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ORIGINAL ARTICLE

The perfusion index is a useful screening tool for peripheral artery disease

Hiroshi Okada[1] · Muhei Tanaka[2] · Takashi Yasuda[3] · Tadaaki Kamitani[4] · Hisahiro Norikae[5] · Tetsuya Fujita[5] · Takashi Nishi[5] · Hirokazu Oyamada[6] · Tetsuro Yamane[7] · Michiaki Fukui[8]

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Abstract

The number of people with peripheral artery disease (PAD) has been increasing globally; therefore, it is important to explore more options to screen patients who are at a risk of developing PAD. The perfusion index (PI) represents the degree of circulation through the peripheral tissues and is measured noninvasively. We investigated the correlation between the PI and ankle-brachial index (ABI) to explore whether the PI could be used a screening tool for PAD. This cross-sectional study included 390 patients. We measured the ABI and PI for all patients. The median ABI value was 1.06 (0.92–1.13); the PI was 1.7% (0.9–3.5). The PI was higher in men than in women ($P < 0.0001$). The PI was positively correlated with the estimated glomerular filtration rate and ABI in both men and women. The sensitivity and specificity of the PI to predict PAD (ABI ≤0.9) were 90.0% and 80.3%, respectively, and the cutoff PI value was 1.5% in men. The sensitivity and specificity of the PI to predict PAD were 82.1% and 79.2%, respectively, and the cutoff PI value was 1.1% in women. PI could be a reliable screening tool for diagnosing PAD because it does not restrict the patient's mobility, can be completed in a short time period, and is associated with reduced costs.

Keywords Peripheral artery disease · Atherosclerosis and cardiovascular diseases

Introduction

During the first decade of the twenty-first century, the number of individuals with peripheral artery disease PAD) increased worldwide [1]. According to the Trans-Atlantic Inter-Society Consensus II group, the overall PAD prevalence (based on objective testing) was between 3 and 10% in several epidemiologic studies, indicating growth from 15 to 20% in people older than 70 years [2]. PAD is a global health issues because it was shown to be associated with a risk of premature mortality and cardiovascular or cerebrovascular events, which have drastically increased recently [3]. Both the American College of Cardiology Foundation and American Heart Association recommend using the ankle-brachial index (ABI) as a screening tool for PAD in patients aged 65 years or over; those aged between 50 and 64 years with risk factors of atherosclerosis such as diabetes, a history of smoking, hyperlipidemia, or hypertension; those aged 49 years or younger who have a history of diabetes with one of the risk factors of atherosclerosis; or those with existing atherosclerosis in another vascular bed [4].

✉ Hiroshi Okada
conti@koto.kpu-m.ac.jp

1 Department of Diabetes and Endocrinology, Matsushita Memorial Hospital, 5-55 Sotojima-cho, Moriguchi 570-8540, Japan

2 Department of Internal Medicine, Kyotamba Hospital, Kyotamba, Japan

3 Department of Nephrology, Matsushita Memorial Hospital, Moriguchi, Japan

4 Department of Cardiology, Matsushita Memorial Hospital, Moriguchi, Japan

5 Department of General Affairs, Matsushita Memorial Hospital, Moriguchi, Japan

6 Department of Gastroenterology, Matsushita Memorial Hospital, Moriguchi, Japan

7 Department of Surgery, Matsushita Memorial Hospital, Moriguchi, Japan

8 Department of Endocrinology and Metabolism, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

However, difficulty is often encountered when using the ABI in some patients, especially those who have the risk factors of PAD. As the PAD population has grown, we are now required to expand our options for measuring PAD easily and noninvasively in a timely manner, without drawbacks such as laborious steps requiring an examination or restrictions to the patient's mobility. The perfusion index PI) is the ratio of pulsatile blood flow to non-pulsatile blood flow in the monitored tissue [5]. To our knowledge, the PI has not been evaluated as a screening tool for PAD, despite its potential advantages. Therefore, we performed a cross-sectional study to investigate the correlation between the ABI and PI to explore whether the PI could be used a screening tool for PAD.

Materials and methods

Ethics

This study was approved by our local research ethics committee and conducted in accordance with the ethical principles of the Declaration of Helsinki. Informed consent was obtained from all the participants.

