Possible Relationship between the Deteriorated Accuracy of Intermittent-Scanning Continuous Glucose Monitoring Device and the Contact Dermatitis: Post-hoc analysis of the ISCHIA Study

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Objective: We previously reported the mean average relative difference (MARD) of the sensor glucose (SG) of the first-generation FreeStyle Libre with the original algorithm, an intermittent scanning continuous glucose monitoring (isCGM) device, was 15.6% in the Effect of Intermittent-Scanning Continuous Glucose Monitoring to Glycemic Control Including Hypoglycemia and Quality of Life of Patients with Type 1 Diabetes Mellitus Study (ISCHIA Study). In the present study, we aimed to further analyze its accuracy in detail by conducting a post-hoc analysis of the study.
Methods: The ISCHIA Study was a multicenter, randomized, cross-over trial to assess the efficacy of isCGM. The SG levels of isCGM and the measured capillary blood glucose (BG) levels of 91 participants were used for the analysis.
Results: Bland-Altman analysis showed bias of −13.0 mg/dl when the SG levels were compared to the BG levels, however no proportional bias was observed (r = 0.085). MARD of the participants without and with contact dermatitis were 15.0 ± 6.0% and 27.4 ± 21.4% (P = 0.001), respectively.
Conclusion: There was negative bias in the SG levels of isCGM compared to the BG levels. There is a possibility that the complication of the contact dermatitis during isCGM use may be related with deteriorated accuracy of the SG levels.

Key words: intermittent scanning continuous glucose monitoring, accuracy, type 1 diabetes, contact dermatitis

INTRODUCTION

The use of continuous glucose monitoring (CGM) to make treatment decisions is becoming common globally [1]. To ensure the safety of such use of CGM, it is important to identify the factors that may affect the accuracy of CGM measurement. We previously reported that the sensor glucose (SG) levels measured by the first-generation FreeStyle Libre (Abbott Diabetes Care, Alameda, CA, USA) were significantly lower than the capillary blood glucose (BG) levels in patients with type 2 diabetes undergoing hemodialysis (HD) [2].

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However, the effect of potential factors on the accuracy of CGM in patients with type 1 diabetes, such as age, diabetes duration, body mass index (BMI) or the presence of the contact dermatitis, remain to be elucidated.

In the Effect of Intermittent-Scanning Continuous Glucose Monitoring to Glycemic Control Including Hypoglycemia and Quality of Life of Patients with Type 1 Diabetes Mellitus Study (ISCHIA Study), we reported that the mean average relative difference (MARD) and mean average difference (MAD) compared to the BG levels measured by the first-generation FreeStyle Libre were 15.6% and 23.2 mg/dl, respectively [3]. However, according to the studies conducted by the manufacturer, its MARD was 11.4% compared to the BG levels [4]. The reason for the difference in MARD between these studies remains unknown.

We aimed to further analyze the accuracy of the SG measured by isCGM and to probe associated factors by post-hoc analysis using the data from the ISCHIA Study.

PATIENTS AND METHODS

Study design

The protocol of the ISCHIA Study was previously published [5]. In brief, it was a multicenter, randomized, cross-over trial to assess the efficacy of isCGM in adult participants with type 1 diabetes (T1D) using multiple daily insulin injections. During the Intervention period of 84 days, the participants used first-generation FreeStyle Libre with the original algorithm and continued self-monitoring of blood glucose (SMBG) three times a day or more using the SMBG function of the FreeStyleLibre Reader. During the Control period of 84 days, the participants continued SMBG three times a day or more using FreeStyle Precision Neo (Abbott Diabetes Care, Alameda, CA, USA), and wore FreeStlye Libre Pro (Abbott Diabetes Care, Alameda, CA, USA). The participants used FreeStyle Precision Neo also during the Run-in period of 28 days and the Washout period of 28 days. The primary endpoint was the decrease in time below range (TBR; <70 mg/dl), and the secondary endpoints included time in range (TIR; 70–180 mg/dl), time above range (TAR; >180 mg/dl), adverse events (AEs), serious AEs, MARD, and MAD. FreeStyle Libre sensors with multiple lot numbers were used (190201P, 190403P, 181009Q, 190415Q, 190531R, 190606P, 190712P, 190604P, 191025Q, 191001P, 191104P, 191103P, 191118R, 6004910, 200412T).

