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Mean and variability of annual haemoglobin A1c are associated with high-risk peripheral artery disease

I-Te Lee[1,2,3,4]

Abstract

Background: Glucose variability is predictive of cardiovascular events and all-cause mortality. However, the association between peripheral artery disease and glucose variability has not been thoroughly investigated. Therefore, the standard deviation of annual haemoglobin A1c was assessed in patients with type 2 diabetes for evaluating the different risks of peripheral artery disease.

Methods: A total of 4144 patients underwent an evaluation for the ankle-brachial index and the percentage of mean arterial pressure at the ankle. The first haemoglobin A1c record was retrospectively collected from each year until the ankle-brachial index measurement.

Results: The standard deviation of annual haemoglobin A1c was higher in patients with ankle-brachial index $\leqslant$0.90 than in those with ankle-brachial index $>$0.90 (1.1 $\pm$ 0.9% vs 1.0 $\pm$ 0.8%, $p = 0.009$) and was higher in patients with percentage of mean arterial pressure $\geqslant$45% than in those with percentage of mean arterial pressure $<$45% (1.1 $\pm$ 0.8% vs 1.0 $\pm$ 0.8%, $p = 0.007$). A high standard deviation and mean of annual haemoglobin A1c are associated with high-risk peripheral artery disease, which is defined as a combination of ankle-brachial index $\leqslant$0.90, percentage of mean arterial pressure $\geqslant$45% or both (odds ratio = 1.306; 95% confidence interval = 1.057–1.615; $p = 0.014$).

Conclusion: Fluctuation in the haemoglobin A1c value indicates higher risk for peripheral artery disease in patients with type 2 diabetes and poor glucose control.

Keywords

Ankle-brachial index, haemoglobin A1c, percentage of the mean arterial pressure, peripheral artery disease, type 2 diabetes, variability

Introduction

Type 2 diabetes mellitus (DM) is a complex metabolic disorder with a clinical manifestation of hyperglycaemia. Reaching a haemoglobin A1c (HbA1c) target with the use of glucose-lowering therapy is an important strategy for the prevention of chronic diabetes-associated complications.[1,2] However, a large prospective observational study recently reported that the HbA1c level is not associated with macrovascular diseases in patients with type 2 DM.[3]

It has been reported that HbA1c variability, defined as the standard deviation (SD) of several measurements, is more predictive of all-cause mortality than the mean of HbA1c in a prospective study of Japanese patients with type 2 DM.[4] Recently, Orsi et al.[5] also reported a similar result in an Italian multicenter study of Renal Insufficiency and Cardiovascular Events (RIACE). Therefore, the SD of a series of HbA1c measurements is useful for predicting the long-term mortality risk of patients with type 2 DM.[6]

Peripheral artery disease (PAD) of the lower extremities is diagnosed based on a low ankle-brachial index (ABI) and is associated with a high mortality rate.[7] In recent decades, PAD has become a modern health problem because of its increasing prevalence and burden, including death and disability.[8,9] DM is an important risk factor for PAD.[9,10] The prevalence of PAD, defined as an ABI value of less than 0.90, is 10% in the Taiwanese population with

[1]Division of Endocrinology and Metabolism, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung City
[2]School of Medicine, National Yang-Ming University, Taipei City
[3]School of Medicine, Chung Shan Medical University, Taichung City
[4]College of Science, Tunghai University, Taichung City

Corresponding author:
I-Te Lee, Division of Endocrinology and Metabolism, Department of Internal Medicine, Taichung Veterans General Hospital, No. 1650, Section 4, Taiwan Boulevard, Taichung 40705.
Email: itlee@vghtc.gov.tw

type 2 DM and 10.4% in the Malay DM population living in Singapore.[11,12]

DM is associated with arterial stiffness, which results in elevated systolic blood pressure and a decrease in the diagnostic sensitivity of PAD using ABI.[13] A composite assessment of ABI and percentage of the mean arterial pressure (%MAP) at the ankle can provide a more accurate diagnostic rate of PAD than ABI assessment alone.[14] Furthermore, using the criterion of %MAP >45% can improve the predictive rate of all-cause mortality in subjects with normal ABI.[15] HbA1c variability is hypothesized to be associated with PAD. Therefore, in this study, the relationship among HbA1c variability, ABI and %MAP was assessed in patients with type 2 DM.

Materials and methods

Study design and subjects

This case-control study was conducted at Taichung Veterans General Hospital in Taiwan. Measurement of ABI was suggested in patients of age ⩾50 years with diabetes, and this suggestion was added to the routine annual diabetes review programme of the hospital information system if ABI data were not available within 3 years. In addition, measurement of ABI was suggested in a clinical suspicion of PAD. Ankle pulse volume waveform was automatically detected when measuring ABI using the validated device (VP-1000 Plus; Omron Healthcare Co. Ltd., Kyoto, Japan). Data collection was performed by retrospectively reviewing electronic medical records. The inclusion criteria were as follows: (1) adults with type 2 diabetes and (2) assessments of ABI and %MAP between 1 August 2016 and 31 July 2018. The exclusion criteria were as follows: (1) an uncompleted four-limb assessment of ABI due to a known history of lower-extremity surgery or haemodialysis treatment, (2) ABI >1.40 and (3) incomplete biochemical data within 3 months of the ABI assessment.