Patients and data collection

This cross-sectional study was performed using participants from a PAD screening program at Matsushita Memorial Hospital, Osaka, Japan. Briefly, the purpose of this program was to detect PAD in the early stage, evaluate underlying risk factors, and promote foot care based on the ABI and PI values. All the data were retrieved from the database of the Peripheral Artery Disease Screening Program in the North Kawachi Area. We collected the data of 390 participants who needed to be admitted to Matsushita Memorial Hospital in Osaka, Japan, for medical treatments between September 2015 and April 2017.

The patient's body mass index (BMI) was measured using the standard protocol. Hypertension was defined when the patient's systolic blood pressure was greater than 140 mmHg and their diastolic blood pressure was greater than 90 mmHg, and/or the patient was using any antihypertensive medications. Diabetes was diagnosed based on the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus [6]. GFR was estimated using the Japanese Society of Nephrology equation: $eGFR = 194 \times Cre^{-1.094} \times age^{-0.287}$ (mL/min/1.73m^2) [7]. For women, the eGFR was multiplied by a correction factor of 0.739. Patients were classified as nonsmokers, past smokers, or current smokers based on a self-administered questionnaire. Patients with a history of any of the following conditions were excluded: implanted cardiac pacemakers, new-onset major cardiovascular events, amputations of any part of the lower extremities, malignancies, or those whose PI measurement could not be obtained.

Measurement of data and the PI

Blood samples were obtained in the morning. The serum total cholesterol and triglyceride concentrations were assessed using standard enzymatic methods.

PI was measured using Masimo SET Radical-7 (Masimo Corporation, Irvine, CA). The patients were placed in the supine position. A Masimo pulse oximeter probe was positioned on each toe and connected to the Masimo SET Radical-7 machine. The patients were asked to rest for 5 min at the beginning of the procedure. The PI was then recorded three times: at 20, 40, and 60 s, after a 5-minute resting period. The average of the three values was calculated and used as the reference value. The Masimo SET Radical-7 calculates the PI as the ratio between the pulsatile and non-pulsatile components of the light reaching the light-sensitive cell of the pulse oximetry probe [6] Research showed that Masimo pulse oximetry measurements tend to underestimate oxy-hemoglobin saturation compared with co-oximetry, with a bias mean difference) of 2% and precision standard deviation of the differences) of 6% [8]. The coefficient of variation of PI was 2.1% (the reliability) and 2.0% (the reproducibility). After the PI was determined bilaterally, the lower value was taken as a representative for each subject.

Measurement of the ABI

The ABI was measured using a VS-1500 Va Sera machine (Fukuda Denshi, Tokyo, Japan). This equipment allows us to measure the pulse volume in both brachial arteries and posterior tibial arteries using the oscillometric method, as well as the blood pressure in the bilateral arms and ankles. For this measurement, the patients were directed to rest comfortably in the supine position for at least 5 min prior to the ABI measurements. Details of this method have been described elsewhere [9]. The ABI and ratio of the systolic blood pressure in the ankle to that in the arm were measured bilaterally. The lower value of the two results was selected and used in this study. An ABI ≤ 0.9 was considered to indicate PAD.

Statistical analysis

The medians and frequencies of potential confounding variables were calculated. Because the triglyceride levels have skewed distributions, log transformation was implemented before a correlation analysis was performed. The participants

were categorized according to sex. The differences between the sexes were assessed using the Chi-square test for categorical variables, and either an unpaired Student's *t* test or Mann–Whitney's *U* test was used for continuous variables. The relationships between the PI and age, BMI, or other variables, as well as the relationship between the PI and ABI, were examined using Spearman's rank correlation analyses. The differences between ABI stages (ABI > 0.9, ABI between 0.9 and 0.7, ABI ≤ 0.7) were assessed using ANOVA. The association between PI and PAD (ABI ≤ 0.9) was analyzed in logistic regression analysis. To examine the effects of various factors on PAD (ABI ≤ 0.9), the following factors which were statistically significant in univariate analysis and those known to be related factors for PAD were considered simultaneously as independent variables for multivariate logistic regression analysis: age, BMI, systolic blood pressure, hemoglobin, glucose, total cholesterol, logarithm of triglycerides, uric acid, e-GFR, smoking status, and PI. A receiver operating characteristic (ROC) curve analysis was performed for the PI to assess its ability to identify PAD (ABI ≤ 0.9).

