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Title:

The agreement between measured HbA1c and optimized target HbA1c based on the Dementia Assessment Sheet for Community-based Integrated Care System 8-items (DASC-8): A cross-sectional study of elderly patients with diabetes

Authors:

Aika Miya ¹, Akinobu Nakamura ¹, Isao Yokota ², Kyu Yong Cho ^{1,3}, Hiraku Kameda ¹, Hiroshi Nomoto ¹, Takahiro Takase ⁴, Kazuno Omori ¹, Mayuko Ono ⁵, So Nagai ⁶, Shinji Taneda ⁷, Hideaki Miyoshi ^{1,8}, Tatsuya Atsumi ¹

Affiliations:

¹ Department of Rheumatology, Endocrinology and Nephrology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan

1 ² Department of Biostatistics, Graduate School of Medicine, Hokkaido University,
2 Sapporo, Japan

3 ³ Clinical Research and Medical Innovation Center, Hokkaido University Hospital,
4 Sapporo, Japan

5 ⁴ Division of Diabetes and Endocrinology, Kushiro Red Cross Hospital, Kushiro, Japan

6 ⁵ Division of Diabetes and Endocrinology, Tomakomai City Hospital, Tomakomai,
7 Japan

8 ⁶ Division of Diabetes and Endocrinology, Department of Medicine, Sapporo Medical
9 Centre, NTT East Corporation, Sapporo, Japan

10 ⁷ Department of Diabetes Centre, Manda Memorial Hospital, Sapporo, Japan

11 ⁸ Division of Diabetes and Obesity, Faculty of Medicine and Graduate School of
12 Medicine, Hokkaido University Graduate School of Medicine, Sapporo, Japan

13

14

15 Author for correspondence:

16 Aika Miya

17 Department of Rheumatology, Endocrinology and Nephrology, Faculty of Medicine and
18 Graduate School of Medicine, Hokkaido University

- 1 N-15, W-7, Kita-ku, Sapporo 060-8638, Japan
- 2 E-mail: miyaaika@huhp.hokudai.ac.jp
- 3 Tel: +81-11-706-5915
- 4 Fax: +81-11-706-7710
- 5
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ABSTRACT

Aim

To investigate the achievement of individualized target HbA1c based on the Japanese guideline after geriatric assessment by the Dementia Assessment Sheet for Community-based Integrated Care System 8-items (DASC-8) and to evaluate patient characteristics acting as barriers to achieving the target HbA1c in elderly outpatients with diabetes.

Methods

This cross-sectional study enrolled 303 Japanese outpatients aged ≥ 65 years with diabetes. Their health status was measured using the DASC-8. The target HbA1c was optimized for each patient by the guideline based on the DASC-8 score and use of drugs potentially associated with severe hypoglycemia. Patient characteristics related to the agreement between measured HbA1c and target HbA1c were extracted by multivariate logistic regression analysis.

Results

Mean age was 73.0 years and mean body mass index (BMI) 24.2 kg/m². The agreement between measured HbA1c and target HbA1c was 43.9% (95% confidence interval: 38.4%–50.0%). In multivariate logistic regression analysis, the agreement in patients with drugs potentially associated with severe hypoglycemia was significantly lower than in

those without these drugs (37.8% vs 60.5%, $P=0.0004$). In patients with these drugs, higher BMI ($P=0.0271$) and higher fasting plasma glucose ($P=0.0034$) were independent related factors for measured HbA1c higher than target HbA1c. Vulnerable elderly patients ($P=0.0116$) and not taking sodium glucose co-transporter-2 (SGLT2) inhibitor ($P=0.0186$) were independent related factors for inappropriately lower HbA1c.

Conclusions

The agreement between measured HbA1c and target HbA1c was low in elderly patients with diabetes.

Keywords

Elderly patient, DASC-8, HbA1c, Diabetes, Guideline

1 INTRODUCTION

2 Diabetes management in elderly people remains largely complicated. Most national
3 and international guidelines have recommended the de-escalation of therapy for elderly
4 patients with diabetes to minimize the frequency of hypoglycemia.^{1, 2} These patients
5 often experience multiple comorbidities, frailty, polypharmacy, and other conditions
6 that increase hypoglycemic risk.³ Moreover, hypoglycemia has been associated with
7 cognitive dysfunction, and mortality in a number of clinical trials that included elderly
8 patients.⁴⁻⁶ However, insufficiently treated hyperglycemia increases the risk of
9 dehydration, diabetic ketoacidosis, and hyperglycemic hyperosmolar syndrome.⁷ There
10 are few clinical trials on glycemic target specific for oldest-old patients with diabetes.⁸

11 Glycemic targets for elderly patients should be set by considering their own
12 characteristics and health status, such as performance of activities of daily living (ADL)
13 and diabetes self-care, life expectancy, and any support available to the patient.^{2, 9}
14 However, comprehensive geriatric assessment in daily clinical practice is sometimes
15 difficult because the evaluations are time-consuming and require the careful cooperation
16 of medical staff.

