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Verification of Kumamoto Declaration 2013 and Glycemic Targets for Elderly Patients with Diabetes in Japan for prevention of diabetic complications: A retrospective longitudinal study using outpatient clinical data

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Keywords
Japanese type 2 diabetes, JDS/JGS guideline, Kumamoto Declaration

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ABSTRACT

Aims/Introduction: The present study examined the association between the onset of micro- and macroangiopathy in type 2 diabetes mellitus patients and levels of glycated hemoglobin (HbA1c) described in the Evidence-based Practice Guideline for the Treatment for Diabetes in Japan 2013 or those indicated in the Japan Diabetes Society and the Japan Geriatrics Society Joint Committee on Improving Care for Elderly Patients with Diabetes.

Materials and Methods: Patients with type 2 diabetes mellitus who visited the outpatient clinic at Kawasaki Medical School Hospital between 2000 and 2016 and received follow up for >2 years were eligible for the present study. Two datasets, comprising 2,424 or 3,316 patients without micro- or macroangiopathy at the start of follow up, were used, respectively. The Cox model was used in two categories of patients, younger and elderly, with the dividing line set at the age of 65 years.

Results: For the prevention of microangiopathy, in all patients, there was found to be no advantage in controlling HbA1c at a level of <6.0% based on the categories in the Evidence-based Practice Guideline for the Treatment for Diabetes in Japan 2013, and there was found to be a disadvantage in maintaining HbA1c ≥8.5% based on the categories in the Japan Diabetes Society and the Japan Geriatrics Society Joint Committee on Improving Care for Elderly Patients with Diabetes guideline. For the prevention of macroangiopathy in younger patients, there seemed to be an advantage in maintaining HbA1c within the range of 6.0–6.9% and <7.0% based on the Evidence-based Practice Guideline for the Treatment for Diabetes in Japan 2013 and the Japan Diabetes Society and the Japan Geriatrics Society Joint Committee on Improving Care for Elderly Patients with Diabetes, respectively.

Conclusions: In all type 2 diabetes mellitus patients, average HbA1c should be maintained <7.0% to prevent microangiopathy. However, in elderly patients, no optimal target for preventing macroangiopathy was found, in contrast to the younger patients in the present study.

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INTRODUCTION

The ultimate goal for individuals with diabetes is to secure years of healthy life and to maintain the quality of life, just as in the case of healthy individuals. To achieve this objective, it is important to prevent the onset and progression of various diabetic complications. This new philosophy was initially described in the Japanese language Evidence-based Practice Guideline for the Treatment for Diabetes in Japan 2013, which was widely announced at the 56th annual meeting of the Japan Diabetes Society, held in Kumamoto, Japan, in 2013, and therefore became known as the "Kumamoto Declaration 2013"[1]. The declaration set the glycated hemoglobin (HbA1c) target level at <7.0% to ensure the prevention of diabetic microvascular complications, while recommending that glycemic control goals be determined individually. In daily clinical practice, in addition to the HbA1c level of 7%, HbA1c of 6 and 8% should also be considered as measures of glycemic control. HbA1c of 6% represents the optimal target for ensuring normalization of glucose levels, in an ideal scenario[1]. Indeed, a recent large clinical trial carried out in Japan (Japan Diabetes Optimal Integrated Treatment study for three major risk factors of cardiovascular diseases [J-DOIT3])[2] showed that strict control of blood glucose levels by maintaining average HbA1c at 6.8% and of several other risk factors prevented micro- and macroangiopathy even when compared with a slightly higher HbA1c of 7.2%.

In contrast, the Japan Diabetes Society (JDS)/Japan Geriatrics Society (JGS) Joint Committee on Improving Care for Elderly Patients with Diabetes was launched in April 2015 (JDS/JGS)[3]. This report recommended that glycemic targets for elderly patients be determined for each patient based on consideration of the patient's age, medication(s) used, cognitive function, basic/instrumental activities of daily living and comorbidities/functional impairments. The HbA1c goals in this report were <7.0% with intact cognitive function and no impairment of activities of daily living, and <8.5% with moderate or severe dementia, impairment (s) of basic activities of daily living, or the presence of multiple comorbidities or functional impairments.

Although these guidelines are useful and have broad utility, two clinical questions arise with respect to the risk of diabetic complications. One question is the risks inherent in strict control of HbA1c at <6.0% in elderly patients. The other is the risks in controlling HbA1c at a level of >8.5% in younger patients. In the present study, we examined the association between target levels of HbA1c described in the Kumamoto Declaration or in the JDS/JGS and the onset of micro- and macroangiopathy in younger and elderly Japanese patients – with the dividing line set at the age of 65 years – who had type 2 diabetes.

MATERIALS AND METHODS

Study population and patient preparation

Patients who visited the diabetes outpatient clinic at Kawasaki Medical School Hospital between 2000 and 2016, and were diagnosed with type 2 diabetes and who could be followed for a period of >2 years were eligible for the present study. To investigate the onset of micro- and macroangiopathy, two datasets were prepared. One comprised 2,424 patients without microangiopathy at the start of follow up with no consideration paid to macroangiopathy. The other dataset totaled 3,316 patients without macroangiopathy at the start of follow up with no consideration paid to microangiopathy. In the dataset comprising 2,424 patients with microangiopathy, 1,006 patients were followed for >2 years and <3 years from whom two sets of HbA1c data during the 3 months from August to October every year were obtained, with the aim of reducing the effects of seasonal variation. In addition, 306, 203, 165, 157, 162, 101, 53, 62, 57, 56, 56, 11, 15 and 14 patients were followed for 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 and 16 years, respectively, from whom HbA1c data based on the number of years they were followed were obtained. In the dataset comprising 3,316 patients for macroangiopathy, 1,166 patients were followed for >2 years and <3 years from whom two sets of HbA1c data were obtained. Furthermore, 470, 288, 240, 235, 256, 149, 81, 103, 87, 86, 101, 15, 21 and 18 patients were followed for 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 and 16 years, respectively, from whom HbA1c data based on the number of years they were followed were obtained. To evaluate the status of prolonged glycemic control, average HbA1c was calculated in every patient for the number of observation years. The hospital's ethics committee approved the study protocol, and information on the study was provided to the public by the Internet, instead of informed consent being obtained from each patient (No. 2847). Data collection for variables, such as type(s) of medication and duration of diabetes, as well as biochemical data, was carried out starting with the first visit for the 3 months from August to October of every year, with the aim of reducing the effect of seasonal variation in HbA1c level described previously[4].