All continuous variables are presented as the median (interquartile range) or absolute number. A P value < 0.05 was considered statistically significant. The size, direction, and statistical significance of relationships were estimated by the hazard ratio with 95% confidence interval (CI).

Results

The characteristics of all the 390 patients who were enrolled in this study are shown in Table 1. The median ABI value was 1.06 (range 0.92–1.13); the median PI value was 1.7% (range 0.9–3.5%). The patients' demographic characteristics in connection with sex are also shown in Table 1. Age ($P = 0.0004$) and total cholesterol ($P = 0.049$) were higher in women than in men. The hemoglobin concentration ($P < 0.001$), uric acid level ($P = 0.01$), and PI value ($P < 0.0001$) were higher in men than in women. More men considered themselves active smokers than women did ($P < 0.0001$).

Table 1 The characteristics of the patients in this study

	All	Men	Women	*P* value
N	390	258	132	–
Age (y)	72 (64–79)	69 (62–77.3)	75 (68–81)	0.0004
BMI (kg/m^2)	23.4 (20.6–26.2)	23.5 (20.7–26.0)	22.9 (20.5–26.5)	0.963
Average SBP (mmHg)	130 (114–142)	129.5 (113.3–141)	131 (114.5–145)	0.200
Average DBP (mmHg)	74 (63.5–83)	74.0 (63–85)	73 (65–83)	0.559
Hemoglobin (g/dl)	12.7 (11–14.1)	13.3 (11.2–14.8)	12.0 (10.8–13.2)	< 0.0001
AST (IU/L)	20.5 (16–28)	21 (16–30)	20 (16–28)	0.169
ALT (IU/L)	16 (11–27)	17 (11–29.5)	14 (11–22)	0.055
Glucose (mmol/L)	7.3 (5.7–10.2)	7.4 (5.8–10.4)	7.1 (5.7–9.8)	0.129
T-CHO (mmol/L)	4.6 (3.9–5.4)	4.5 (3.7–5.4)	4.7 (4.2–5.5)	0.049
Triglycerides (mmol/L)	1.3 (0.9–2.0)	1.3 (0.9–2.0)	1.4 (1.0–2.0)	0.413
Albumin (g/dl)	3.9 (3.2–4.2)	3.9 (3.2–4.2)	4.0 (3.2–4.2)	0.844
Uric acid (μmol/L)	327 (256–405)	339 (268–419)	300 (242–376)	0.010
e-GFR (ml/min/1.73 m^2)	59 (18.3–75.7)	58.3 (15.5–76.8)	60.3 (23.7–75)	0.686
CRP (mg/dl)	0.2 (0.05–0.5)	0.2 (0.06–0.59)	0.14 (0.04–0.3)	0.879
History of CVD (−/+)	171/219	107/151	64/68	0.174
Hypertension (−/+)	127/263	90/168	37/95	0.265
Diabetes (−/+)	191/199	121/137	70/62	0.207
Hemodialysis (−/+)	369/21	244/14	125/7	0.263
Antihypertensive drugs (−/+)	164/226	117/141	47/85	0.065
Statin (−/+)	237/153	166/92	80/52	0.470
Smoking status (never/past/recent)	171/78/141	71/67/120	100/11/21	< 0.0001
Ankle brachial index	1.06 (0.92–1.13)	1.07 (0.94–1.14)	1.03 (0.86–1.12)	0.082
Perfusion index	1.7 (0.9–3.5)	1.9 (1.0–4.1)	1.2 (0.7–2.5)	< 0.0001

Data are expressed as the median (interquartile range) or absolute number

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *AST* aspartate transaminase, *ALT* alanine transaminase, *T-CHO* total cholesterol, *e-GFR* estimated glomerular filtration rate, *CRP* C-reactive protein, *CVD* cardiovascular disease

Table 2 shows the correlation between the PI and other variables. In the group of men, the PI was positively correlated with BMI ($r = 0.32$, $P < 0.0001$), hemoglobin concentration ($r = 0.20$, $P = 0.001$), estimated glomerular filtration rate (eGFR) ($r = 0.19$, $P = 0.002$), and ABI ($r = 0.54$, $P < 0.0001$). The PI was negatively correlated with age ($r = -0.17$, $P = 0.006$). In the group of women, the PI was positively correlated with the total cholesterol level ($r = 0.27$, $P = 0.004$), eGFR ($r = 0.23$, $P = 0.008$), and ABI ($r = 0.62$, $P < 0.0001$). PI was 3.38 (1.5–4.7), 0.67 (0.31–1.03) and 0.48 (0.15–0.6) in ABI>0.9, ABI between 0.9 and 0.7, ABI ≤0.7 stage in men, respectively ($P < 0.05$). PI was 2.33 (1.1–3.1), 0.85 (0.35–0.92) and 0.51 (0.25–0.69) in ABI > 0.9, ABI between 0.9 and 0.7, ABI ≤ 0.7 stage in women, respectively ($P < 0.05$).