Study participants and setting

The participants were recruited at the study cites reported previously [3]. The study was conducted in outpatient setting and the data was collected between 15 March 2019 and 5 January 2021. Ninety-three participants completed the study. The CONSORT flow diagram was reported elsewhere [3].

Variables

The SG levels were measured by isCGM, and the BGlevels were measured by SMBG. MARD and MAD were used as indices of the accuracy of isCGM. Age, diabetes duration, BMI and presence of the contact dermatitis were selected as potential factors that may affect MARD and MAD.

Data sources

Among 93 participants who completed the study, two participants were excluded because of the lack of the BG data during the Intervention period. As the result, the SG data and the BG data of 91 participants, downloaded from the FreeStyle Reader during the Intervention period of the ISCHIA Study, were used for this post-hoc analysis. AE reports of the ISCHIA Study were used to identify the occurrence of contact dermatitis.

Study size

A study size of 104 was calculated for the primary endpoint (time below range) in this study [5].

Statistical analysis

The paired SG and the BG levels had time stamp differences less than 3 minutes. Calculation of MARD and MAD were described elsewhere [6]. MARD and MAD were calculated using pooled data of the paired glucose levels. Comparisons among the groups were performed by a paired Student's *t*-test. Pearson's *r* correlation coefficient was used to evaluate the linear correlation between two variables, and interpreted as follows: Less than 0.3 was considered poor correlation, 0.3 to 0.5 fair, 0.6 to 0.8 moderately strong, and at least 0.8 very strong [7]. Bland-Altman analysis was performed to analyze the agreement between the two different methods [8]. The upper limit of agreement (ULoA) and lower limit of agreement (LLoA) correspond to the upper and lower bounds of the 95% confidence interval of the difference between the two methods, respectively. Proportional bias was calculated as the correlation coefficient between the means of the two methods and the differences of the two methods. Passing-Bablok regression analysis was used to determine the accuracy of the SG levels against the BG levels in the reference method [9]. Consensus error grid analysis was used to evaluate clinical significance of the inaccuracies in the measurements of glucose levels. Box plots were used to demonstrate the distribution of numeric data. Analyses were conducted using R version 3.4.3 (R Project for Statistical Computing, Vienna, Austria).

Ethics

All procedures were in accordance with the Helsinki Declaration of 1964 and later versions. Written informed consent was obtained from all the participants. This study was conducted in accordance with the Clinical Trials Act [10], and is registered in the Japan Registry of Clinical Trials (jRCT1052180075). The study protocol received Certified Review Board approval from National Hospital Organization Osaka National Hospital (N2018002, originally approved on February 14, 2019, Version 0.7; the latest revision was approved on May 19, 2021, Version 1.8).

RESULTS

The characteristics of the participants are shown in Table 1. Overall, 14,895 pairs of the SG levels and BG levels were used for the analysis. The mean SG levels and BG levels were 143.3 ± 69.3 mg/dl and 156.2 ± 71.7 mg/dl, respectively ($P < 0.001$). There was a very strong positive correlation between the SG levels and

Table 1 The characteristics of the participants

	N = 91
Age, years	51.9 (15.0)
Male, %	48.4
Diabetes duration, years	18.2 (10.1)
	16 (10, 25)
HbA1c, %	7.3 (0.7)
BMI, kg/m²	22.7 (2.9)
isCGM-naïve, %	47.3
MARD, %	15.6 (7.5)

Numbers are mean (standard deviation), median (25%, 75%) or percentage.

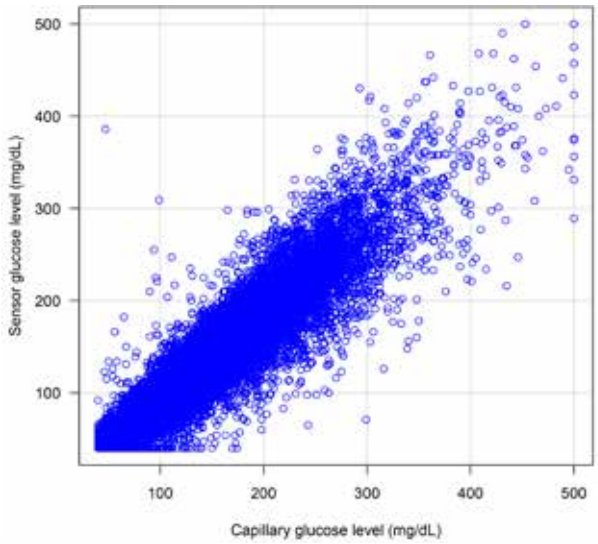

Fig. 1 Correlation between the SG levels and the BG levels.
The correlation between the SG levels and the BG levels was very strong ($r = 0.916$, $P < 0.001$).