We divided the patients by the average HbA1c value for each year during the observation period into four groups based on the Kumamoto Declaration[1], as follows: group K1, HbA1c <6%; group K2, 6% ≤ HbA1c < 7%; group K3, 7-% ≤ HbA1c < 8%; and group K4, HbA1c ≥8%. In addition, we divided the patients by average HbA1c value into four groups with modifications based on the JDS/JGS[3], as follows: group E1, HbA1c <7%; group E2, 7% ≤HbA1c < 8%; group E3, 8% ≤ HbA1c < 8.5%; and group E4, HbA1c ≥8.5%. Furthermore, to investigate the appropriateness of these cut-off values for younger and elderly patients, patients were divided into two categories by age at the start of the follow-up period: younger (aged <65 years) and elderly patients (aged ≥65 years).

We compared the frequency of onset of micro- or macroangiopathy among the aforementioned four groups in the younger and elderly patients using the two individualized datasets. In all patients, macroangiopathy was assessed as follows: the diagnosis of the occurrence of ischemic heart disease events was made by cardiologists based on clinical symptoms

(chest pain), characteristic electrocardiography changes (ST change), cardiac enzyme levels (elevated cardiac enzymes), and findings in coronary angiography (stenosis) and/or echocardiography (ventricular asynergy), in accordance with established guidelines. Cerebral vascular disease was defined as validated definite or probable hospitalized cerebral infarction, and cerebral hemorrhage or subarachnoid hemorrhage diagnosed by neurosurgical experts based on clinical symptoms and neuroimaging findings, in accordance with established guidelines[4]. In all patients, microangiopathy was evaluated as follows: diabetic retinopathy was diagnosed by ophthalmologists[5], and classified from normal to dialysis stage in accordance with classification of diabetic nephropathy 2014[6], based on the status of estimated glomerular filtration rate and albuminuria. Diabetic neuropathy was assessed by the physician in charge based on the abbreviated criteria published by the Diabetic Neuropathy Study Group in Japan[7]. In addition, we used duration of diabetes, medication(s) for hypertension and/or dyslipidemia, and body mass index (BMI) at the start of follow up as possible risk factors contributing to the onset of micro- and macroangiopathy.

Statistical analysis

The data are expressed as the mean and standard deviation. Continuous variables at the start of follow up were compared using an age and sex-adjusted analysis of covariance (ANCOVA) for comparisons among HbA1c groups. To confirm the effect of target HbA1c levels in the two guidelines on the onset of micro- and macroangiopathy, the rate was calculated in three ways. First, we included micro- and macroangiopathy that occurred during all the years of follow up, accounting for person-years of observation. Second, the Cox proportional hazards model was used to compare the reference group K2 with groups K1, K3 and K4, or to compare the reference group E1 with groups E2, E3 and E4 after adjustment for age, sex, duration of diabetes, medication(s) for hypertension and/or dyslipidemia, and BMI at the start of follow up as confounders in addition to crude analyses. That is, the development of micro- or macrovascular complications was designated as a dependent variable (1, development; 0, no development during observation period). When using the Cox model, reference groups were set to K2 for the Kumamoto Declaration and to E1 for the JDS/JGS, because these groups had the lowest hazard ratios for the development of microangiopathy compared with other groups in younger and elderly patients, respectively, in preliminary analyses carried out in advance. Third, the Cox proportional hazards model was used to calculate hazard ratios per unit of average HbA1c (i.e., %), following the same adjustment as was described above. *P*-values of <0.05 were considered to show statistical significance. Statistical analyses were carried out using the SAS software program (version 8 for Windows; SAS Institute, Cary, NC, USA).

RESULTS

Onset of microangiopathy in four glycemic control groups based on the two guidelines in patients without diabetic microangiopathy at baseline

The mean age and follow-up period were 53.1 ± 9.9 years and 4.55 ± 3.63 years, respectively, in younger patients (aged <65 years) at the start of this study. The mean age and follow-up period were 72.2 ± 5.2 years and 4.05 ± 3.43 years, respectively, in elderly patients (aged ≥65 years) at the start of the study. The numbers of younger and elderly patients in each group classified in accordance with the average HbA1c value based on the Kumamoto Declaration were as follows: 137 and 107 in group K1, 760 and 566 in group K2, 340 and 279 in group K3, and 167 and 68 in group K4, respectively. Table 1 shows the clinical characteristics at baseline. The numbers of younger and elderly patients in each group classified by average HbA1c value based on the JDS/JGS guidelines were as follows: 897 and 673 in group E1, 340 and 279 in group E2, 66 and 37 in group E3, and 101 and 31 in group E4, respectively. Table 2 shows the clinical characteristics at baseline.

The Cox proportional hazards model was used in analysis of the four categories based on the Kumamoto Declaration, with the crude hazard ratios of K1, K3 and K4 in younger patients, compared with the reference group K2. The crude hazard ratios of K1, K3 and K4 were 1.07 (95% confidence interval [CI] 0.69–1.67, $P = 0.76$), 1.37 (95% CI 1.09–1.72, $P = 0.006$) and 1.89 (95% CI 1.45–2.48, $P < 0.0001$), respectively. In elderly patients, the crude hazard ratios of K1, K3 and K4, compared with the reference group K2, were 0.78 (95% CI 0.51–1.20, $P = 0.26$), 1.31 (95% CI 1.04–1.66, $P = 0.023$) and 1.57 (95% CI 1.10–2.25, $P = 0.013$), respectively. After adjustment was carried out for age, sex, duration of diabetes, medication(s) used for hypertension or dyslipidemia and BMI at the start of the study, the hazard ratios of K1, K3 and K4 in younger patients, compared with the reference group K2, were 1.02 (95% CI 0.62–1.66, $P = 0.95$), 1.35 (95% CI 1.06–1.72, $P = 0.014$) and 1.94 (95% CI 1.43–2.64, $P < 0.0001$), respectively (Figure 1a). In elderly patients, the hazard ratios of K1, K3 and K4, compared with the reference group K2, were 0.82 (95% CI 0.52–1.29, $P = 0.39$), 1.27 (95% CI 0.98–1.64, $P = 0.069$) and 1.46 (95% CI 0.99–2.15, $P = 0.057$), respectively (Figure 1b). These results were comparable with the results of the rate for person-years.