Table 2 The correlation between the perfusion index and other variables

	Men		Women	
	r	*P* value	*r*	*P* value
Age	−0.17	0.006	−0.05	0.58
Body mass index	0.32	<0.0001	0.12	0.21
Systolic blood pressure	−0.008	0.90	−0.10	0.25
Diastolic blood pressure	−0.02	0.73	−0.09	0.29
Hemoglobin	0.20	0.001	0.10	0.25
Glucose	0.04	0.54	0.08	0.38
Total cholesterol	0.07	0.26	0.27	0.004
Logarithm of TG	0.13	0.08	0.03	0.82
Uric acid	−0.05	0.48	−0.03	0.78
e-GFR	0.19	0.002	0.23	0.008
Ankle brachial index	0.54	<0.0001	0.62	<0.0001

TG triglyceride, *e-GFR* estimated glomerular filtration rate

Table 3 shows the unadjusted and adjusted logistic regression analysis. The adjusted logistic regression analysis revealed that PI was associated with an increased odds of PAD (ABI ≤ 0.9) in men (odds ratio; 0.05, 95% CI 0.01–0.16) or women (odds ratio; 0.16, 95% CI 0.04–0.39), respectively.

Table 4 shows the cutoff values and other related diagnostic values in each group after the ROC analysis was applied.

Table 3 Unadjusted odds ratios and multivariate adjusted odd ratios for peripheral artery disease

	Crude		Multiple	
	Odds ratio	*P*	Odds ratio	*P*
Men				
Age	1.05 (1.02–1.08)	0.0008	1.05 (0.98–1.12)	0.16
Body mass index	0.79 (0.69–0.88)	<0.0001	0.82 (0.63–1.03)	0.09
Systolic blood pressure	0.99 (0.98–1.01)	0.75	0.99 (0.96–1.03)	0.67
Hemoglobin	0.92 (0.82–1.04)	0.20	1.10 (0.74–1.66)	0.63
Glucose	1.00 (0.99–1.00)	0.98	1.01 (0.99–1.02)	0.09
Total cholesterol	0.99 (0.99–1.00)	0.49	1.00 (0.98–1.02)	0.89
Logarithm of TG	0.33 (0.09–1.11)	0.07	1.48 (0.02–124.0)	0.85
Uric acid	0.98 (0.83–1.14)	0.79	0.87 (0.59–1.27)	0.48
e-GFR	0.99 (0.98–0.99)	0.002	0.97 (0.94–1.00)	0.03
Smoking status never	1	–	1	–
Past or recent	1.14 (0.59–2.32)	0.70	5.12 (1.04–35.0)	0.04
Perfusion index	0.04 (0.01–0.10)	<0.0001	0.05 (0.01–0.16)	<0.0001
Women				
Age	1.03 (0.99–1.07)	0.08	1.13 (1.01–1.23)	0.03
Body mass index	0.97 (0.89–1.06)	0.49	0.97 (0.80–1.16)	0.75
Systolic blood pressure	1.02 (1.00–1.04)	0.06	1.03 (0.99–1.08)	0.18
Hemoglobin	0.93 (0.76–1.13)	0.45	1.07 (0.60–1.96)	0.82
Glucose	1.00 (0.99–1.01)	0.72	1.01 (0.99–1.02)	0.15
Total cholesterol	0.99 (0.97–0.99)	0.01	0.98 (0.95–1.00)	0.08
Logarithm of TG	1.51 (0.26–8.31)	0.64	5.24 (0.08–593.0)	0.45
Uric acid	1.24 (0.99–1.60)	0.06	0.92 (0.54–1.55)	0.76
e-GFR	0.97 (0.95–0.98)	<0.0001	0.97 (0.93–1.00)	0.08
Smoking status never	1	–	1	–
Past or recent	3.55 (1.53–8.30)	0.003	22.2 (3.3–266.8)	0.0008
Perfusion index	0.13 (0.05–0.30)	<0.0001	0.16 (0.04–0.39)	<0.0001