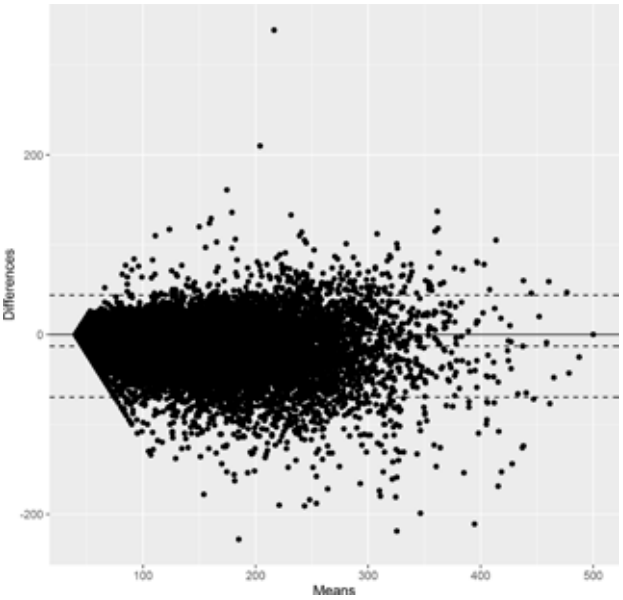

Fig. 2 Bland-Altman analysis comparing the SG levels and the BG levels.
The horizontal axis represents the means of the two methods and the vertical axis represents the difference of the two methods (SG−BG). There was bias of −13.0 mg/dl when the SG levels were compared to the BG levels, with ULoA being 43.8 mg/dl and LLoA −69.7 mg/dl. No proportional bias was observed ($r = 0.085$).

the BG levels ($r = 0.916$, $P < 0.001$) (Fig. 1). The Bland-Altman analysis showed bias of −13.0 mg/dl when the SG levels were compared to the BG levels, with no proportional bias ($r = 0.085$) (Fig. 2). The bias was shown by Passing-Bablok regression analysis for the SG levels (vertical axis) versus the reference BG levels (horizontal axis) with the slope of 0.97 (95% confidence intervals [CI] 0.96 – 0.97) and the corresponding intercept of −6.20 mg/dl (95% CI −7.07 – −5.29). Consensus error grid analysis showed that the 99.5% of the measurements of the SG measurements belonged to Zones A and B (Fig. 3). MARD and MAD in different glucose ranges are displayed in Table 2.

There was no significant correlation between MARD and age, diabetes duration, or BMI (Table 3). There were four participants who had contact dermatitis among the AE reports during the Intervention period [3]. The mean SG levels and BG levels (14,282 pairs) of those without contact dermatitis were 143.0 ± 69.5 mg/dl and 155.8 ± 72.1 mg/dl, respectively ($P < 0.001$). The mean SG levels and BG levels (613 pairs) of those with contact dermatitis were 150.3 ± 65.5 mg/dl and 165.7 ± 62.4 mg/dl, respectively ($P < 0.001$). The MARD of those without contact dermatitis and with contact dermatitis were 15.0 ± 6.0% and 27.4 ± 21.4%, respectively ($P = 0.001$), and the MAD were 22.3 ± 9.6 mg/dl and 42.7 ± 32.8 mg/dl, respectively ($P < 0.001$). Box plots of MARD and MAD of those without contact dermatitis and with contact dermatitis are displayed in Fig. 4A, B. The Bland-Altman analysis of those without contact dermatitis showed bias of −12.9 mg/dl, with no proportional bias ($r = 0.092$). (Fig. 5A), whereas participants with contact dermatitis showed bias of −15.4 mg/dl, with no proportional bias ($r = -0.106$) (Fig. 5B).