17 To evaluate cognitive impairment and disability in daily functioning, many useful
18 tools have been developed.¹⁰⁻¹³ Among them, the Dementia Assessment Sheet for

Community-based Integrated Care System 8-items (DASC-8) is well validated and convenient for classifying patients in the community into the appropriate categories for geriatric assessment.¹⁴

The Japan Diabetes Society (JDS)/Japan Geriatrics Society (JGS) Joint Committee on Improving Care for Elderly Patients with Diabetes in 2016 developed glycemic targets for elderly patients with diabetes. This national guideline is intended to improve quality of care for patients who are at risk for hypoglycemia. The glycemic target is to be determined for each patient by taking into account age, the risk for hypoglycemia, background and health status (Supplementary Table S1).² However, how closely real-world clinical practices adhere to this national guideline is currently unknown.

This study had two goals. One was to investigate the actual state of the achievement of individualized target HbA1c determined based on the national guideline after applying the DASC-8 to elderly Japanese outpatients with diabetes. Second, we evaluated patient characteristics that are barriers to achieving the optimized target HbA1c.

METHODS

Study population and design

This multicenter cross-sectional study enrolled elderly (≥ 65 years) Japanese outpatients with diabetes from Hokkaido University Hospital, Manda Memorial Hospital, NTT Sapporo Medical Center, Hokkaido Chuo Rosai Hospital, Kushiro Red Cross Hospital, and Tomakomai City Hospital. Patients aged ≥ 65 years were eligible if they consented to undergo assessments of their cognitive functions and ADL. We recruited patients whatever their background, including category of diabetes, HbA1c level, sex, duration of diabetes, complications from diabetes, and social conditions such as caregiver support or nursing homestay. Patients were recruited and provided fasting blood samples.

The study was registered with the University Hospital Medical Information Network (UMIN) Center, registration number UMIN000037177. The study protocol was approved by the institutional review board at Hokkaido University Hospital Clinical Research and Medical Innovation Center (019-0063), and it was conducted in accordance with the Declaration of Helsinki. Prior to the study enrollment, signed informed consent was obtained from each patient, as well as from family members or other supportive adults attending the patients, if applicable. If participants were

1 recognized by the attending physician as unable to provide informed consent because of
2 dementia, the patients provided assent to have a family member or another supportive
3 adult provide informed consent on their behalf, and we obtained proxy consent from
4 them.

6 **Biochemical analyses and data collection**

7 For this study, blood samples were collected after an overnight fast to measure
8 levels of HbA1c, plasma glucose, C-peptide as a marker of endogenous insulin
9 secretion, and estimated glomerular filtration rate. These parameters were measured
10 using standard techniques. The weight and height of the patients were measured using a
11 calibrated scale. The body mass index (BMI) was calculated as the weight (in kg)
12 divided by height (in m²). Other data including age, sex, duration of diabetes, treatment
13 regimen, complications from diabetes, medical history, physical activity, and social
14 conditions were collected using a questionnaire administered by the attending
15 physicians.

17 **DASC-8**

Patients' cognitive functions and ADL were measured using the DASC-8.^{14, 15} The classification of the three categories using the DASC-8 score was conducted based on previously published guidelines.² Specifically, participants with a DASC-8 score ≤ 10 , 11–16, or ≥ 17 were classified as Categories I, II, or III, respectively. Category I represented the patient with intact cognitive function in the absence of ADL impairment, Category II the patient with mild cognitive impairment and mild dementia/instrumental ADL impairment but without basic ADL (BADL) impairment, and Category III the patient with moderate or severe dementia plus BADL impairment. To evaluate cognitive impairment objectively, a family member or another supportive adult attending the patient was asked to answer the DASC-8. For some elderly patients visiting alone, a well-trained physician or medical staff member asked the questions and recorded the answers.

Selection of target HbA1c for patients

The individualized target HbA1c range was determined for each patient by the DASC-8 category classified as Category I, II, or III, and by the use of drugs potentially associated with severe hypoglycemia (e.g. insulin formulations, sulfonylureas, glinides) based on the Japanese guideline stipulated by the JDS/JGS Joint Committee on

Improving Care for Elderly Patients with Diabetes.² In this national guideline, specific lower limit is not recommended for the target HbA1c range for patients without drugs potentially associated with severe hypoglycemia. However, both upper and lower limits of the target HbA1c range are set for patients with these drugs to prevent severe hypoglycemia in daily clinical practice (Supplementary Table S1).