In patients with repeated ABI assessments during the inclusion period, only data from the first assessment were recorded. Anthropometric and laboratory data were collected within 3 months of the ABI assessment. To calculate the mean and SD of HbA1c within 10 years, the annual HbA1c values were collected using the first available record of the HbA1c level in each year after 1 January 2007, until the ABI assessment. Patients were excluded if they had annual HbA1c records for less than 3 years before the ABI assessment. The median duration of collected annual HbA1c was 8 years [interquartile range (IQR), 4–11 years]. This research protocol was approved by the Institutional Review Board of Taichung Veterans General Hospital, with a waiver for obtaining informed consent.

Biochemical assessments

Biochemical data, including fasting glucose, HbA1c, total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides and creatinine, were collected at our hospital. HbA1c was measured using a cation-exchange high-performance liquid chromatography method (National Glycohemoglobin Standardization Program certified; G8®, Tosoh, Tokyo, Japan). Glucose levels were measured using an oxidase–peroxidase method (Wako Diagnostics, Tokyo, Japan). Total cholesterol, triglycerides and creatinine were measured using commercial kits (Beckman Coulter, Inc., Fullerton, USA). Low HDL cholesterol was defined as a serum HDL level less than 40 mg/dL (1.03 mmol/L) in men or 50 mg/dL (1.29 mmol/L) in women. The estimated glomerular filtration rate (eGFR) was calculated as $186 \times (\text{serum creatinine, mg/dL})^{-1.154} \times (\text{age, years})^{-0.203}$ ($\times 0.742$, if female) based on the Modification of Diet in Renal Disease equation.[16] Cardiovascular disease (CVD) was defined as a known history of coronary artery disease or stroke. Annual HbA1c variability was calculated using the SD of the annual HbA1c levels.

Ankle-brachial profiles

ABI assessment was performed in the supine position after patients rested for at least 5 min. The higher systolic blood pressure of the two arms was recorded as the brachial pressure. The right and left ABI values were calculated by dividing the systolic pressure in each ankle by the recorded brachial pressure.[17] The %MAP was automatically determined based on the ankle pulse volume waveform. The %MAP indicates the height of the mean area of the arterial wave divided by the peak amplitude. The reproducibilities of ABI and %MAP were examined by repeated assessments of a group of 20 subjects. Highly positive correlations of ABI ($r=0.90$, $p<0.001$) and %MAP ($r=0.73$, $p<0.001$) were observed between the first and second measurements. The 95% confidence intervals (CIs) were 0.02 ± 0.01 for the bias of ABI and $-0.33 \pm 0.67\%$ for %MAP between the repeated measurements based on the Bland–Altman plots. Abnormal ABI was defined as ABI ⩽0.90 and abnormal %MAP was defined as %MAP ⩾45%.[15] The lower value of ABI and higher value of %MAP between the lower limbs in an individual were recorded for the analyses. I categorized the group of patients with ABI >0.90 and %MAP <45% as low-risk PAD and categorized the others (i.e. all patients in the three groups of ABI >0.90 with %MAP ⩾45%, ABI ⩽0.90 with %MAP <45% and ABI ⩽0.90 with %MAP ⩾45%) as high-risk PAD.

Statistical analyses

Statistical analyses were performed using an independent sample *t*-test to detect the significant differences in the continuous variables between two groups. One-way analysis of variance was performed to compare the differences in continuous variables among more than two groups, whereas chi-square tests were performed to detect the differences in categorical variables.