Table 2 MARD and MAD in different glucose ranges

	Range		
	< 70 mg/dL	70 – 180 mg/dL	> 180 mg/dL
MARD, %	17.6	14.9	14.0
MAD, mg/dL	9.9	18.2	33.8

Table 3 Correlation between MARD and age, diabetes duration, or BMI

	r	*P*
Age, years	0.029	0.793
Diabetes duration	0.039	0.724
BMI	0.095	0.391

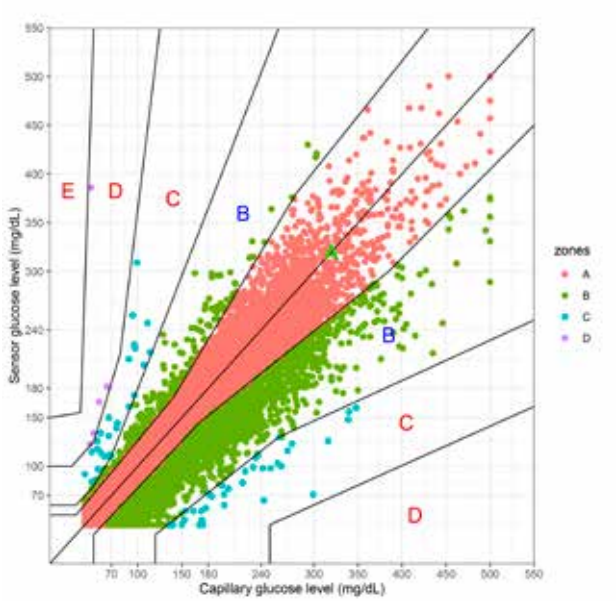

Fig. 3 Consensus error grid analysis of the SG levels and the BG levels.
Zone A, 75.2%; zone B, 24.3%; zone C, 0.4%; zone D, 0.0%; zone E 0.0%.

DISCUSSION

In this post-hoc analysis, although the SG levels were significantly lower than the BG levels, strong correlation was confirmed between them. Bland-Altman analysis showed negative bias when the SG levels of the first-generation FreeStyle Libre with the original algorithm were compared to the BG levels, with no proportional bias. The slope value and the intercept value obtained by Passing-Bablok regression analysis were significant, but considered to be clinically negligible. The consensus error grid analysis suggested that the clinical impact of the inaccuracies in the SG levels was modest. The complication of contact dermatitis was related with greater MARD and MAD.

These observations suggest the necessity of using conventional SMBG when required, especially to confirm hypoglycemia, as this negative bias in the SG levels might lead to the overdiagnosis of hypoglycemia [11]. Furthermore, it appears important to educate patients to conduct SMBG when the SG level does not much the clinical symptoms or user's prediction. Currently, newer version of the algorithm in FreeStyle Libre is available [12], and its accuracy also needs to be evaluated independently from the manufacturer.

In this study, age, diabetes duration, and BMI were not associated with MARD. However, a negative correlation between BMI and MARD was previously reported [13]. A study conducted in obese subjects reported that MARD did not differ between walking or sitting [14]. A study also reported significant differences of MARD between glucose ranges [15]. Bias was reported to be the main cause of in subjects with poor accuracy of FreeStyle Libre [16].

Skin problems are common among CGM users [17]. A previously study that evaluated the accuracy of Guardian Sensor 3 sensor (Medtronic, Northridge, CA, USA) reported one case of contact dermatitis among 158 participants with T1D; however the relationship between accuracy and contact dermatitis was not investigated [18]. Furthermore, an observational study reported that 5.5% of FreeStyle Libre users needed to visit dermatologists due to cutaneous adverse events (CAEs) [19]. Isobornyl acrylate had been considered