The Cox proportional hazards model was used in analysis of the four categories based on the JDS/JGS guidelines, with the crude hazard ratios of E2, E3 and E4 in younger patients, compared with the reference group E1. The crude hazards ratios of E2, E3 and E4 were 1.36 (95% CI 1.09–1.70, $P = 0.006$), 1.90 (95% CI 1.30–2.76, $P = 0.0009$) and 1.87 (95% CI 1.35–2.58, $P = 0.0002$), respectively. In elderly patients, the crude hazard ratios of E2, E3 and E4, compared with the reference group E1, were 1.36 (95% CI 1.09–1.71, $P = 0.008$), 1.55 (95% CI 1.00–2.40, $P = 0.051$) and 1.78 (95% CI 1.03–3.08, $P = 0.037$),

Table 1 | Baseline clinical characteristics in each group based on the Kumamoto Declaration among younger patients and elderly patients without microangiopathy at baseline

Younger patients				
	<6.0%	6.0–<7.0%	7.0–<8.0%	≥8.0%
M/F (*n*)	104/33	461/299	204/136	98/69
Development of microangiopathy during follow-up period (neuro/retino/nephro)	22 (8/2/13)	176 (124/26/66)	137 (69/37/87)	79 (45/26/60)
Age (years)	52.7 ± 10.7	54.5 ± 8.8	53.5 ± 9.6	46.6 ± 11.7*
Rates/1,000 person-years	48.6	52.6	75.3	102.3
Duration of type 2 diabetes (years)	3.7 ± 4.7	5.1 ± 6.5	6.8 ± 6.6*	6.8 ± 6.9*
BMI (kg/m^2)	25.6 ± 4.7	25.3 ± 4.6	25.1 ± 4.5	27.1 ± 5.3*
Mean HbA1c (%)	5.7 ± 0.4*z	6.5 ± 0.6	7.4 ± 0.9*	8.8 ± 1.7*
SBP (mmHg)	126 ± 16	126 ± 16	126 ± 16	126 ± 17
DBP (mmHg)	74 ± 11	74 ± 11	74 ± 12	74 ± 13
TCH (mg/dL)	189 ± 34	192 ± 34	198 ± 36	209 ± 54*
HDLC (mg/dL)	52 ± 14	53 ± 14	51 ± 14	48 ± 16*
TG (mg/dL)	141 ± 71	159 ± 146	175 ± 129	254 ± 385*
Treatment for diabetes (*n*)				
Insulin/SU/glinides/TZD	3/5/3/17	17/76/86/106	32/64/46/44	46/33/8/20
BG/α-GI/DPP4I	19/9/16	152/84/78	78/48/26	55/20/19
SGLT2I/GLP-1RA	0/0	0/3	0/3	0/1
Treatment for dyslipidemia (*n*)	60	327	122	43
Treatment for hypertension (*n*)	48	292	106	33
Elderly patients				
	<6.0%	6.0–<7.0%	7.0–<8.0%	≥8.0%
M/F (*n*)	66/41	339/227	164/115	35/33
Development of microangiopathy during follow-up period (neuro/retino/nephro)	25 (11/1/16)	166 (79/28/109)	126 (72/50/74)	37 (29/17/19)
Age (years)	72.0 ± 4.9	71.7 ± 5.0	73.0 ± 5.6	73.9 ± 5.3*
Rates/1,000 person-years	63.8	73.3	106.9	125.0
Duration of type 2 diabetes (years)	6.8 ± 8.4	6.7 ± 7.6	9.5 ± 8.6*	11.3 ± 10.8*
BMI (kg/m^2)	23.1 ± 3.3	23.6 ± 3.5	23.2 ± 3.5	23.7 ± 4.3
Mean HbA1c (%)	5.8 ± 0.4*	6.5 ± 0.5	7.4 ± 0.8*	9.0 ± 1.6*
SBP (mmHg)	125 ± 15	127 ± 16	127 ± 16	133 ± 19
DBP (mmHg)	69 ± 10	70 ± 10	70 ± 10	73 ± 10
TCH (mg/dL)	185 ± 33	198 ± 84	192 ± 37	192 ± 41
HDLC (mg/dL)	57 ± 18	54 ± 17	52 ± 14	50 ± 14
TG (mg/dL)	127 ± 72	139 ± 76	143 ± 76	156 ± 89
Treatment for diabetes (*n*)				
Insulin/SU/glinides/TZD	1/7/11/10	14/78/70/62	27/80/37/24	16/18/7/0
BG/α-GI/DPP4I	9/14/9	62/68/57	38/40/19	7/10/1
SGLT2I/GLP-1RA	0/0	0/0	1/0	0/0
Treatment for dyslipidemia (*n*)	39	341	83	16
Treatment for hypertension (*n*)	61	275	116	15

Data are shown as mean ± standard deviation. *$P < 0.05$ compared with the category of "6.0–7.0%" after adjustment for age and sex. α-GI, alpha-glucosidase inhibitors; BG, biguanide; BMI, body mass index; DBP, diastolic blood pressure; DPP4I, dipeptidyl peptidase-4 inhibitors; F, female; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; HDLC, high-density lipoprotein cholesterol; M, male; nephro, nephropathy; neuro, neuropathy; retino, retinopathy; SBP, systolic blood pressure; SGLT2I, sodium–glucose co-transporter 2 inhibitors; SU, sulfonylureas; TCH, total cholesterol; TG, triglycerides; TZD, thiazolidinedione.

respectively. After adjustment for the same factors as those described above, the hazard ratios of E2, E3 and E4 in younger patients, compared with the reference group E1, were 1.35 (95% CI 1.07–1.71, $P = 0.013$), 1.96 (95% CI 1.29–2.97, $P = 0.0017$) and 1.93 (95% CI 1.35–2.77, $P = 0.0004$), respectively (Figure 2a). In elderly patients, the hazard ratios of E2, E3 and E4, compared with the reference group E1, were 1.30 (95% CI 1.01–1.68, $P = 0.039$), 1.36 (95% CI 0.85–2.17,

Table 2 | Baseline clinical characteristics in each group based on the Japan Diabetes Society/Japan Geriatrics Society among younger patients and elderly patients without microangiopathy at baseline