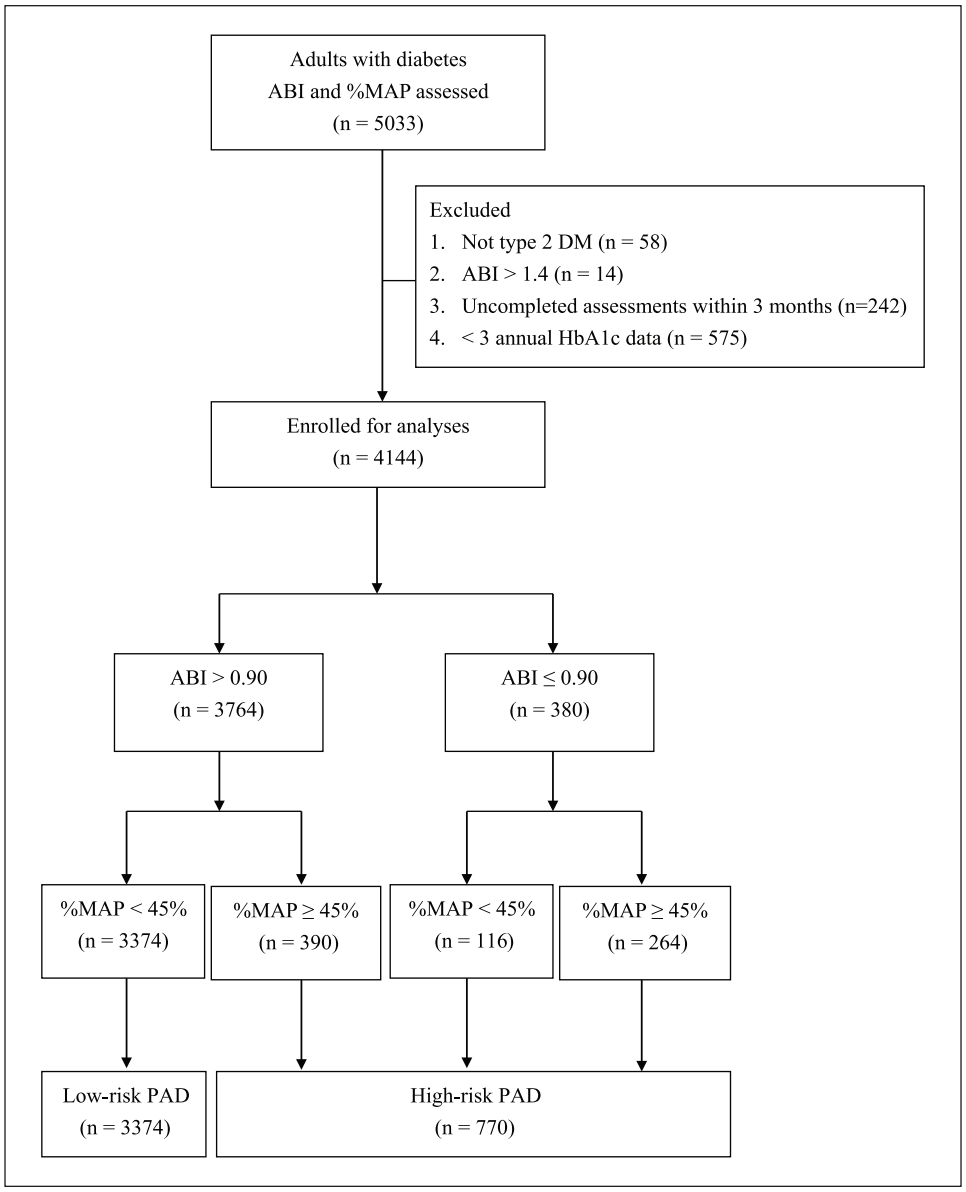

Figure 1. Flow diagram of the enrolment of study subjects.
%MAP: percentage of the mean arterial pressure; ABI: ankle-brachial index; PAD: peripheral artery disease.

Multivariate logistic regression analysis was used to analyse the factors associated with high-risk PAD. Hypertension was defined as systolic blood pressure ⩾140 mmHg, diastolic blood pressure ⩾90 mmHg or the current use of antihypertensive drugs. Antidiabetic drugs were not included in the regression analysis model. ABI, brachial-ankle pulse wave velocity (baPWV) and %MAP were not included in the regression analysis model because they were associated with the criteria for PAD diagnosis.

The relationship between the annual HbA1c values and time was determined by Spearman's correlation in the subgroup of patients with high HbA1c. Patients with a negative correlation coefficient were categorized as having improved glucose control and the others were categorized as having worse glucose control. Statistical analysis was performed using SPSS version 22.0 software (IBM Corp., Armonk, NY, USA).

Results

A total of 4144 patients were enrolled in this study (Figure 1). The mean age of patients was 66 ± 10 years and 2247 (54.2%) patients were male. Table 1 shows the clinical characteristics of patients with ABI ⩽0.90 and ABI >0.90. Patients with ABI ⩽0.90 were older; had higher proportions of CVD and hypertension, higher systolic blood pressure, lower diastolic blood pressure, lower total and HDL cholesterol levels and lower eGFR; and were more likely to use antiplatelet drugs than

Table 1. Characteristics of enrolled patients categorized based on ABI or %MAP.

