there was no significant difference in HbA1c between medicated patients aged ≥90 years treated with or without sulfonylurea. These results might suggest that sulfonylurea was necessary for appropriate glycemic control, because type 2 diabetes in Japanese patients is characterized more by impaired insulin secretion compared with white patients.

The Japan Diabetes Society recommend that sulfonylureas should be initiated at its minimum dose, and titrated depending on renal function and glycemic control, because the use of sulfonylurea is a risk factor for hypoglycemia in elderly patients with diabetes. In the present study, tapering dosage or withdrawal of sulfonylurea were attempted in all patients aged ≥90 years regardless of HbA1c levels. However, approximately one-quarter of these patients were prescribed a high dosage (gliclazide >40 mg/day, glimepiride >2 mg/day or glibenclamide >1.25 mg/day). This might reflect how difficult glycemic control is in elderly patients with diabetes. Our results showed that

| Table 6 | Hypoglycemic episodes and reasons for continuing sulfonylurea of 25 patients with diabetes aged ≥90 years treated with sulfonylurea |
|-----------------|-----------------|-----------------|
| HbA1c (%) | 6.0 ≤ HbA1c <7.0, n = 5 | 7.0 ≤ HbA1c <8.0, n = 16 | 8.0 ≤ HbA1c <9.0, n = 4 |
| eGFR (mL/min/1.73 m²) | 6.6 (6.5, 6.7) | 7.3 (7.2, 7.6) | 8.7 (8.3, 8.7) |
| Proteinuria | 593 (521, 673) | 49.4 (40.8, 675) | 65.0 (47.8, 76.9) |
| Presence of hypoglycemic episodes within 2 years | 0 | 5 | 1 |
| Reasons for continuing sulfonylurea | Tapering dosage, but unable to withdraw sulfonylurea | Resuming after changing from sulfonylurea to other medication | Adding of sulfonylurea because of worsening of glycemic control by other medication Unknown |
| | 0 | 2 | 1 |
| | 6 | 3 | 0 |
| | 2 | 1 | 1 |
| | 7 | | |

Data are n or median (interquartile range). eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin.
two out of four patients treated with combination therapy of insulin and sulfonylurea had hypoglycemic episodes even though they were treated with a small dosage of sulfonylurea (glimepiride 1 mg/day). Therefore, doctors might have to stop sulfonylurea regardless of its dosage when patients aged ≥90 years have insulin treatment. It should be noted that the reasons of continuing sulfonylurea in some patients were unknown in the present study. Recently, “reverse clinical inertia” has been advocated. In contrast with clinical inertia, which means the failure of clinicians to initiate or intensify therapy when indicated, reverse clinical inertia is acknowledged as the failure to stop or reduce therapy when no longer needed. Reverse clinical inertia might have existed in two sulfonylurea-treated patients aged ≥90 years whose reasons for continuing sulfonylurea was unknown, and their HbA1c levels were well below 7%, which is below the lower limit of glycemic control targets for elderly patients with diabetes. Furthermore, a patient whose HbA1c level was <7% resumed sulfonylurea after changing from sulfonylurea to another medication, because the patient was eager to resume sulfonylurea, although there was no adverse effect nor worsening of glycemic control with the new medication. Sulfonylureas are the oldest class of oral antihyperglycemic agents that entered the pharmaceutical market in the mid-1950s, and are still widely prescribed because of their potent glucose-lowering effect and lower cost. Hence, sulfonylureas are familiar to patients with long diabetes history, and patients aged ≥90 years might feel more comfortable using sulfonylureas. Furthermore, lower cost might be an important factor for elderly patients, because they tend to be on many medications and live on a fixed income. These factors might have resulted in the request to resume sulfonylurea by such patients. We should keep in mind the existence of reverse clinical inertia by both doctors and patients, because the cause of clinical inertia is multifactorial, including factors that are physician-related, patient-related and healthcare system-related.

Several limitations of the present study should be acknowledged. First, this study was a single-center observational study and the number of patients with diabetes aged ≥90 years old might not be enough; therefore, it might not represent patients with diabetes aged ≥90 years in Japan. To generalize our findings, a further multicenter study is required. Second, we might have underestimated hypoglycemic events by not being able to detect hypoglycemia due to not using continuous glucose monitoring systems. It was reported in a multicenter cross-sectional study that the duration of hypoglycemia was longer at night than during the daytime in type 2 diabetes patients treated with sulfonylureas; therefore, further study using continuous glucose monitoring system is required. Third, we were unable to obtain the information of retinopathy, functional parameters (e.g., activities of daily living, dementia) and environmental information (e.g., living alone) from the medical records, although all patients with diabetes aged ≥90 years had sufficient activities of daily living to visit our clinic regularly and they were not admitted in a nursing home.

In summary, the present retrospective observational study shows the features of diabetes outpatients aged ≥90 years in an urban diabetes clinic in Tokyo. Although tapering the dosage or withdrawal of sulfonylurea were attempted in patients aged ≥90 years, sulfonylurea was widely continued for glycemic control. In this study, for the first time, we showed the reasons for continuing sulfonylurea for patients aged ≥90 years, despite the proposal by the Joint Committee of Japan Diabetes Society and the Japan Geriatrics Society in 2016, “Glycemic control (HbA1c) goals in elderly patients with diabetes,” raising HbA1c goals and setting the lower limit of HbA1c for elderly patients. We should also pay attention to the possibility of reverse clinical inertia not only by doctors, but also by patients themselves.

ACKNOWLEDGMENT
We acknowledge great appreciation to staff members, especially Nobuhiro Tachibana and Rieko Ichihashi, for their skilled assistance.

DISCLOSURE
The authors declare no conflict of interest. Approval of the research protocol: Approval by the Committee of Ethics in the Institute of Medical Science, Asahi Life Foundation.

Informed consent: Obtained in the form of opt-out on our website.

Registry and the registration no. of the study/trial: 13 January 2021, No. 12605.

Animal studies: N/A.

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