TG triglyceride, *e-GFR* estimated glomerular filtration rate

Table 4 Cutoff points and related diagnostic value in the receiver operating characteristic curve analysis

	Men	Women
N	258 (516 legs)	132 (264 legs)
Cutoff point	1.50	1.10
Sensitivity	90.0	82.1
Specificity	80.3	79.2
Area under the curve	0.93	0.85
P value	< 0.0001	< 0.0001

The sensitivity and specificity in the group of men were 90.0% and 80.3% ($P < 0.0001$), respectively; in the group of women, the sensitivity and specificity were 82.1% and 79.2% ($P < 0.0001$), respectively. Additionally, the area under the curve AUC) for the PI was 0.93 in the group of men and 0.85 in the group of women (Fig. 1).

When the cutoff PI value was raised to 2.0, the sensitivity and the specificity were 94.4% and 68.5%, respectively, in the group of men and 91.1% and 50.2%, respectively, in the group of women.

Discussion

Our study explored the competency of the PI to predict PAD. Because the AUC for the PI to identify PAD was high, we strongly believe that the PI would be one of the most accurate parameters to assess the risk of PAD.

In the primary care setting, being able to diagnose PAD has an important role of determining the prognostic value. Research has shown that the age-adjusted prevalence of PAD was approximately 12%, and men and women are equally affected by this disease [10,11]. Criqui et al. [12] stated that regardless of the degree of the disease, the survival rates of both symptomatic and asymptomatic PAD patients are lower than those of patients without this disease. In addition, Diehm et al. [2] stated that the mortality rate was not different between symptomatic and asymptomatic patients with PAD, but those groups had a significantly higher mortality rate than did those without the disease. Moreover, the cumulative survival rates of patients suffering from claudication were reported to be 94.6% at 1 year, 79.4% at 3 years, 67.3% at 5 years, and 37.4% at 10 years [13], and the survival rate of patients who underwent amputation within 5 years was 5% [14]. The mortality rate of patients with critical leg ischemia, which is considered to be the most severe clinical manifestation of PAD, has been reported to be 25% per year [15]. Complications such as cardiovascular disease (CVD) could cause higher mortality in patients with PAD.

Hirsch et al. [16] analyzed the feasibility of detecting PAD in 6,979 patients in a primary care setting. They reported that PAD was detected in 1,865 patients 29%); 44% had PAD without evidence of CVD. The rest of the patients 56%) had evidence of CVD [15]. PAD is a prevalent disease and has an important manifestation in those with systemic atherosclerosis. It is important for health care personnel to detect PAD in the early stage, evaluate the underlying risk factors, and promote foot care for all patients. The assessment of PAD should be a routine task in the primary care setting.

Gerhard-Herman reiterated that the American Heart Association/American College of Cardiology recommended using the ABI to detect PAD [4]. However, difficulties are often encountered in daily practice when performing PAD screening using the ABI and it has been reported that ABI measurement is often incorrectly performed procedure in the general practices [17]. Completing the entire procedure is time consuming because of specific instructions that the patients are required to follow. The patients are required to rest in the supine position quietly for a minimum of