Younger patients				
	<7.0%	7.0–<8.0%	8.0–<8.5%	≥8.5%
M/F (*n*)	565/332	204/136	39/27	59/42
Development of microangiopathy during follow-up period (neuro/retino/nephro)	198 (74/28/137)	137 (69/37/87)	33 (17/11/27)	46 (28/15/33)
Age (years)	54.2 ± 9.2	53.5 ± 9.6	48.4 ± 12.5*	45.5 ± 11.2*
Rates/1,000 person-years	52.1	75.3	105.4	100.2
Duration of type 2 diabetes (years)	4.9 ± 6.3	6.8 ± 6.6	6.9 ± 6.4	6.8 ± 7.2
BMI (kg/m^2)	25.3 ± 4.6	25.1 ± 4.5	26.9 ± 5.2*	27.3 ± 5.3*
Mean HbA1c (%)	6.4 ± 0.6	7.4 ± 0.9*	8.2 ± 1.6*	9.2 ± 1.7*
SBP (mmHg)	126 ± 16	126 ± 16	127 ± 18	125 ± 16
DBP (mmHg)	74 ± 11	74 ± 12	77 ± 11	72 ± 14
TCH (mg/dL)	192 ± 34	198 ± 36	202 ± 35	214 ± 62*
HDLC (mg/dL)	53 ± 14	51 ± 14	49 ± 10	48 ± 18*
TG (mg/dL)	157 ± 137	175 ± 129	195 ± 125	291 ± 477*
Treatment for diabetes (*n*)				
Insulin/SU/glinides/TZD	20/81/89/123	32/64/46/44	18/13/5/8	28/20/3/0
BG/α-GI/DPP4I	171/93/94	78/48/26	26/8/7	29/12/12
SGLT2I/GLP-1RA	0/3	0/3	0/1	0/0
Treatment for dyslipidemia (*n*)	387	122	14	29
Treatment for hypertension (*n*)	340	106	13	20
Elderly patients				
	<7.0%	7.0–<8.0%	8.0–<8.5%	≥8.5%
M/F (*n*)	405/268	164/115	21/16	14/17
Development of microangiopathy during follow-up period (neuro/retino/nephro)	191 (90/29/125)	126 (72/50/74)	23 (20/9/9)	14 (9/8/10)
Age (years)	71.8 ± 5.0	73.0 ± 5.6*	74.0 ± 5.8	73.7 ± 4.7
Rates/1,000 person-years	71.9	106.9	127.8	120.7
Duration of type 2 diabetes (years)	6.7 ± 7.7	9.5 ± 8.6*	12.4 ± 12.1*	9.7 ± 8.8
BMI (kg/m^2)	23.5 ± 3.5	23.2 ± 3.5	24.2 ± 3.9	22.9 ± 4.6
Mean HbA1c (%)	6.4 ± 0.6	7.4 ± 0.8*	8.5 ± 1.6*	9.6 ± 1.4*
SBP (mmHg)	127 ± 15	127 ± 16	128 ± 17	139 ± 21*
DBP (mmHg)	70 ± 10	70 ± 10	72 ± 11	75 ± 10
TCH (mg/dL)	196 ± 78	192 ± 37	192 ± 35	192 ± 47
HDLC (mg/dL)	55 ± 17	52 ± 14	50 ± 15	51 ± 13
TG (mg/dL)	137 ± 75	143 ± 76	158 ± 86	154 ± 94
Treatment for diabetes (*n*)				
Insulin/SU/glinides/TZD	15/85/81/72	27/80/37/24	6/10/4/0	10/8/3/0
BG/α-GI/DPP4I	71/82/66	38/40/19	4/7/0	55/3/1
SGLT2I/GLP-1RA	0/0	1/0	0/0	0/0
Treatment for dyslipidemia (*n*)	259	83	8	8
Treatment for hypertension (*n*)	336	116	14	10

Data are shown as mean ± standard deviation. *$P < 0.05$ compared with the category of "<7.0%" after adjustment for age and sex. α-GI, alpha-glucosidase inhibitors; BG, biguanide; BMI, body mass index; DBP, diastolic blood pressure; DPP4I, dipeptidyl peptidase-4 inhibitors; F, female; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; HDLC, high-density lipoprotein cholesterol; M, male; nephro, nephropathy; neuro, neuropathy; retino, retinopathy; SBP, systolic blood pressure; SGLT2I, sodium–glucose co-transporter 2 inhibitors; SU, sulfonylureas; TCH, total cholesterol; TG, triglycerides; TZD, thiazolidinedione.

$P = 0.20$) and 1.79 (95% CI 1.00–3.19, $P = 0.049$), respectively (Figure 2b). These results were comparable with the results of the rate from person-years.

In addition, the adjusted hazard ratio for average HbA1c (%) was 1.26 (95% CI 1.14–1.40, $P < 0.0001$) in younger patients and 1.22 (95% CI 1.06–1.41, $P = 0.007$) in elderly patients, which

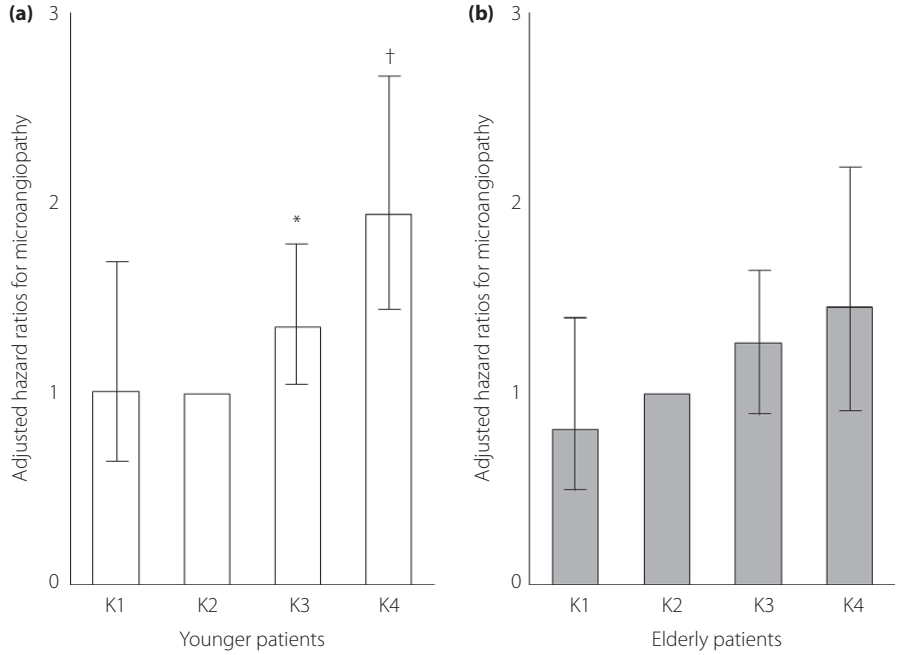

Figure 1 | Adjusted hazard ratios for microangiopathy in (a) younger and (b) elderly patients. The patients were divided into four groups by average glycated hemoglobin (HbA1c) value during the observation period based on the Kumamoto Declaration. Group K1, HbA1c <6%; group K2, 6% ≤ HbA1c < 7%; group K3, 7% ≤ HbA1c < 8%; and group K4, HbA1c ≥8%. *P < 0.05 compared with group K2. †P < 0.01 compared with group K2.