Data analysis

We first assessed the agreement between measured HbA1c and target HbA1c, along with a 95% confidence interval, in all patients. Second, we carried out similar stratified analysis and evaluated the agreement in patients with and without drugs potentially associated with severe hypoglycemia. We used Fisher's exact test to compare the agreement between the groups. Next, we explored specific characteristics to be barriers to achieving target HbA1c in each group after we divided patients into subgroups based on whether their measured HbA1c levels were above the higher limit of the target HbA1c range (above HbA1c), within the range, or inappropriately below the lower limit of target HbA1c range (inappropriately below HbA1c). We used the Mann-Whitney U-test or Kruskal-Wallis test to compare median for continuous variables (such as age), and chi-square test or Fisher's exact test to compare proportions

for categorical variables between the groups. Results are shown as median (interquartile range) for continuous variables and count (percentage) for categorical variables. The candidate variables chosen from significant variables with $P<0.05$ in the univariate analysis were included in multivariate logistic regression analysis after we confirmed that there were no indications of multicollinearity between these variables. All tests were two-sided, and $P<0.05$ was considered to represent statistical significance. Data analyses were conducted using JMP Pro, version 16.0.0 (SAS Institute, Inc., Cary, NC, USA).

1 **RESULTS**

2 **Patient characteristics**

3 Of a total of 312 patients enrolled in the study, 303 patients (137 women) were
4 included in the subsequent analyses (Supplementary Figure S1). Their characteristics are
5 shown in Table 1. The overall median age of the patients was 73 years, their median BMI
6 24.2 kg/m². According to the DASC-8 score, the proportion of patients classified into
7 Categories I, II, and III were 63.4% (*n*=192), 26.7% (*n*=81) and 9.9% (*n*=30), respectively.

9 **The agreement between measured HbA1c and target HbA1c**

10 The agreement between measured HbA1c and target HbA1c was 43.9% in whole [95%
11 confidence interval (CI): 38.4%–50.0%]. Table 2 shows the agreement in each group
12 classified based on the DASC-8 category and use of drugs potentially associated with
13 severe hypoglycemia. The agreement in patients with these drugs was significantly lower
14 than those without these drugs (37.8% vs 60.5%, *P*=0.0004). In Category I, there was no
15 significant difference in this agreement between patients with and without these drugs
16 (41.5% vs 54.4%, *P*=0.1008). In Categories II and III, the agreement in those with these
17 drugs was significantly lower than those without these drugs (32.8% vs 64.7%, *P*=0.0250
18 and 30.4% vs 100.0%, *P*=0.0017, respectively).

Patient characteristics as barriers to achieving target HbA1c in patients with drugs potentially associated with severe hypoglycemia

Of the 303 patients, 222 patients were receiving drugs potentially associated with severe hypoglycemia. These patients were divided into the following three subgroups: above HbA1c ($n=86$), within the range ($n=84$), and inappropriately below HbA1c ($n=52$). The biochemical and anthropometric characteristics of each subgroup are shown in Table 1. The DASC-8 category, HbA1c, BMI, fasting plasma glucose (FPG), use of glucagon-like peptide-1 receptor agonist (GLP-1 RA), use of dipeptidyl peptidase-4 (DPP-4) inhibitor, and use of sodium-glucose cotransporter 2 (SGLT2) inhibitor differed between the three subgroups. No significant difference in social conditions was observed between the three subgroups. There was no significant difference in hemoglobin level between the three subgroups (data was not shown).

The variance inflation factor (VIF) for FPG and HbA1c was 1.188 (this was less than the cutoff of 2.0). No indications of multicollinearity were found for these variables. FPG was included in the multivariate analysis because it was considered a potential confounder. The VIF values for the other candidate variables (chosen from among significant variables with $P < 0.05$ in the univariate analysis) were all less than

3.0 (Supplementary Table S2). Thus, there were no indications of multicollinearity for these variables. With the exception of HbA1c, these variables were included in multivariate logistic regression analysis. Multivariate logistic regression analysis showed that higher BMI [odds ratio (OR) 1.10, 95% CI: 1.01–1.20, $P=0.0271$] and higher FPG (OR 1.01, 95% CI: 1.00–1.02, $P=0.0034$) were independently associated with measured HbA1c higher than the target HbA1c (Table 3). Classification as Category III (OR 4.30, 95% CI: 1.3–13.32, $P=0.0116$) and not taking a SGLT2 inhibitor (OR 0.24, 95% CI: 0.07–0.79, $P=0.0186$) were independent factors for inappropriately lower measured HbA1c than the target HbA1c (Table 3).