	All (N = 4144)	ABI > 0.90 (*n* = 3764)	ABI ⩽ 0.90 (*n* = 380)	*p**	%MAP < 45% (*n* = 3490)	%MAP ⩾ 45% (*n* = 654)	*p*#
Age (year)	66 ± 10	65 ± 10	71 ± 12	<0.001	65 ± 10	71 ± 12	<0.001
Male, *n* (%)	2247 (54.2%)	2036 (54.1%)	211 (55.5%)	0.630	1935 (55.4%)	312 (47.7%)	<0.001
Currently smoking, n (%)	487 (11.8%)	431 (11.5%)	56 (14.7%)	0.070	411 (11.8%)	76 (11.6%)	0.962
CVD, *n* (%)	827 (20.0%)	656 (17.4%)	171 (45.0%)	<0.001	593 (17.0%)	234 (35.8%)	<0.001
BMI (kg/m^2)	25.8 ± 4.0	25.8 ± 4.0	25.7 ± 4.3	0.692	25.9 ± 4.0	25.3 ± 4.2	0.001
Systolic BP (mmHg)	137 ± 20	137 ± 19	143 ± 24	<0.001	136 ± 19	145 ± 24	<0.001
Diastolic BP (mmHg)	77 ± 11	77 ± 11	75 ± 12	<0.001	77 ± 11	76 ± 12	0.004
Mean of annual HbA1c (%)	7.6 ± 1.2	7.6 ± 1.2	7.7 ± 1.3	0.076	7.6 ± 1.2	7.7 ± 1.2	0.005
SD of annual HbA1c (%)	1.0 ± 0.8	1.0 ± 0.8	1.1 ± 0.9	0.009	1.0 ± 0.8	1.1 ± 0.8	0.007
Fasting glucose (mmol/L)	8.0 ± 3.4	8.0 ± 3.4	8.3 ± 3.5	0.052	8.0 ± 3.4	8.1 ± 3.3	0.673
HbA1c (%)	7.4 ± 1.5	7.4 ± 1.5	7.6 ± 1.6	0.109	7.4 ± 1.5	7.5 ± 1.6	0.095
Total cholesterol (mmol/L)	4.1 ± 0.9	4.1 ± 0.9	3.9 ± 0.9	0.001	4.1 ± 0.9	4.0 ± 0.9	0.014
HDL cholesterol (mmol/L)	1.3 ± 0.4	1.3 ± 0.4	1.2 ± 0.3	<0.001	1.3 ± 0.4	1.2 ± 0.4	<0.001
Triglyceride (mmol/L)	1.6 ± 1.2	1.6 ± 1.3	1.6 ± 1.1	0.218	1.6 ± 1.3	1.5 ± 1.1	0.391
eGFR (mL/min/1.73 m^2)	76 ± 29	78 ± 28	58 ± 32	<0.001	79 ± 27	62 ± 32	<0.001
ABI	1.1 ± 0.2	1.1 ± 0.1	0.6 ± 0.3	<0.001	1.1 ± 0.1	0.9 ± 0.3	<0.001
baPWV (cm/sec)	1878 ± 513	1863 ± 470	2027 ± 812	<0.001	1836 ± 434	2105 ± 777	<0.001
%MAP	40.9 ± 4.4	40.3 ± 3.8	47.1 ± 5.4	<0.001	39.5 ± 3.1	48.2 ± 2.9	<0.001
Antiplatelet, *n* (%)	1349 (32.6%)	1080 (28.7%)	269 (70.8%)	<0.001	990 (28.4%)	359 (54.9%)	<0.001
Statins, *n* (%)	3036 (73.3%)	2749 (73.0%)	287 (75.5%)	0.324	2550 (73.1%)	486 (74.3%)	0.540
Hypertension, *n* (%)	3326 (80.3%)	2975 (79.0%)	351 (92.4%)	<0.001	2745 (78.7%)	581 (88.8%)	<0.001
Antihypertensive agents, *n* (%)	2407 (58.1%)	2118 (56.3%)	289 (76.1%)	<0.001	1942 (55.6%)	465 (71.1%)	<0.001
ACE inhibitor or ARB, *n* (%)	1753 (42.3%)	1554 (41.3%)	199 (52.4%)	<0.001	1431 (41.0%)	322 (49.2%)	<0.001
α-Blocker, *n* (%)	326 (7.9%)	267 (7.1%)	59 (15.5%)	<0.001	218 (6.2%)	108 (16.5%)	<0.001
β-Blocker, *n* (%)	963 (23.2%)	826 (21.9%)	137 (36.1%)	<0.001	744 (21.3%)	219 (33.5%)	<0.001
Calcium channel blocker, *n* (%)	240 (5.8%)	205 (5.4%)	35 (9.2%)	0.004	190 (5.4%)	50 (7.6%)	0.034
Diuretics, *n* (%)	458 (11.1%)	360 (9.6%)	98 (25.8%)	<0.001	315 (9.0%)	143 (21.9%)	<0.001
Insulin therapy, *n* (%)	984 (23.7%)	854 (22.7%)	130 (34.2%)	<0.001	775 (22.2%)	209 (32.0%)	<0.001
Oral antihyperglycemic drugs	3707 (89.5%)	3405 (90.5%)	302 (79.5%)	<0.001	3170 (90.8%)	537 (82.1%)	<0.001
Insulin secretagogues, *n* (%)	1562 (37.7%)	1439 (38.2%)	123 (32.4%)	0.028	1318 (37.8%)	244 (37.3%)	0.860
Metformin, *n* (%)	1556 (37.5%)	1460 (38.8%)	96 (25.3%)	<0.001	1365 (39.1%)	191 (29.2%)	<0.001
Thiazolidinediones, *n* (%)	926 (22.3%)	854 (22.7%)	72 (18.9%)	0.109	806 (23.1%)	120 (18.3%)	0.009
α-Glucosidase inhibitors, *n* (%)	422 (10.2%)	387 (10.3%)	35 (9.2%)	0.569	345 (9.9%)	77 (11.8%)	0.163
DPP4 inhibitors	2513 (60.6%)	2302 (61.2%)	211 (55.5%)	0.037	2137 (61.2%)	376 (57.5%)	0.080
SGLT2 inhibitors	468 (11.3%)	439 (11.7%)	29 (7.6%)	0.023	423 (12.1%)	45 (6.9%)	<0.001

%MAP: percentage of the mean arterial pressure; ABI: ankle-brachial index; ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor antagonist; baPWV: brachial-ankle pulse wave velocity; BMI: body mass index; BP: blood pressure; CVD: cardiovascular disease; DPP4: dipeptidyl peptidase-4; eGFR: estimated glomerular filtration rate; HbA1c: hemoglobin A1c; HDL: high-density lipoprotein; SD: standard deviation; SGLT2: sodium glucose cotransporter 2.

Continuous data are presented as the mean ± SD, and categorical data are presented as numbers (percentages).

*p denotes a significant difference between patients with ABI > 0.90 and ABI ⩽ 0.90.

#p denotes a significant difference between patients with %MAP < 45% and %MAP ⩾ 45%.

patients with ABI >0.90. A higher %MAP and higher baPWV were observed in patients with ABI ⩽0.90 than those with ABI >0.90 ($p < 0.001$, both).

Table 1 also shows the characteristics of patients with %MAP ⩾45% and %MAP <45%. Patients with %MAP ⩾45% were older; were more likely to be female, to have CVD and hypertension and to use antiplatelet drugs; and had lower body mass index, higher systolic and lower diastolic blood pressures, lower total and HDL cholesterol levels, lower eGFR, lower ABI and higher baPWV than patients with %MAP <45%.