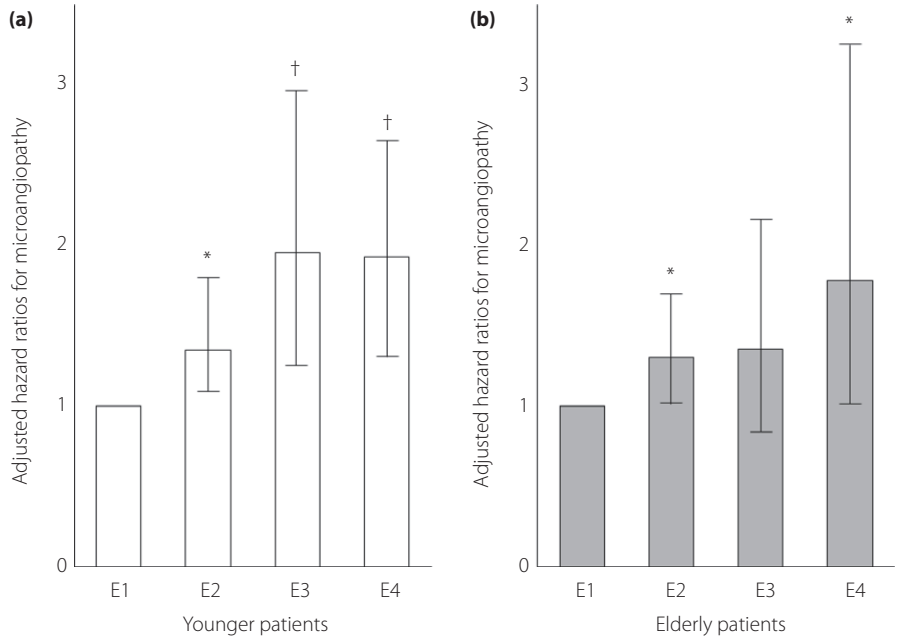

Figure 2 | Adjusted hazard ratios for microangiopathy in (a) younger and (b) elderly patients. The patients were divided into four groups by average glycated hemoglobin (HbA1c) value during the observation period based on the Japan Diabetes Society/Japan Geriatrics Society guidelines. Group E1, HbA1c <7%; group E2, 7% ≤ HbA1c < 8%; group E3, 8% ≤ HbA1c < 8.5%; and group E4, HbA1c ≥8.5%. *P < 0.05 compared with group E1. †P < 0.01 compared with group E1.

indicated the benefit of strict glycemic control for the prevention of microangiopathy in all patients in the present study.

Onset of macroangiopathy in four glycemic control groups based on the two guidelines in patients without diabetic macroangiopathy at baseline

The mean age and follow-up period were 53.5 ± 9.6 years and 4.83 ± 3.64 years, respectively, in younger patients (aged <65 years). The mean age and follow-up period were 72.5 ± 5.3 years and 4.63 ± 3.50 years, respectively, in elderly patients (aged ≥65 years). The numbers of younger and elderly patients in each group divided by the average HbA1c value based on the Kumamoto Declaration were as follows: 157 and 122 in group K1, 942 and 687 in group K2, 547 and 444 in group K3, and 281 and 136 in group K4, respectively. Table 3 shows the clinical characteristics at baseline. The numbers of younger and elderly patients in each group divided by the average HbA1c value based on the JDS/JGS guidelines were as follows: 1,099 and 809 in group E1, 547 and 444 in group E2, 107 and 71 in group E3, and 134 and 65 in group E4, in younger and elderly patients, respectively. Table 4 shows the clinical characteristics at baseline.

The Cox proportional hazards model was used in analysis of the four categories based on the Kumamoto Declaration, with the crude hazard ratios of K1, K3 and K4 in younger patients, compared with the reference group K2. The crude hazard ratios of K1, K3 and K4 were 0.77 (95% CI 0.39–1.52, $P = 0.44$), 1.59 (95% CI 1.22–2.07, $P = 0.0005$) and 1.36 (95% CI 0.97–1.91, $P = 0.079$), respectively. In elderly patients, the crude hazard ratios of K1, K3 and K4, compared with the reference group K2, were 0.84 (95% CI 0.50–1.41, $P = 0.51$), 0.95 (95% CI 0.74–1.22, $P = 0.69$) and 0.96 (95% CI 0.66–1.41, $P = 0.84$), respectively. After adjustment was carried out for the same factors described above, the hazard ratios of K1, K3 and K4 in younger patients, compared with the reference group K2, were 0.79 (95% CI 0.38–1.63, $P = 0.52$), 1.69 (95% CI 1.27–2.24, $P = 0.0003$) and 1.55 (95% CI 1.06–2.27, $P = 0.0233$), respectively (Figure 3a). These results were comparable with the results of the rate from person-years. In elderly patients, the hazard ratios of K1, K3 and K4, compared with the reference group K2, were 0.79 (95% CI 0.45–1.42, $P = 0.43$), 0.94 (95% CI 0.72–1.23, $P = 0.66$) and 0.98 (95% CI 0.65–1.47, $P = 0.92$), respectively (Figure 3b).

The Cox proportional hazards model was used in analysis of the four categories based on the JDS/JGS guidelines, with the crude hazard ratios of E2, E3 and E4, compared with the reference group E1. The crude hazard ratios of E2, E3,and E4 were 1.63 (95% CI 1.26–2.10, $P = 0.0002$), 1.37 (95% CI 0.86–2.19, $P = 0.18$) and 1.41 (95% CI 0.92–2.14, $P = 0.11$), respectively, in younger patients. In elderly patients, the crude hazard ratios of E2, E3 and E4, compared with the reference group E1, were 0.97 (95% CI 0.76–1.24, $P = 0.97$), 0.82 (95% CI 0.48–1.40, $P = 0.47$) and 1.18 (95% CI 0.71–1.94, $P = 0.52$), respectively. After adjustment was carried out for the same factors described above, the hazard ratios of E2, E3 and E4, compared with the reference group E1, were 1.72 (95% CI 1.30–2.27, $P = 0.0001$), 1.63 (95% CI 1.00–2.65, $P = 0.048$) and 1.54 (95% CI 0.96–2.48, $P = 0.072$), respectively, in younger patients (Figure 4a). In elderly patients, the hazard ratios of E2, E3 and E4, compared with the reference group E1, were 0.96 (95% CI 0.74–1.25, $P = 0.78$), 0.80 (95% CI 0.46–1.40, $P = 0.44$) and 1.27 (95% CI 0.75–2.15, $P = 0.37$), respectively (Figure 4b). These results were comparable with the results of the rate from person-years.

The adjusted hazard ratio for average HbA1c (%) was 1.26 (95% CI 1.10–1.43, $P = 0.0006$) in younger patients and 1.02 (95% CI 0.87–1.19, $P = 0.83$) in elderly patients, which indicated a benefit in strict glycemic control for the prevention of macroangiopathy only in younger patients in the present study.

DISCUSSION

The present retrospective study validated the HbA1c categories as defined in the Kumamoto Declaration, indicating a disadvantage in blood glucose control of >7.0% in average HbA1c for younger patients for preventing micro- and macroangiopathy. At the same time, the study validated the HbA1c categories indicated in the Improving Care for Elderly Patients with Diabetes, showing an advantage and disadvantage in blood glucose control of <7.0% and >8.5% in average HbA1c, respectively, for elderly patients for preventing microangiopathy. These results showed the validity of the two guidelines for Japanese patients with type 2 diabetes.