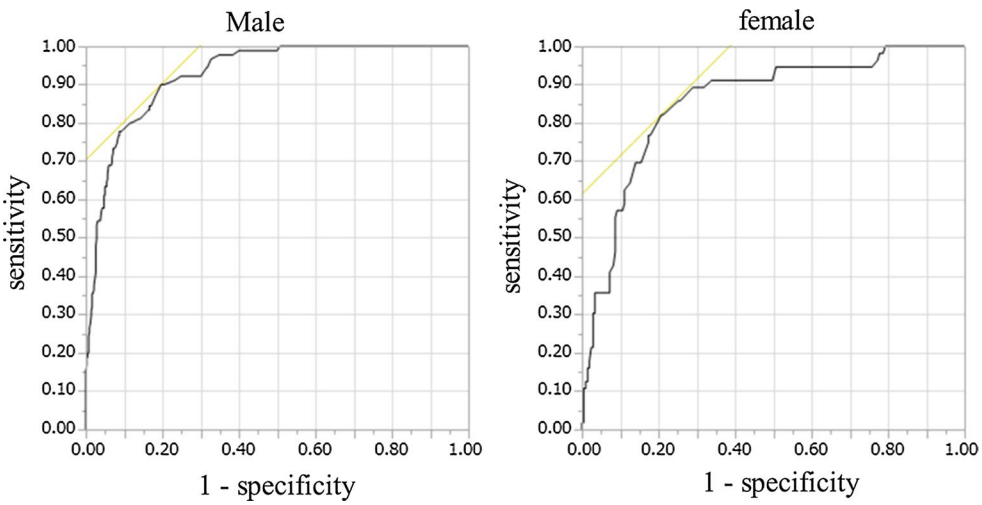

Fig. 1 The receiver operating characteristic curve and area under the receiver operating characteristic curve showing the ability of the perfusion index to determine the presence of peripheral artery disease

5 min prior to the procedure. Their mobility is completely restricted and they are not permitted to change their positions during the measurement process. This process often creates discomfort around the measurement sites for the patients because of the pressure that is applied by the cuffs. In addition, the ABI screening process is not applied to patients with aneurysms or deep phlebothrombosis.

However, the PI takes only a few minutes to complete and is very simple. The patients are only required to wear lightweight, small sensors on one of their toes, and the results are automatically indicated on the computer screen. Multiple steps are not required and the patients will not lose control of their mobility while wearing the sensors. Further, the PI equipment is less expensive than the ABI equipment.

Moreover, the ABI value might be falsely elevated in patients with diabetes and those undergoing dialysis. This is because, for patients with these conditions, it is difficult for the cuffs to compress the patients' arteries because of calcification of the arterial walls, and this will often cause the ABI value to be higher than 1.0. Previous study has reported that the prevalence of PAD among patients with an ABI>1.3 is high 58%) [18]. Compared with the ABI value, the PI value would not be affected by calcification of the arterial walls. This is because the PI measures the ratio of pulsatile blood flow to non-pulsatile blood flow in the monitored tissues.

Two recent studies have been reported the new semiquantitative ultrasonographic score for PAD assessment [2,19]. They have suggested that the ultrasonographic lower limb atherosclerosis score could facilitate better evaluation of the progression of PAD and its prospective role in cardiovascular risk stratification. Unfortunately, however, we have not evaluated the presence of atherosclerotic lesions by ultrasonography and have no data for the ultrasonographic lower limb atherosclerosis score in this study.

This study had several limitations. It is uncertain if the results of our study are applicable to people of other ethnicities because we targeted Japanese men and women. Moreover, because the number of patients was limited, the volume of the information we gathered from the patients may be insufficient. Although our investigation showed that the PI would be an accurate and efficient screening tool for PAD in terms of cost and adaptability, a further investigation using a large volume of information with more participants of various ethnicities would be crucial to provide better care and promote the patients' conditions and healing processes.

The PI is an effective index because of its potential advantages. It does not restrict the patient's mobility, allows the health care worker to complete the procedure in a short time period, and is associated with reduced costs that are related to labor and materials. As a screening tool, the PI could be considered the first line of the diagnostic procedure for PAD in any clinical setting, including health care systems in developing countries with a lack of resources and materials.

Compliance with ethical standards

Conflict of interest Michiaki Fukui received grants from the Japan Society for the Promotion of Science, AstraZeneca Plc, Astellas Pharma Inc., Nippon Boehringer Ingelheim Co., Ltd., Daiichi Sankyo Co., Ltd., Eli Lilly Japan K.K., Kyowa Hakko Kirin Company Ltd., Kissei Pharmaceutical Co., Ltd., MSD K.K., Mitsubishi Tanabe Pharma Corporation, Novo Nordisk Pharma Ltd., Sanwa Kagaku Kenkyusho Co., Ltd., Sanofi K.K., Ono Pharmaceutical Co., Ltd., and Takeda Pharmaceutical Co., Ltd., outside the submitted work. The sponsors were not involved in the study design; the collection, analysis, and interpretation of data; the writing of this manuscript; or the decision to submit the article for publication. The authors, their immediate families, and any research foundations with which they are affiliated have not received any financial payments or other benefits from any commercial entity related to the subject of this article. The authors declare that although they are affiliated with a department that is supported financially by a pharmaceutical company, the authors received no current funding for this study, and this does not alter their adherence to all the journal policies on sharing data and materials. The other authors have no conflict of interest to disclose.

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