It is notable that the SD of annual HbA1c (1.1 ± 0.9% vs 1.0 ± 0.8%, $p = 0.009$) but not the mean of annual HbA1c (7.7 ± 1.3% vs 7.6 ± 1.2%, $p = 0.076$) was significantly higher in patients with ABI ⩽0.90 than in patients with ABI >0.90. Both the mean of annual HbA1c (7.7 ± 1.2% vs 7.6 ± 1.2%, $p = 0.005$) and the SD of annual HbA1c (1.1 ± 0.8% vs 1.0 ± 0.8%, $p = 0.007$) were significantly higher in patients with MAP ⩾45% and %MAP <45%. There were no significant differences in fasting glucose or single HbA1c level detected within 3 months of the ABI assessment between patients with ABI ⩽0.90 and

ABI >0.90 or between patients with MAP ⩾45% and %MAP <45%.

Because several of the same associated factors were observed in patients with ABI <0.90 and %MAP ⩾45%, all patients were divided into four groups: ABI >0.90 with %MAP <45%, ABI >0.90 with %MAP ⩾45%, ABI ⩽0.90 with %MAP <45% and ABI ⩽0.90 with %MAP ⩾45%. The characteristics of the patients in these four groups are shown in Table 2. The mean and SD of annual HbA1c showed a significant and increasingly positive trend from the ABI >0.90 with %MAP <45% group to the ABI ⩽0.90 with %MAP ⩾45% group ($p=0.026$ and 0.021, respectively).

Based on the median mean (7.4%) and median SD (0.775%) of annual HbA1c, all patients were divided into four groups: lower mean with lower SD, higher mean with lower SD, lower mean with higher SD and higher mean with higher SD. The mean and interquartile range (IQR) of annual HbA1c mean and annual HbA1c SD in these four groups are shown Table 3. The prevalence of high-risk PAD showed a positive trend from the lower mean with lower SD group to the higher mean with higher SD group (16.2% in the lower mean with lower SD group, 15.5% in the higher mean with lower SD group, 18.4% in the lower mean with higher SD group and 22.0% in the higher mean with higher SD group; $p<0.001$). Similarly, the prevalence of either ABI ⩽0.90 or %MAP ⩾45% also showed a positive trend among these four groups ($p=0.001$ for ABI ⩽0.90 and $p<0.001$ for %MAP ⩾45%; Figure 2).

Using multivariate logistic regression analyses, a higher mean with a higher SD of annual HbA1c, independent of the currently measured HbA1c level, was significantly associated with high-risk PAD compared to a lower mean with a lower SD (odds ratio=1.306; 95% CI=1.057–1.615; $p=0.014$) after adjusting for the potential associated risk factors, which were selected from Table 2, including age, gender, CVD history, hypertension, the use of antiplatelet agents, total and HDL cholesterol levels, eGFR, systolic and diastolic blood pressures and current use of antihypertensive drugs (Table 4).

To understand the relationship between the HbA1c trajectories and high-risk PAD in patients with HbA1c ⩾7.4%, 502 patients with a low SD of annual HbA1c were grouped into the stable group, 1026 patients with a decreasing trend of annual HbA1c were grouped into the improving group and 544 patients with an increasing trend of annual HbA1c were grouped into the worsening group. The mean and IQR of annual HbA1c mean and annual HbA1c SD in these three groups are shown in Table 5. There was a significant positive trend of high-risk PAD across these three groups ($p=0.003$, Figure 3). Patients with a high SD of annual HbA1c, either in the worsening group (odds ratio=1.639, 95% CI=1.198–2.241, $p=0.002$) or the improving group (odds ratio=1.484, 95% CI=1.117–1.971, $p=0.006$), were significantly associated with high-risk PAD compared to those with a low SD of annual HbA1c.

Discussion

The main findings of this study were that a higher variability of annual HbA1c was observed in patients with a lower ABI value and patients with a higher %MAP value. Furthermore, high variability with a high mean of HbA1c was significantly associated with high-risk PAD, defined as a composite of ABI ⩽0.90, %MAP ⩾45% or both. Hyperglycaemic pulses have been reported to induce inflammation and oxidation.[18,19] The oxidative stress induced by the fluctuation of glucose might be associated with endothelial dysfunction.[20–22] Although several studies have reported the effects of HbA1c variability on mortality and CVD, the relationship between PAD and HbA1c variability has rarely been reported in type 2 DM.[4–6,23–25] Gorst et al.[26] reported that a high SD of HbA1c is significantly associated with an increased risk of not only all-cause mortality but also nephropathy in patients with type 2 DM in a meta-analysis study. This meta-analysis also included an Italian multicenter study that showed a significant association between a high SD of HbA1c and ulceration/gangrene of the lower limbs.[26,27] Our results indicate that an association between HbA1c variability and high-risk PAD exists.

HbA1c has been reported to be associated with PAD, defined as ABI ⩽0.90, in a Korean population with type 2 DM.[28] In the Atherosclerosis Risk in Communities (ARIC) study, the baseline HbA1c was a strong predictor for the occurrence of PAD.[29] Hjellestad et al.[30] reported that preoperative HbA1c could predict mortality in patients with type 2 DM after surgical treatment for PAD. The mean HbA1c over 5 years could predict all-cause mortality in aged French patients with type 2 DM.[31] However, in this study, the mean of annual HbA1c levels was not significantly different between patients with ABI ⩽0.90 and those with ABI >0.90. On the contrary, the mean of annual HbA1c levels was significantly higher in patients with %MAP ⩾45% than in those with %MAP <45%. It has been reported that the HbA1c increment is associated with arterial stiffness.[32,33] Therefore, the mean annual HbA1c level might be significantly associated with PAD when using the definition of %MAP ⩾45% instead of ABI ⩽0.90.