For validation of the Kumamoto Declaration, HbA1c 6.0% was set as the optimal target for ensuring normalization of blood glucose levels, ideally based on appropriate diet/exercise therapy alone or with drug therapy, without causing adverse events, such as hypoglycemia[1]. In addition, the target was set for relatively young individuals with a short duration of diabetes without a history of cardiovascular disease[1]. This approach is reasonable, because only a small percentage of patients would receive benefits from an average HbA1c at <6.0% in comparison with HbA1c of 6.0–6.9%, given the present study's results regarding both micro- and macroangiopathy. In contrast, blood glucose control for average HbA1c of ≥7.0% had obvious disadvantages in terms of micro- and macroangiopathy among patients aged <65 years in the present study. Accordingly, maintaining HbA1c between 6.0 and 7.0% could be meaningful for patients aged <65 years. Indeed, in the American Diabetes Association consensus guideline, glycemic recommendations for many non-pregnant adults with diabetes are <7.0% HbA1c[8]. On the contrary, however, for elderly patients, these benefits were less obvious in terms of preventing microangiopathy, whereas no benefit was observed in terms of preventing macroangiopathy, after adjustment was made for several factors. There are two possible reasons for this discrepancy of results between the two age categories. One is that the follow-up period was relatively short, and the other is that the participation number of elderly patients was small compared with that of younger patients.

Table 3 | Baseline clinical characteristics in each group based on the Kumamoto Declaration among younger patients and elderly patients without macroangiopathy at baseline

Younger patients				
	<6.0%	6.0–<7.0%	7.0–<8.0%	≥8.0%
M/F (*n*)	116/41	571/371	328/219	155/126
Development of macroangiopathy during follow-up period (IHD/CVD)	9 (4/5)	105 (56/59)	121 (63/68)	48 (28/20)
Age (years)	52.9 ± 10.5	54.6 ± 8.8	54.0 ± 9.1	49.4 ± 11.2*
Rates/1,000 person-years	17.0	24.2	40.1	33.6
Duration of type 2 diabetes (years)	4.9 ± 5.6	5.9 ± 6.6	8.8 ± 7.5*	9.4 ± 7.8*
BMI (kg/m^2)	25.5 ± 4.9	25.1 ± 4.6	25.0 ± 4.7	26.2 ± 5.1*
Mean HbA1c (%)	5.8 ± 0.4*	6.6 ± 0.6	7.5 ± 1.1*	8.9 ± 1.6*
SBP (mmHg)	125 ± 16	126 ± 16	127 ± 17	127 ± 18
DBP (mmHg)	73 ± 12	74 ± 11	74 ± 12	74 ± 12
TCH (mg/dL)	185 ± 34	189 ± 35	194 ± 35	204 ± 49*
HDLC (mg/dL)	52 ± 14	53 ± 15	51 ± 14	51 ± 16
TG (mg/dL)	141 ± 73	156 ± 135	174 ± 182	221 ± 307*
Treatment for diabetes (*n*)				
Insulin/SU/glinides/TZD	7/4/6/18	47/99/105/139	85/109/66/69	96/49/12/33
BG/α-GI/DPP4I	25/10/22	218/104/102	140/86/49	96/36/24
SGLT2I/GLP-1RA	0/1	1/8	0/7	0/3
Treatment for dyslipidemia (*n*)	73	389	180	88
Treatment for hypertension (*n*)	65	405	183	87
Elderly patients				
	<6.0%	6.0–<7.0%	7.0–<8.0%	≥8.0%
M/F (*n*)	68/54	404/283	243/201	66/70
Development of macroangiopathy during follow-up period (IHD/CVD)	16 (6/10)	148 (73/93)	110 (64/56)	32 (26/8)
Age (years)	72.3 ± 4.8	72.1 ± 5.2	73.1 ± 5.4*	72.9 ± 5.2
Rates/1,000 person-years	36.0	48.3	48.5	49.3
Duration of type 2 diabetes (years)	7.6 ± 9.1	8.8 ± 9.3	13.0 ± 9.7*	13.9 ± 8.8*
BMI (kg/m^2)	23.0 ± 3.3	23.5 ± 3.5	23.3 ± 3.6	23.4 ± 3.8
Mean HbA1c (%)	5.8 ± 0.4*	6.5 ± 0.6	7.4 ± 0.8*	8.7 ± 1.4*
SBP (mmHg)	125 ± 15	127 ± 16	127 ± 16	131 ± 19
DBP (mmHg)	68 ± 10	69 ± 10	69 ± 10	71 ± 11
TCH (mg/dL)	183 ± 33	194 ± 78	192 ± 36	191 ± 40
HDLC (mg/dL)	57 ± 17	54 ± 18	54 ± 16	53 ± 15
TG (mg/dL)	129 ± 62	135 ± 73	137 ± 98	147 ± 96
Treatment for diabetes (*n*)				
Insulin/SU/glinides/TZD	7/4/6/18	47/99/105/139	85/109/66/69	96/49/12/33
BG/α-GI/DPP4I	25/10/22	218/104/102	140/86/49	96/36/24
SGLT2I/GLP-1RA	0/1	1/8	0/7	0/3
Treatment for dyslipidemia (*n*)	73	389	180	88
Treatment for hypertension (*n*)	65	405	183	87

Data are shown as mean ± standard deviation. *$P < 0.05$ compared with the category of "6.0–7.0%: after adjustment for age and sex. α-GI, alpha-glucosidase inhibitors; BG, biguanide; BMI, body mass index; DBP, diastolic blood pressure; CVD, cerebral vascular disease; DPP4I, dipeptidyl peptidase-4 inhibitors; F, female; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; HDLC, high-density lipoprotein cholesterol; IHD, ischemic heart disease; M, male; SBP, systolic blood pressure; SGLT2I, sodium–glucose co-transporter 2 inhibitors; SU, sulfonylureas; TCH, total cholesterol; TG, triglycerides; TZD, thiazolidinedione.