SGLT2 inhibitor is generally not used in elderly patients with moderate or severe dementia and BADL impairment. In this study, there was a trend toward less frequent use of SGLT2 inhibitor in patients with drugs potentially associated with severe hypoglycemia classified as Category III (71.2%, 26.9%, and 1.9% in Categories I, II, and III, respectively). To discuss whether use of this agent affects achieving a glycemic target, we carried out a similar stratified analysis for patients with drugs potentially associated with severe hypoglycemia not classified as Category III. The 199 patients with these drugs classified in Categories I and II were allocated to three subgroups: above HbA1c ($n=82$), within the range ($n=77$), and inappropriately below HbA1c ($n=40$). The biochemical and

anthropometric characteristics of each subgroup are shown in Supplementary Table S3. HbA1c, BMI, FPG, use of GLP-1 RA, and use of SGLT2 inhibitor differed between the three subgroups. Multivariate logistic regression analysis showed that higher BMI (OR 1.10, 95% CI: 1.01–1.21, $P=0.0282$) and higher FPG (OR 1.01, 95% CI: 1.00–1.02, $P=0.0041$) were independently associated with measured HbA1c higher than the target HbA1c (Supplementary Table S4). Not taking SGLT2 inhibitor (OR 0.21, 95% CI: 0.05–0.66, $P=0.0067$) was an independent related factor for an inappropriately lower measured HbA1c than the target HbA1c (Supplementary Table S4).

Patient characteristics as barriers to achieving target HbA1c in patients without drugs potentially associated with severe hypoglycemia

Because no lower limit was specified for the target HbA1c,² the 81 patients not taking drugs potentially associated with severe hypoglycemia were divided into the following two subgroups: above HbA1c ($n=32$), within the range ($n=49$). The biochemical and anthropometric characteristics of each subgroup are shown in Table 1. The significant variables with $P<0.05$ in the univariate analysis except HbA1c were included in multivariate logistic regression analysis. Higher FPG (OR 1.03, 95% CI:

1 1.01–1.06, $P=0.0058$) was independently associated with measured HbA1c higher than
2 the target HbA1c (Table 3).

3 **DISCUSSION**

4 Our present study reported the achievement of individualized target HbA1c
5 determined based on the national guideline for the first time after assessing patient
6 characteristics and health status by using the DASC-8. We identified characteristics
7 related to the achievement of target HbA1c in elderly Japanese outpatients with diabetes
8 in a real-world clinical practice. Regarding of results of special interest, the agreement
9 between measured HbA1c and target HbA1c was low. This finding was especially
10 apparent in patients treated with drugs potentially associated with severe hypoglycemia.
11 Importantly, more than 20% of patients had inappropriately low HbA1c. In patients
12 treated with these drugs, body weight and FPG were related to higher HbA1c levels.
13 Classified as not being in good health and not taking SGLT2 inhibitor were
14 characteristics found to be related factors for inappropriately low HbA1c levels.

15 There was no data available until now that evaluated diabetes management on the
16 national guideline after screening of dementia and ADL impairment using the DASC-8
17 score. Although the cross-sectional studies of elderly patients reported the agreement
18 between measured and target HbA1c,¹⁶ the individualized target HbA1c levels were

1 determined at the discretion of the attending physicians. Even the relationship between
2 characteristics of elderly patients and measured HbA1c was reported, those patients had
3 not been assessed for ADL or health status.^{17, 18} Our results would be valuable because
4 we evaluated those factors appropriately by using the DASC-8 and determined target
5 HbA1c based on the national guideline after enrolling outpatients with complex and
6 diverse backgrounds.

7 This guideline set the lower limit of target HbA1c for patients with drugs
8 potentially associated with severe hypoglycemia, but not without these drugs.² This
9 difference could be the primary reason why use of these drugs was a barrier to attaining
10 appropriate HbA1c levels in elderly patients. More importantly, the achievement of
11 target HbA1c in patients with these drugs was lower than that in those without these
12 drugs, especially in patients classified as Categories II and III. The use of drugs
13 potentially associated with severe hypoglycemia in patients classified as Category III
14 was associated with inappropriately low levels of HbA1c. Notably, more than 50% of
15 vulnerable elderly patients had inappropriately low HbA1c. Since this high percentage
16 was observed in diabetic clinics, it should also be carefully considered in general
17 hospitals. These results suggested that attending physicians tended to manage diabetes
18 intensively for elderly patients unless they experienced some episodes of hypoglycemia.