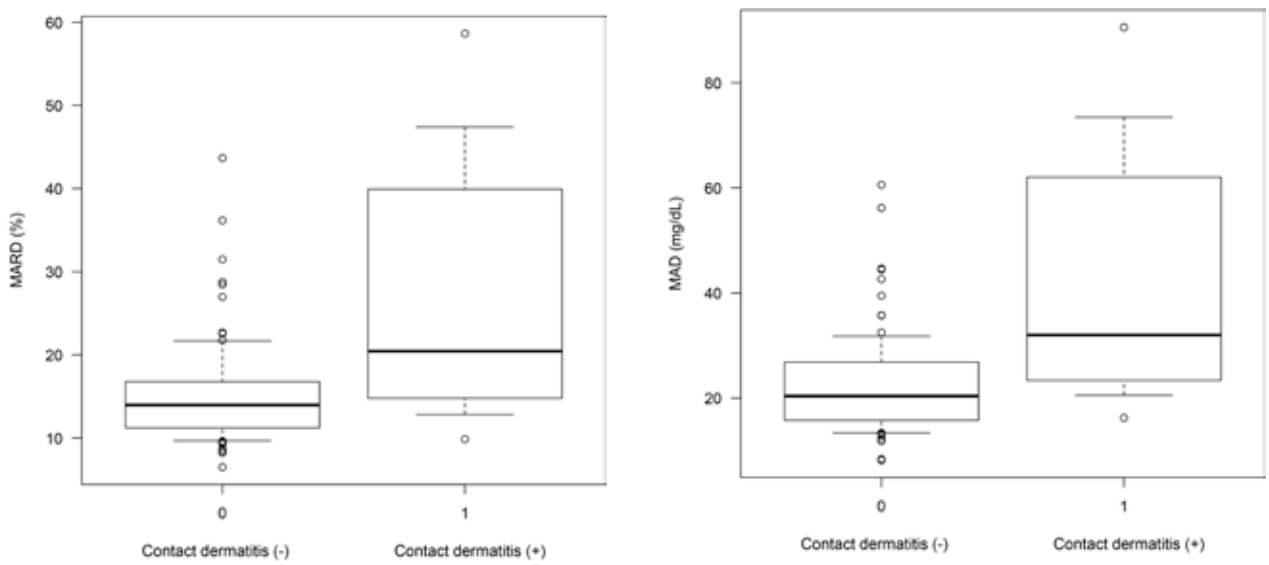

Fig. 4. Box plots of MARD and MAD in participants without or with contact dermatitis.
(A) MARD of participants without contact dermatitis and with contact dermatitis was 15.0 ± 6.0% and 27.4 ± 21.4%, respectively ($P = 0.001$). (B) The MAD of participants without contact dermatitis and with contact dermatitis was 22.3 ± 9.6 mg/dl and 42.7 ± 32.8 mg/dl, respectively ($P < 0.001$).