Using the JDS/JGS criteria, controlling the average HbA1c to <7.0% had benefits in terms of microangiopathy compared with the group with HbA1c of >8.5% in all patients. This result might indicate that blood glucose control of >8.5% had a disadvantage, even in elderly patients aged >65 years. Furthermore, compared with maintaining HbA1c at a level of <7.0%, an average HbA1c of ≥7.0% had significantly elevated risks in younger patients. In elderly patients, compared with

Table 4 | Baseline clinical characteristics in each group based on the Japan Diabetes Society/Japan Geriatrics Society among younger patients and elderly patients without macroangiopathy at baseline

Younger patients				
	<7.0%	7.0–<8.0%	8.0%–<8.5%	≥8.5%
M/F (*n*)	687/412	328/219	59/48	96/78
Development of macroangiopathy during follow-up period (IHD/CVD)	114	121	21	27
Age (years)	54.3 ± 9.1	54.0 ± 9.1	52.3 ± 11.3	47.7 ± 10.8*
Rates/1,000 person-years	23.4	40.1	34.3	33.1
Duration of type 2 diabetes (years)	5.8 ± 6.5	8.8 ± 7.5*	10.0 ± 7.5*	9.0 ± 8.0*
BMI (kg/m^2)	25.2 ± 4.7	25.0 ± 4.7	25.6 ± 4.7	26.7 ± 5.3*
Mean HbA1c (%)	6.5 ± 0.7	7.5 ± 1.1*	8.3 ± 1.4*	9.3 ± 1.6*
SBP (mmHg)	126 ± 16	127 ± 17	128 ± 18	126 ± 17
DBP (mmHg)	74 ± 11	74 ± 12	75 ± 12	73 ± 12
TCH (mg/dL)	189 ± 35	194 ± 35	201 ± 38*	206 ± 54*
HDLC (mg/dL)	53 ± 14	51 ± 14	52 ± 13	50 ± 17
TG (mg/dL)	154 ± 128	174 ± 182	186 ± 137	240 ± 370*
Treatment for diabetes (*n*)				
Insulin/SU/glinides/TZD	54/103/111/157	85/109/66/69	37/21/5/14	59/28/7/19
BG/α-GI/DPP4I	243/114/124	140/86/49	33/11/7	63/25/17
SGLT2I/GLP-1RA	1/9	0/7	0/1	0/2
Treatment for dyslipidemia (*n*)	462	180	34	54
Treatment for hypertension (*n*)	470	189	33	54
Elderly patients				
	<7.0%	7.0–<8.0%	8.0–<8.5%	≥8.5%
M/F (*n*)	472/337	243/201	37/34	29/36
Development of macroangiopathy during follow-up period (IHD/CVD)	164	110	15	17
Age (years)	72.1 ± 5.1	73.1 ± 5.4*	72.7 ± 5.2	73.1 ± 5.3
Rates/1,000 person-years	46.8	48.5	42.6	57.2
Duration of type 2 diabetes (years)	8.6 ± 9.3	13.0 ± 9.7*	13.6 ± 8.5*	14.3 ± 9.3*
BMI (kg/m^2)	23.4 ± 3.5	23.3 ± 3.6	23.8 ± 3.8	23.0 ± 3.8
Mean HbA1c (%)	6.4 ± 0.6	7.4 ± 0.8*	8.3 ± 1.3*	9.2 ± 1.2*
SBP (mmHg)	127 ± 16	127 ± 16	131 ± 17	132 ± 22
DBP (mmHg)	69 ± 10	69 ± 10	72 ± 10	71 ± 11
TCH (mg/dL)	192 ± 73	192 ± 36	190 ± 38	193 ± 43
HDLC (mg/dL)	54 ± 18	54 ± 16	51 ± 15	54 ± 16
TG (mg/dL)	134 ± 71	137 ± 98	148 ± 86	146 ± 108
Treatment for diabetes (*n*)				
Insulin/SU/glinides/TZD	33/101/97/69	58/146/41/36	16/18/4/4	18/24/3/5
BG/α-GI/DPP4I	99/90/78	64/70/25	6/15/3	6/11/4
SGLT2I/GLP-1RA	0/1	1/0	0/1	0/0
Treatment for dyslipidemia (*n*)	291	134	19	18
Treatment for hypertension (*n*)	413	219	32	36

Data are shown as mean ± standard deviation. *$P < 0.05$ compared with the category of "<7.0%" after adjustment for age and sex. α-GI, alpha-glucosidase inhibitors; BG, biguanide; BMI, body mass index; DBP, diastolic blood pressure; CVD, cerebral vascular disease; DPP4I, dipeptidyl peptidase-4 inhibitors; F, female; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; HDLC, high-density lipoprotein cholesterol; IHD, ischemic heart disease; M, male; SBP, systolic blood pressure; SGLT2I, sodium–glucose co-transporter 2 inhibitors; SU, sulfonylureas; TCH, total cholesterol; TG, triglycerides; TZD, thiazolidinedione.

maintaining HbA1c at <7.0%, maintaining average HbA1c at between 7.0 and 8.0% had significantly elevated risks. These results show that the optimal target of average HbA1c in terms of preventing microangiopathy might be <7.0% for all patients, supporting the JDS/JGS consensus, which defines the lower and upper limits of the glycemic target to ensure safer glycemic control by accounting for patient background and health status, comorbidities, risk of severe hypoglycemia, and life expectancy[3].

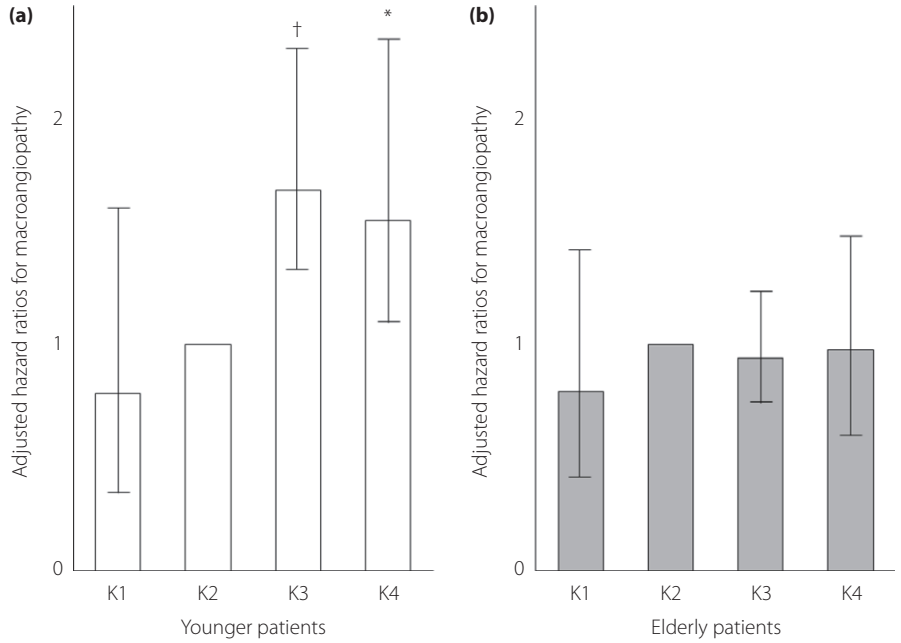

Figure 3 | Adjusted hazard ratios for macroangiopathy in (a) younger and (b) elderly patients. The patients were divided into four groups by average glycated hemoglobin (HbA1c) value during the observation period based on the Kumamoto Declaration. Group K1, HbA1c <6%; group K2, 6% ≤ HbA1c < 7%; group K3, 7% ≤ HbA1c < 8%; and group K4, HbA1c ≥8%. *P < 0.05 compared with group K2. †P < 0.01 compared with group K2.