1 However, patients with cognitive impairment have a higher risk of symptomatic or
2 asymptomatic hypoglycemia when they received drugs potentially associated with
3 severe hypoglycemia.^{16, 19} Physicians should design the glycemic targets for to be higher
4 for patients in Category III based on the guideline to minimize hypoglycemia.

5 The safety and effectiveness of SGLT2 inhibitor were reported recently in elderly
6 patients with diabetes, but SGLT2 inhibitor should be at least used with caution,
7 particularly for elderly patients with frailty or sarcopenia after they have been
8 sufficiently educated about sick-day rules.²⁰⁻²² Although not taking an SGLT2 inhibitor
9 was a related factor for inappropriately low HbA1c levels for patients not in Category
10 III (Supplementary Table S4), it would be difficult to discuss whether SGLT2 inhibitor
11 affects appropriate HbA1c levels due to a cross-sectional design. Unfortunately, we did
12 not assess sarcopenia status in this study. Attending physicians might tend not to add
13 SGLT2 inhibitor to patients with below target HbA1c from the past. The lack of
14 assessment of these factors may represent a limitation of the study.

15 Use of drugs potentially associated with severe hypoglycemia is associated with
16 weight gain, leading to worsening insulin resistance.²³ Previous studies reported that
17 sarcopenia was much more prevalent in obese than nonobese patients,²⁴ and that
18 sarcopenic obesity was associated with increased insulin resistance and higher levels of

HbA1c.²⁵ These findings supported our results that higher body weight made diabetes management more difficult in patients treated with drugs potentially associated with severe hypoglycemia, and FPG contributes to the determination of HbA1c.²⁶

The present study had several limitations. The 303 elderly patients in this study might not reflect the general population. The proportion of patients classified into Categories II and III expected to have dementia (36.6%) in our data was higher than the prevalence of dementia (15%) in elderly Japanese individuals nationwide.²⁷ We included patients regardless of glycemic control and social conditions. Diabetes is associated with a two-fold greater risk factor for dementia and mild cognitive impairment.^{28, 29} Therefore, patients' heterogeneity in this study was suggested to represent the general characteristics of elderly Japanese patients with diabetes. Our results could be applicable not only in elderly Japanese patients but also in other ethnic groups in countries with an aging society.

The present study was carried out at diabetic outpatient clinics which can conduct comprehensive geriatric assessment appropriately thanks to the careful cooperation of diabetes specialist staff. Under the circumstances, the choice of antidiabetic drugs and managing weight rather than the patient's ADL or health status might be relevant to the

1 agreement between measured HbA1c and target HbA1c. It is unknown whether the
2 current results are applicable to general patients cared for by general practitioners.

3 Because of a study of outpatients, our findings do not apply to inpatients. Although
4 we have discussed the relationship between sarcopenic obesity and glucose tolerance,
5 sarcopenia was not evaluated. The existence of other unassessed confounders, including
6 the frequency of hypoglycemia, depressive moods, diet, or inflammation might have
7 affected HbA1c. These findings need to be validated in a prospective, randomly
8 selected population.

9 In conclusion, the agreement between measured HbA1c and target HbA1c based on
10 the national guideline was low in elderly patients with diabetes. Among vulnerable
11 elderly patients who had received drugs potentially associated with severe
12 hypoglycemia, more than 50% exhibited inappropriately low HbA1c.

13

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DATA AVAILABILITY

The analyzed datasets are available from the corresponding author on reasonable request.

DISCLOSURE STATEMENT

This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors have no conflicts of interest for the submitted work.

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1 **SUPPLEMENTARY TABLE LEGENDS**

2 Supplementary Table S1

3 Glycemic targets (HbA1c values) for older patients stipulated by the JDS/JGS Joint

4 Committee on Improving Care for Elderly Patients with Diabetes

5

6 Supplementary Table S2

7 Calculated variance inflation factors

8

9 Supplementary Table S3

10 Patient backgrounds in patients with drugs potentially associated with severe hypoglycemia

11 classified as Categories I and II

12

13 Supplementary Table S4

14 Clinical factors of higher and inappropriately lower measured HbA1c compared with target

15 HbA1c by multivariate logistic regression analysis in patients with drugs potentially

16 associated with severe hypoglycemia classified as Categories I and II

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18 **SUPPLEMENTARY FIGURE LEGEND**

- 1 Supplementary Figure S1
- 2 Flow chart of patients during the study.