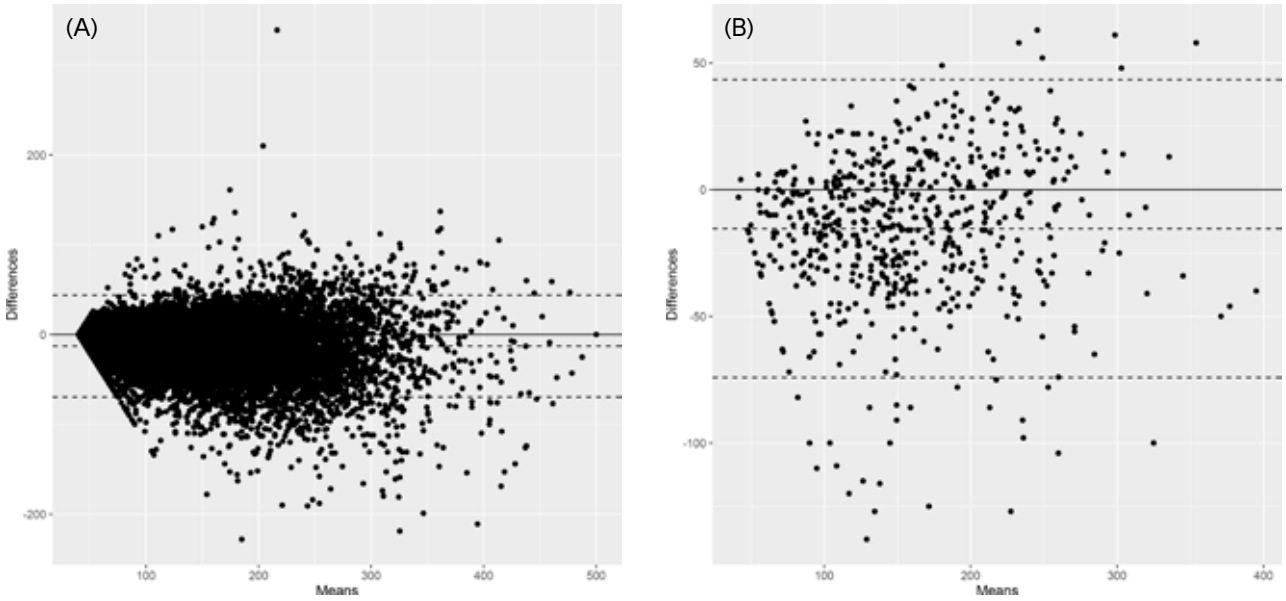

Fig. 5. Bland-Altman analysis in participants without or with contact dermatitis.
(A) Participants without contact dermatitis showed bias of −12.9 mg/dl with ULoA being 43.8 mg/dl and LLoA −69.5 mg/dl. No proportional bias was observed ($r = 0.092$). (B) Participants with contact dermatitis showed bias of −15.4 mg/dl with ULoA being 43.4 mg/dl and LLoA −74.2 mg/dl. No proportional bias was observed ($r = -0.106$).

as one of the causes of CAE [19–22]; however, Abbott reported that they no longer use isobornyl acrylate in FreeStyle Libre sensors [23]. Contact dermatitis is an inflammation of skin with eczematous regions infiltrated with mononuclear cells, mainly T cells, and the presence of intercellular epidermal edema [24]. The edema of the interstitial tissue may be related to the inaccuracies of the measurement by CGM. In fact, we reported inaccuracies of the first-generation FreeStyle Libre sensors in patients undergoing HD, in whom edema in the subcutaneous interstitial tissue is common [2].

There are several limitations in this study. In this study, the degree of severity of contact dermatitis was not evaluated, and previous history of skin problems and allergy was not investigated. Considering the sensor glucose levels were obtained in patients with AE reports of contact dermatitis, it is likely they were diagnosed as contact dermatitis after using the FreeStyle Libre sensor; however, further detail is unclear from the AE reports. The number of the participants with the AE report of contact dermatitis was low; thus a future observational study with greater sample size is required to confirm the hypothesis that contact dermatitis is related to deteriorated accuracy of CGM sensors. Due to the nature of the post-hoc analysis, the sample

size may not be optimized to assess these observations, and there is possibility that data-dredging bias could not be completely excluded. Moreover, recall bias may have led to the underestimation of the occurrence of contact dermatitis. The data set used for this pot-hoc analysis did not include the information of the speed of the change in blood glucose levels; therefore, the effect of the rapid change in the sensor glucose levels is unclear. In addition, the information regarding the day of the usage after sensor replacement was not included in this data set, because this data set was optimized to analyze the primary outcome, TBR. Although there was no AE report including the term "dehydration," no data was collected regarding the hydration status of the study participants.

Our findings may not be generalized to other versions of FreeStyle Libre or CGMs from other manufacturers. The relationship between the accuracy of CGM and affecting factors may need to be evaluated in each product. It is also possible that the accuracy of FreeStyle Libre sensor may differ among lots and periods of manufacturing. The present study may represent the accuracy of the sensors distributed during the study period; however, sensors distributed during other periods may have different quality. In fact, FreeStyle Libre sensors with specific lot numbers (6916030 and 6916031), shipped from Abbot between October 19, 2022 and November 15, 2022 in Japan, were reported to be not satisfying the required quality and therefore had to be recalled [25, 26]. Further improvement in the quality control of FreeStyle Libre sensors may be required to minimize the difference of the accuracy between lots.

CONCLUSION

Compared to the BG levels, negative bias was observed in the SG levels of the first-generation FreeStyle Libre with the original algorithm which was used in the ISCHIA study. However, despite this negative bias, the clinical impact of the inaccuracy was suggested to be modest. Users of FreeStyle Libre need to confirm the SG level by SMBG when required.

There is possible relationship between the deteriorated accuracy of isCGM and contact dermatitis. Therefore, patients who experience contact dermatitis during the use of isCGM need to pay attention to its accuracy.

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Masao Toyoda, Yushi Hirota, Ken Kato, Ryuji Kouyama, Akio Kuroda, Munehide Matsuhisa, and Junnosuke Miura, designed the study, collected the data and drafted the manuscript. Atsuhito Tone designed the study and drafted the manuscript. Shota Suzuki drafted the manuscript. Kunihiro Nishimura and Naoki Sakane, designed the study and conducted statistical analyses. Kunichi Kouyama, Yuka Matoba, Shu Meguro, and Akira Shimada, collected the data and drafted the manuscript. Takashi Murata chaired the study, designed the study, collected the data and drafted the manuscript. Kiminori Hosoda supervised the project and drafted the manuscript.