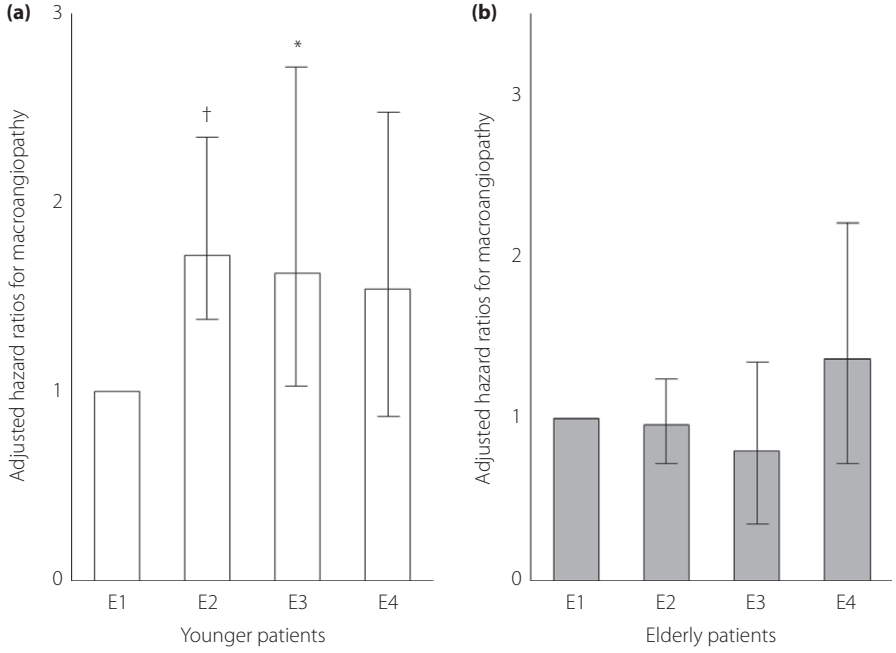

Figure 4 | Adjusted hazard ratios for macroangiopathy in (a) younger and (b) elderly patients. The patients were divided into four groups by average glycated hemoglobin (HbA1c) value during the observation period based on the Japan Diabetes Society/Japan Geriatrics Society guidelines. Group E1, HbA1c < 7%; group E2, 7% ≤ HbA1c < 8%; group E3, 8% ≤ HbA1c < 8.5%; and group E4, HbA1c ≥8.5%. *P < 0.05 compared with group E1. †P < 0.01 compared with group E1.

These results are consistent with American Diabetes Association guidelines for older adults[9], which show that older adults who are healthy with few coexisting chronic illnesses and intact cognitive function and functional status should have lower glycemic goals (HbA1c 7.5%), whereas those with multiple coexisting chronic illnesses, cognitive impairment or functional dependence should have less stringent glycemic goals (HbA1c 8.0–8.5%) or IDF guidelines for older patients with type 2 diabetes[10], which suggest that glycemic control targets should be individualized taking into account functional status, comorbidities (especially the presence of established cerebral vascular disease), history and risk of hypoglycemia, and presence of microvascular complications.

Contrary to microangiopathy prevention, it was difficult to establish an HbA1c target for preventing macroangiopathy in elderly patients, because an average HbA1c threshold in elderly patients was not clear, despite the fact that a threshold of <7.0% had benefits in younger patients in both guidelines. Patients aged 45–69 years with type 2 diabetes in J-DOIT3[2] showed benefits from strict control of maintaining average HbA1c at 6.8% in terms of the risk factors of nephropathy, retinopathy and cerebrovascular disease, compared with results obtained by maintaining HbA1c at 7.2%.

Considering the "legacy effect" from the UK Prospective Diabetes Study 80[11], the benefit of glycemic control in terms of macroangiopathy would be attenuated in elderly patients compared with younger patients. Also, in a previous cohort study designed to include patients aged 80 years[12] and in which the mean age was 71 years with type 2 diabetes[13], mortality had a U-shaped relationship with HbA1c at baseline. In another study, Japanese Elderly Intervention Trial (J-EDIT), with Japanese type 2 diabetes patients aged >65 years suggested the existence of a J-shaped incidence for stroke according to HbA1c distribution at the landmark time-point[14], whereas the present study investigated the relationship between average HbA1c during observation and the onset of macroangiopathy. Because of the limited patient numbers and short observation period in the present study, it was difficult to investigate patients with lower and higher HbA1c to clarify the existence of a U or J shape, although the data from this study did suggest a faint U shape, in other words, a slight elevation in risks with an average HbA1c of <7% and that of >8.5%, as shown in Figure 4b. Other risks associated with macroangiopathy were adjusted only for BMI and medication(s) for hypertension and dyslipidemia, not for data on blood pressure and cholesterol levels.

Further study is required to clarify the optimal level of HbA1c for elderly diabetes patients. A recent systematic review[15] showed that the paradigm of reducing blood glucose level as close as possible to normal (i.e., tight glycemic control of HbA1c <7%), independently of medication, when compared with conventional control (HbA1c 7.5–8.5%) did not have an impact on micro- and macrovascular outcomes, such as end-stage renal disease/dialysis, renal death, blindness, mortality, and cardiovascular endpoints, although the evidence is clear that chronic hyperglycemia is associated with an increased risk of adverse micro- and macrovascular outcomes[16,17]. To consider subject characteristics, surrogate markers, and outcome, several studies therefore need to be compared and evaluated.

The present study had several limitations. First, it was a retrospective observational study with a limited study population. The observation period was also limited. It was therefore difficult to subdivide HbA1c levels into more detailed categories. Second, diabetes medication was not considered. Diabetes medication was chosen by the physician in charge based on a patient-centered approach considering the best available evidence in terms of benefits, harms, patient values, preferences and context in time, not only target HbA1c level. It was therefore difficult to discover the relationship between glycemic complications and HbA1c levels. Finally, we did not evaluate the habits and comorbid factors, such as smoking status, diet, cognitive function, frailty and daily activity. Because the aim of glycemic control for elderly patients with diabetes is not only prevention of complications but also maintaining quality of life, as well as prevention of geriatric syndrome, glycemic control only targeting HbA1c level is insufficient[15].

In conclusion, the glycemic control target for younger patients with type 2 diabetes should be <7.0% for average HbA1c to prevent micro- and macroangiopathy. On the contrary, the target for elderly patients with type 2 diabetes should be set individually to prevent macroangiopathy, and the target should be <7.0% to prevent microangiopathy.

DISCLOSURE

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