Table 1. Patient backgrounds overall and those in patients with/without drugs potentially associated with severe hypoglycemia

	Whole	Patients with drugs potentially associated with hypoglycemia					Patients without drugs potentially associated with hypoglycemia			
			inappropriately			<i>P</i> value				
			above	within the range	below			above	within the range	<i>P</i> value
n (%)	303 (100.0)	222	86 (38.7)	84 (37.8)	52 (23.4)		81	32 (39.5)	49 (60.5)	
Age (years)	73 (69, 78)	75 (70, 80)	72 (69, 80)	74 (69, 79)	76 (72, 80)	0.0692	72 (68, 76)	71 (67, 75)	72 (69, 76)	0.1877
Number of female, n (%)	137 (45.2)	101 (45.5)	42 (48.8)	38 (45.2)	21(40.4)	0.6258	36 (44.4)	15 (46.9)	21 (42.9)	0.7220
BMI (kg/m ²)	24.2 (21.8, 26.7)	24.0 (21.7, 26.7)	25.4 (22.2, 28.3)	23.5 (20.9, 25.6)	23.1 (20.8, 26.1)	0.0136*	24.2 (22.0, 26.4)	24.6 (23.1, 28.6)	23.4 (21.6, 25.8)	0.0320*
Diabetes duration (years)	19 (11, 26)	20 (12, 30)	20 (13, 28)	21 (10, 31)	20 (15, 30)	0.8863	12 (6, 20)	14 (7, 20)	12 (4, 20)	0.3916
HbA1c (%)	7.2 (6.7, 7.9)	7.5 (6.9, 8.1)	8.2 (8.0, 8.9)	7.3 (7.0, 7.6)	6.5 (6.1, 6.8)	<0.0001*	6.8 (6.3, 7.1)	7.2 (7.1, 7.6)	6.4 (6.2, 6.8)	<0.0001*
HbA1c (mmol/mol)	55 (49, 62)	58 (51, 65)	66 (63, 73)	56 (52, 59)	47 (43, 50)	<0.0001*	50 (45, 54)	55 (54, 59)	46 (44, 50)	<0.0001*

FPG (mg/dL)	138 (116, 166)	146 (121, 178)	162 (129, 200)	143 (119, 158)	133 (109, 157)	0.0005*	126 (112, 142)	138 (126, 152)	117 (104, 135)	0.0001*
Fasting CPR (ng/mL)	1.5 (0.9, 2.2)	1.4 (0.7, 2.2)	1.5 (0.6, 2.3)	1.1 (0.5, 2.0)	1.5 (0.9, 2.1)	0.3027	1.9 (1.4, 2.6)	2.1 (1.5, 2.7)	1.6 (1.2, 2.3)	0.0928
eGFR	58.5 (45.1, 71.2)	57.1 (44.6, 70.2)	55.1 (44.1, 68.2)	61.5 (45.1, 71.7)	55.8 (39.6, 68.2)	0.1796	63.1 (48.6, 76.9)	63.0 (50.2, 78.5)	63.1 (44.1, 75.8)	0.6602
DASC-8 score, n (%)	10 (8, 12)	10 (8, 13)	10 (8, 13)	9 (8, 12)	11 (9, 14)	0.0698	9 (8, 11)	9 (8, 10)	9 (8, 12)	0.0569
Category I	192 (63.4)	135 (60.8)	53 (61.6)	56 (66.7)	26 (50.0)		57 (70.4)	26 (81.3)	31 (63.3)	
Category II	81 (26.7)	64 (28.8)	29 (33.7)	21 (25.0)	14 (26.9)	0.0078*	17 (21.0)	6 (18.8)	11 (22.5)	0.0612
Category III	30 (9.9)	23 (10.4)	4 (4.7)	7 (8.3)	12 (23.1)		7 (8.6)	0 (0)	7 (14.3)	
Physically active (≥10METs/week), n (%)	231 (76.2)	165 (74.3)	63 (73.3)	68 (81.0)	34 (65.4)	0.1247	66 (81.5)	26 (81.3)	40 (81.6)	0.9654
Complications, n (%)										
Diabetic neuropathy	218 (71.9)	164 (73.9)	68 (79.1)	61 (72.6)	35 (67.3)	0.4960	54 (66.7)	25 (78.1)	29 (59.2)	0.0771
Diabetic retinopathy	113 (38.3)	96 (44.4)	38 (44.7)	38 (46.3)	20 (40.8)	0.8257	17 (21.5)	7 (21.9)	10 (21.3)	0.9493