In this study, a high mean of annual HbA1c had a superimposing effect on high variability of HbA1c in association with PAD, and this finding is consistent with the effect observed for all-cause mortality in the RIACE study.[5] In line with this study, a longitudinal study of a Chinese population with type 2 DM reported that higher glucose variability predicted all-cause mortality in patients with fasting glucose greater than 7 mmol/L but not in those with fasting glucose less than 7 mmol/L.[34] By contrast, Skriver et al.[24] reported that a high HbA1c variability was predictive of all-cause mortality only in patients with HbA1c <8% but not in those with HbA1c >8%. Ma et al.[23] also reported a better ability of HbA1c variability to predict all-cause mortality in patients with HbA1c <7.3% than in those with HbA1c >7.3%. The contradictory results regarding whether HbA1c variability depends on the mean HbA1c still require further

Table 2. Characteristics of the enrolled patients categorized based on a combination of the ABI and %MAP.

	Low-risk PAD	High-risk PAD			*p**	High-risk PAD	*p#*
	ABI >0.90 and %MAP <45% (*n* = 3374)	ABI >0.90 and %MAP ⩾45% (*n* = 390)	ABI ⩽0.90 and %MAP <45% (*n* = 116)	ABI ⩽0.90 and %MAP ⩾45% (*n* = 264)		ABI ⩽0.90 or %MAP ⩾45% (*n* = 770)	
Age (years)	65 ± 10	70 ± 12	66 ± 12	73 ± 11	<0.001	71 ± 12	<0.001
Male, *n* (%)	1878 (55.7%)	158 (40.5%)	57 (49.1%)	154 (58.3%)	<0.001	369 (47.9%)	<0.001
Currently smoking, *n* (%)	394 (11.7%)	37 (9.5%)	17 (14.7%)	39 (14.8%)	0.157	93 (12.1%)	0.803
CVD, *n* (%)	559 (16.6%)	97 (24.9%)	34 (29.3%)	137 (51.9%)	<0.001	268 (34.8%)	<0.001
BMI (kg/m^2)	25.8 ± 4.0	25.6 ± 4.4	27.4 ± 4.6	24.9 ± 4.0	<0.001	25.6 ± 4.3	0.278
Systolic BP (mmHg)	136 ± 19	145 ± 23	138 ± 19	146 ± 26	<0.001	144 ± 24	<0.001
Diastolic BP (mmHg)	77 ± 11	77 ± 12	75 ± 10	75 ± 13	0.001	76 ± 12	<0.001
Mean of annual HbA1c (%)	7.6 ± 1.2	7.7 ± 1.2	7.7 ± 1.4	7.7 ± 1.3	0.026	7.7 ± 1.3	0.002
SD of annual HbA1c (%)	1.0 ± 0.8	1.0 ± 0.8	1.1 ± 0.8	1.1 ± 0.9	0.021	1.1 ± 0.8	0.004
Fasting glucose (mmol/L)	8.0 ± 3.4	7.9 ± 3.1	8.3 ± 2.9	8.4 ± 3.7	0.227	8.1 ± 3.3	0.452
HbA1c (%)	7.4 ± 1.5	7.5 ± 1.5	7.6 ± 1.6	7.5 ± 1.6	0.177	7.6 ± 1.6	0.033
Total cholesterol (mmol/L)	4.1 ± 0.9	4.0 ± 0.9	3.9 ± 0.9	4.0 ± 0.9	0.005	4.0 ± 0.9	0.001
HDL cholesterol (mmol/L)	1.3 ± 0.4	1.3 ± 0.4	1.2 ± 0.4	1.2 ± 0.3	<0.001	1.2 ± 0.4	<0.001
Triglyceride (mmol/L)	1.6 ± 1.3	1.5 ± 1.2	1.8 ± 1.2	1.6 ± 1.0	0.133	1.6 ± 1.2	0.909
eGFR (mL/min/1.73 m^2)	79 ± 27	69 ± 32	72 ± 32	52 ± 30	<0.001	64 ± 32	<0.001
ABI	1.1 ± 0.1	1.1 ± 0.1	0.7 ± 0.3	0.6 ± 0.3	<0.001	0.9 ± 0.3	<0.001
baPWV (cm/s)	1838 ± 434	2084 ± 672	1779 ± 435	2136 ± 911	<0.001	2056 ± 745	<0.001
%MAP	39.5 ± 3.1	47.1 ± 1.8	40.6 ± 3.1	49.9 ± 3.3	<0.001	47.1 ± 4.0	<0.001
Antiplatelet, *n* (%)	938 (27.8)	142 (36.4)	52 (44.8%)	217 (82.2)	<0.001	411 (53.4)	<0.001
Statins, *n* (%)	2463 (73.0)	286 (73.3)	87 (75.0%)	200 (75.8)	0.768	573 (74.4)	0.450
Hypertension, *n* (%)	2644 (78.4)	331 (84.9)	101 (87.1)	250 (94.7)	<0.001	682 (88.6)	<0.001
Antihypertensive agents, *n* (%)	1862 (55.2)	256 (65.6)	80 (69.0)	209 (79.2)	<0.001	545 (70.8)	<0.001
ACE inhibitor or ARB, *n* (%)	1375 (40.8)	179 (45.9)	56 (48.3)	143 (54.2)	<0.001	378 (49.1)	<0.001
α-blocker, *n* (%)	207 (6.1)	60 (15.4)	11 (9.5)	48 (18.2)	<0.001	119 (15.5)	<0.001
β-blocker, *n* (%)	711 (21.1)	115 (29.5)	33 (28.4)	104 (39.4)	<0.001	252 (32.7)	<0.001
Calcium channel blocker, *n* (%)	181 (5.4)	24 (6.2)	9 (7.8)	26 (9.8)	0.019	59 (7.7)	0.017
Diuretics, *n* (%)	292 (8.7)	68 (17.4)	23 (19.8)	75 (28.4)	<0.001	166 (21.6)	<0.001
Insulin therapy, *n* (%)	735 (21.8)	119 (30.5)	40 (34.5)	90 (34.1)	<0.001	249 (32.3)	<0.001
Oral antihyperglycaemic drugs	3070 (91.0)	335 (85.9)	100 (86.2)	202 (76.5)	<0.001	637 (82.7)	<0.001
Insulin secretagogues, *n* (%)	1278 (37.9)	161 (41.3)	40 (34.5)	83 (31.4)	0.069	284 (36.9)	0.636
Metformin, *n* (%)	1323 (39.2)	137 (35.1)	42 (36.2)	54 (20.5)	<0.001	233 (30.3)	<0.001
Thiazolidinediones, *n* (%)	776 (23.0)	78 (20.0)	30 (25.9)	42 (15.9)	0.027	150 (19.5)	0.039
α-glucosidase inhibitor, *n* (%)	337 (10.0)	50 (12.8)	8 (6.9)	27 (10.2)	0.214	85 (11.0)	0.421
DPP4 inhibitors	2075 (61.5)	227 (58.2)	62 (53.4)	149 (56.4)	0.090	438 (56.9)	0.020
SGLT2 inhibitors	409 (12.1)	30 (7.7)	14 (12.1)	15 (5.7)	0.001	59 (7.7)	<0.001