CONFLICT OF INTEREST

The author(s) declare the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Masao Toyoda discloses the following relationships: personal fees from Nipro, Medtronic, Terumo, Abbott Japan, MSD, Eli Lilly, Novartis, Takeda, Sumitomo Pharma, Sanofi, Novo Nordisk, Daiichi Sankyo, Tanabe-Mitsubishi, Ono, Boehringer Ingelheim, AstraZeneca, and Astellas; grants from Abbott Japan, Life Scan, Sumitomo Pharma and Roche DC Japan. Takashi Murata received lecture fees from Sanofi, Novo Nordisk, Kyowa Kirin and research grants from AstraZeneca, Novo Nordisk, Eli Lilly. Yushi Hirota discloses the following relationships: personal fees from Novartis, Novo Nordisk, Otsuka Pharma, AstraZeneca, Eli Lilly, Sanofi, MSD, Abbott Japan, Daiichi Sankyo, Sanwa Kagaku, Sumitomo Pharma, Terumo, Medtronic, Kowa, Kyowa Kirin, Teijin Pharma, Kissei Pharmaceutical, Ono, Pfizer, Takeda, Mochida Pharmaceutical, Taisho Pharma, Roche DC Japan, Bayer and Tanabe-Mitsubishi; grants from Medtronic, Sumitomo Pharma, Kyowa Kirin, and Abbott Japan. Ken Kato discloses the following relationships: personal fees from Medtronic, Sanofi, Novo Nordisk, Eli Lilly, Ono, Kowa, Arkray, Sanwa Kagaku, Takeda, Astellas, Tanabe-Mitsubishi, Terumo, Boehringer Ingelheim, and Abbott Japan. Ryuji Kouyama discloses the following relationships: personal fees from Sanofi, Eli Lilly, Novo Nordisk, MSD, Novartis, Takeda, Sumitomo Pharma, Taisho Pharma, Ono, Astellas, Tanabe-Mitsubishi, Boehringer Ingelheim, and AstraZeneca. Akio Kuroda discloses the following relationships: personal fees from Novo Nordisk, Eli Lilly, Sanofi, Medtronic, and Life Scan. Munehide Matsuhisa discloses the following relationships: personal fees from Tanabe-Mitsubishi, Novartis, Novo Nordisk, Sanofi, Astellas, MSD, Terumo, Abbott Japan, Sumitomo Pharma, Boehringer Ingelheim, Ono, and Eli Lilly; grants from Sanofi, Novo Nordisk, Boehringer Ingelheim, Sysmex, and Nissui. Shu Meguro discloses the following relationships: personal fees from Abbott Japan, Eli Lilly Astellas, AstraZeneca, Bayer, Daiichi Sankyo, EA Pharma, Kyowa Kirin, Kowa, Life Scan, Tanabe-Mitsubishi, Mochida Pharmaceutical, MSD, Boehringer Ingelheim, Novo Nordisk, Ono, Otsuka Pharma, Sanofi, Sanwa Kagaku, Sumitomo Pharma, Taisho Pharma, Teijin Pharma, and Teijin Health Care. Junnosuke Miura discloses the following relationships: personal fees from Novo Nordisk, Novartis, Eli Lilly, Sanofi, Sanwa Kagaku, Medtronic, Kowa, Taisho Pharma, Sumitomo Pharma, Life Scan, Abbott Japan, Terumo, AstraZeneca, PHC, and Astellas. Akira Shimada discloses the following relationships: personal fees from Eli Lilly, Novo Nordisk, Sanofi, Abbott Japan, Sumitomo Pharma, and Terumo. Atsuhito Tone discloses the following relationships: personal fees from Sanofi, Medtronic, Eli Lilly, Life Scan, Novo Nordisk, Kowa, Tanabe-Mitsubishi, MSD, Sumitomo Pharma, Astellas, Taisho Pharma, Ono, Abbott Japan, Boehringer Ingelheim, AstraZeneca, Terumo, Nipro, H2, Teijin Pharma, Otsuka Pharma, and Roche DC Japan. Naoki Sakane discloses the following relationships: personal fees from Takeda, Sanofi, Life Scan, Sumitomo Pharma, Boehringer Ingelheim, and Novo Nordisk. Other author declares no conflict of interest.

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