Diabetic nephropathy	162 (53.5)	131 (59.0)	51 (59.3)	45 (53.6)	35 (67.3)	0.2850	31 (38.3)	15 (46.9)	16 (32.7)	0.1980
Hypertension	225 (74.3)	170 (76.6)	70 (81.4)	62 (73.8)	38 (73.1)	0.4011	55 (67.9)	20 (62.5)	35 (71.4)	0.4001
Dyslipidemia	221 (72.9)	163 (73.4)	68 (79.1)	61 (72.6)	34 (65.4)	0.2065	58 (71.6)	25 (78.1)	33 (67.4)	0.2930
Stroke or TIA	43 (14.2)	30 (13.5)	16 (18.6)	7 (8.33)	7 (13.5)	0.1469	13 (16.1)	6 (18.8)	7 (14.3)	0.5926
Cardiovascular disease	64 (21.1)	53 (23.9)	21 (24.4)	21 (35.0)	11 (21.2)	0.8675	11 (13.6)	6 (18.8)	5 (10.2)	0.2724
Osteoporosis	50 (16.5)	38 (17.1)	18 (20.9)	10 (11.9)	10 (19.2)	0.2653	12 (14.8)	6 (18.8)	6 (12.2)	0.4204
Malignancy	83 (27.4)	60 (27.0)	20 (23.3)	22 (26.2)	18 (34.6)	0.3382	23 (28.4)	11 (34.4)	12 (24.5)	0.3348
Social conditions, n (%)						0.1075				0.6196
Living with a partner	161 (53.1)	117 (52.7)	38 (44.2)	53 (63.1)	26 (50.0)		44 (54.3)	19 (59.4)	25 (51.0)	
Living with children	70 (23.1)	50 (22.5)	26 (30.2)	10 (11.9)	14 (26.9)		20 (24.7)	6 (18.8)	14 (28.6)	
Living with elder parents	2 (0.7)	2 (0.9)	1(1.2)	0 (0)	1(1.9)		0 (0)	0 (0)	0 (0)	

Living alone	63 (20.8)	47 (21.2)	18 (20.9)	20 (23.8)	9 (17.3)		16 (20.0)	7 (21.9)	9 (18.4)	
Nursing home stay	7 (2.3)	6 (2.7)	3 (3.5)	1 (1.2)	2 (3.9)		1 (1.2)	0 (0)	1 (2.0)	
Diabetes treatment, n (%)										
Drugs potentially										
associated with severe	222 (73.3)	222 (100.0)	86 (100.0)	84 (100.0)	52 (100.0)		0 (0)	0 (0)	0 (0)	
hypoglycemia										
Insulin use	149 (49.2)	149 (67.1)	56 (65.1)	61 (72.6)	32 (61.5)	0.3603	0 (0)	0 (0)	0 (0)	
Sulfonylurea	57 (18.8)	57 (25.7)	24 (27.9)	21 (25.0)	12 (23.1)	0.8072	0 (0)	0 (0)	0 (0)	
Glinide	52 (17.2)	52 (23.4)	20 (23.3)	19 (22.6)	13 (25.0)	0.9495	0 (0)	0 (0)	0 (0)	
α -glucosidase inhibitor	37 (12.2)	29 (13.1)	14 (16.3)	11 (13.1)	4 (7.7)	0.3492	8 (9.9)	2 (6.3)	6 (12.2)	0.3767
Metformin	142 (46.9)	102 (46.0)	43 (50.0)	36 (42.9)	23 (22.6)	0.6208	40 (49.4)	20 (62.5)	20 (40.8)	0.0564
Thiazolidine	18 (5.9)	11 (5.0)	3 (3.5)	5 (6.0)	3 (5.8)	0.7249	7 (8.6)	4 (12.5)	3 (6.1)	0.3180

GLP-1 receptor agonist	57 (18.8)	51 (23.0)	30 (34.9)	16 (19.1)	5 (9.6)	0.0016*	6 (7.4)	4 (12.5)	2 (4.1)	0.1573
DPP-4 inhibitor	194 (64.0)	131 (59.0)	42 (48.8)	50 (59.5)	39 (75.0)	0.0101*	63 (77.8)	23 (71.9)	40 (81.6)	0.3018
SGLT2 inhibitor	81 (26.7)	52 (23.4)	26 (30.2)	21 (25.0)	5 (9.6)	0.0196*	29 (35.8)	19 (59.4)	10 (20.4)	0.0003*
Injecting oneself	148 (64.3)	143 (87.7)	58 (87.9)	56 (88.9)	29 (85.3)	0.8749	5 (83.3)	4 (100.0)	1 (50.0)	0.1213
Number of concomitant antidiabetic drugs, n	3 (2, 3)	3 (2, 4)	3 (2, 4)	3 (2, 4)	3 (2.3)	0.1356	2 (1, 3)	2 (1, 3)	2 (1, 2)	0.0136*

Values are expressed as median (interquartile range) or number (%) of patients in each category. The Mann-Whitney U-test, Kruskal-Wallis test, chi-square test or Fisher’s exact test was used for comparisons of the parameters.