%MAP: percentage of mean arterial pressure; ABI: ankle-brachial index; ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor antagonist; baPWV: brachial-ankle pulse wave velocity; BMI: body mass index; BP: blood pressure; CVD: cardiovascular disease; DPP4: dipeptidyl peptidase-4; eGFR: estimated glomerular filtration rate; HbA1c: haemoglobin A1c; HDL: high-density lipoprotein; SD: standard deviation; SGLT2: sodium glucose cotransporter 2. Continuous data are presented as the mean ± SD and categorical data are presented as numbers (%).

*p denotes a significant difference across the four groups.

#p denotes a significant difference between patients with low-risk PAD (ABI >0.9 and %MAP <45%) and those with high-risk PAD (ABI ⩽0.90 and/or %MAP ⩾45%).

Table 3. Mean and interquartile range (IQR) of annual HbA1c mean and annual HbA1c standard deviation (SD) in patients grouped based on median mean (7.4%) and median SD (0.775%) of annual HbA1c.

	Mean of annual HbA1c			SD of annual HbA1c		
	Mean	IQR	*p*	Mean	IQR	*p*
Low mean/low SD	6.6	(6.3, 7.0)	<0.001	0.4	(0.3, 0.6)	<0.001
High mean/low SD	8.1	(7.6, 8.3)		0.5	(0.4, 0.7)	
Low mean/high SD	7.0	(6.8, 7.2)		1.2	(0.9, 1.4)	
High mean/high SD	8.7	(7.9, 9.2)		1.7	(1.0, 2.0)	

SD: standard deviation; HbA1c: haemoglobin A1c.