BMI: body mass index; FPG: fasting plasma glucose; CPR: C-peptide; eGFR: estimated glomerular filtration rate; GLP-1: glucagon-like peptide-1; DPP-4: dipeptidyl peptidase-4; SGLT2: sodium-glucose cotransporter 2; TIA: transient ischemic attack

Table 2. Agreement between measured HbA1c and target HbA1c among groups classified on the basis of the DASC-8 category and use of drugs potentially associated with severe hypoglycemia.

		Whole	Category I	Category II	Category III
		n= 222	n= 135	n= 64	n= 23
Patients with drugs potentially associated with severe hypoglycemia	above	38.7% (95% CI: 32.6–45.3)	39.3% (95% CI: 31.4–47.7)	45.3% (95% CI: 33.7–57.4)	17.4% (95% CI: 7.0–37.1)
	within the range	37.8%** (95% CI: 31.7–44.4)	41.5% (95% CI: 33.5–50.0)	32.8%† (95% CI: 22.6–45.0)	30.4%‡‡ (95% CI: 15.6–50.9)
	inappropriately below	23.4% (95% CI: 18.3–29.4)	19.3% (95% CI: 13.5–26.7)	21.9% (95% CI: 13.5–33.4)	52.1% (95% CI: 33.0–70.8)
		n= 81	n= 57	n= 17	n= 7
Patients without drugs potentially associated with severe hypoglycemia	above	39.6% (95% CI: 29.6–50.4)	45.6% (95% CI: 33.3–58.4)	35.3% (95% CI: 17.3–58.7)	0%
	within the range	60.5% (95% CI: 49.6–70.4)	54.4% (95% CI: 41.6–66.6)	64.7% (95% CI: 41.3–82.7)	100.0% (95% CI: 64.6–100.0)

***P* < 0.01 vs patients without drugs potentially associated with severe hypoglycemia

†*P* < 0.05 vs category II without drugs potentially associated with severe hypoglycemia

‡‡*P* < 0.01 vs category III without drugs potentially associated with severe hypoglycemia

Table 3. Clinical factors of higher and inappropriately lower measured HbA1c compared with the target HbA1c by multivariate logistic regression analysis

Clinical factors of higher measured HbA1c than target HbA1c in patients with drugs potentially associated with severe hypoglycemia

	Odds ratio	95% CI	<i>P</i> value
Category II / Category I	1.0402	0.4887 to 2.2141	0.9186
Category III / Category I	0.5077	0.1218 to 2.1159	0.3519
Category III / Category II	0.4880	0.1136 to 2.0975	0.3349
BMI (kg/m ²)	1.1003	1.0130 to 1.2016	0.0271*
FPG (mg/dL)	1.0117	1.0043 to 1.0200	0.0034*
Use of GLP-1 receptor agonist	2.5037	0.8828 to 7.1009	0.0844
Use of DPP-4 inhibitor	1.1352	0.4682 to 2.7524	0.7789
Use of SGLT2 inhibitor	1.3240	0.6237 to 2.8105	0.4649

Clinical factors of inappropriately lower measured HbA1c than target HbA1c in patients with drugs potentially associated with severe hypoglycemia

	Odds ratio	95% CI	<i>P</i> value
Category II / Category I	2.0069	0.8173 to 4.9278	0.1285
Category III / Category I	4.2953	1.3852 to 13.3196	0.0116*

Category III / Category II	2.1403	0.6267 to 7.3090	0.2246
BMI (kg/m ²)	1.0815	0.9793 to 1.2018	0.1297
FPG (mg/dL)	0.9922	0.9807 to 1.0030	0.1694
Use of GLP-1 receptor agonist	0.3554	0.0810 to 1.5594	0.1703
Use of DPP-4 inhibitor	1.1791	0.4204 to 3.3064	0.7542
Use of SGLT2 inhibitor	0.2422	0.0744 to 0.7886	0.0186*

Clinical factors of higher measured HbA1c than target HbA1c in patients without drugs potentially associated with severe hypoglycemia

	Odds ratio	95% CI	<i>P</i> value
BMI (kg/m ²)	1.1011	0.9636 to 1.2680	0.1546
FPG (mg/dL)	1.0346	1.0114 to 1.0623	0.0058*
Number of concomitant antidiabetic drugs	1.1826	0.5511 to 2.5589	0.6650
Use of SGLT2 inhibitor	3.3512	0.7965 to 15.2225	0.1040

BMI: body mass index; FPG: fasting plasma glucose; GLP-1: glucagon-like peptide-1; DPP-4: dipeptidyl peptidase-4; SGLT2:

sodium-glucose cotransporter 2