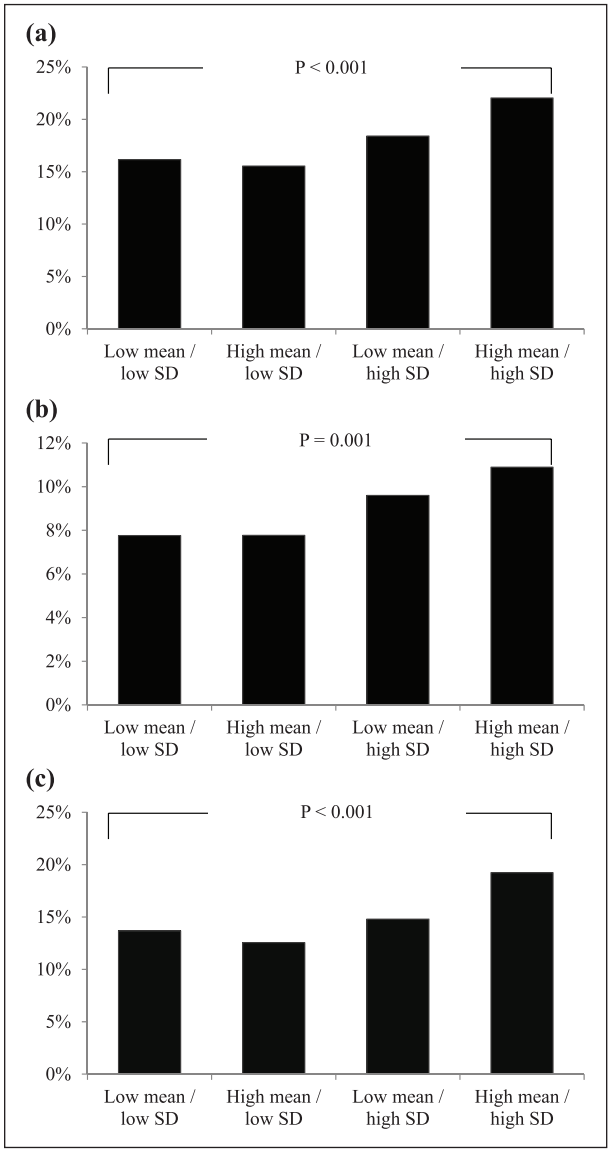

Figure 2. Percentage of patients with (a) high-risk peripheral artery disease (defined by a combination of ankle-brachial index (ABI) ⩽0.9, percentage of the mean arterial pressure (%MAP) ⩾45% or both), (b) ABI ⩽0.9 and (c) %MAP ⩾45% across the four patient groups categorized based on the median mean (7.4%) and median standard deviation (SD) (0.775%) of annual HbA1c.

study. Recently, Dhatariya et al.[35] reported that patients with a high HbA1c value and high HbA1c variability had a prolonged healing time of foot wounds compared to that in patients with a low HbA1c values and low HbA1c variability. Therefore, a high HbA1c variability is a significant risk for foot complications in patients with a high HbA1c value. Furthermore, Lee et al.[25] reported that a significant association between HbA1c variability and cardiovascular events only existed in patients with preserved renal function. Our results show that a higher mean of HbA1c and a higher variability indicate an increased risk for PAD, independent of advanced chronic kidney disease.

Due to the advancement in technology, the ankle pulse volume waveform can be simultaneously accessed via measuring ABI. Peripheral artery occlusion results in a flattened wave form and increased %MAP, which have a better diagnostic accuracy for arterial occlusion than using the ankle systolic pressure to calculate ABI in an incompressible artery, specifically in patients with diabetes.[36,37] Hashimoto et al.[38] reported that adding a criterion of %MAP ⩾45% could improve the accuracy of PAD diagnosis. We previously reported that using a composite of ABI ⩽0.90 and %MAP ⩾45% could predict long-term mortality.[15] Therefore, in this study, the high-risk PAD group might be associated with an accurate PAD diagnosis as well as a higher risk of mortality.

In this study, the proportion of males was not significantly different between patients with ABI ⩽0.90 and >0.90, but the proportion of males was lower in patients with %MAP ⩾45% than in those with %MAP <45%. It was reported that females had a higher risk of arterial stiffness than males[39] and that being females was an independent risk factor for arterial stiffness in type 2 DM.[40] Using %MAP might be helpful to identify PAD compared to ABI, which is falsely elevated due to arterial stiffness.[36]

Lee et al.[41] previously reported that the mortality rate was significantly different between a high variability and a low variability of fasting glucose trajectories during a 2-year study period. Laiteerapong et al.[42] reported that unstable HbA1c trajectories were associated with a high risk of microvascular diseases and that only an initial high HbA1c with a rapidly decreasing pattern was associated with mortality in a 10-year study of patients with newly

Table 4. Logistic regression analysis showing the factors associated with high-risk PAD.

	OR	95% CI	p*	p	OR	95% CI	p*	p	OR	95% CI	p*	p	OR	95% CI	p*	p
Low mean/low SD	1			<0.001	1			<0.001	1			0.005	1			0.026
High mean/low SD	0.955	(0.724, 1.258)	0.742		0.968	(0.732, 1.282)	0.822		0.934	(0.686, 1.270)	0.661		0.933	(0.685, 1.272)	0.663	
Low mean/high SD	1.170	(0.899, 1.522)	0.242		1.206	(0.923, 1.576)	0.169		1.064	(0.805, 1.406)	0.661		1.058	(0.799, 1.400)	0.694	
High mean/high SD	1.467	(1.226, 1.756)	<0.001		1.561	(1.300, 1.875)	<0.001		1.371	(1.112, 1.690)	0.003		1.306	(1.057, 1.615)	0.014	
Age ⩾65 years					2.527	(2.138, 2.987)		<0.001	1.952	(1.636, 2.330)		<0.001	1.794	(1.499, 2.147)		<0.001
Male					0.775	(0.660, 0.910)		0.002	0.666	(0.561, 0.791)		<0.001	0.677	(0.568, 0.807)		<0.001
CVD history									1.464	(1.186, 1.808)		<0.001	1.408	(1.133, 1.751)		0.002
Hypertension									1.164	(0.903, 1.501)		0.240				
Current use of antiplatelet agents									2.085	(1.719, 2.530)		<0.001	2.002	(1.642, 2.440)		<0.001
HbA1c ⩾7%									1.066	(0.881, 1.290)		0.510	1.080	(0.891, 1.310)		0.431
Total cholesterol ⩾4 mmol/L									0.818	(0.689, 0.971)		0.022	0.825	(0.693, 0.982)		0.030
Low HDL cholesterol									1.265	(1.064, 1.504)		0.008	1.254	(1.053, 1.493)		0.011
eGFR <30 mL/min/1.73 m^2									0.402	(0.305, 0.529)		<0.001	0.517	(0.388, 0.691)		<0.001
Systolic BP ⩾140 mmHg													1.539	(1.283, 1.845)		<0.001
Diastolic BP ⩾90 mmHg													0.716	(0.537, 0.954)		0.023
ACE inhibitor or ARB													1.013	(0.853, 1.203)		0.881
α-blocker													1.681	(1.279, 2.208)		<0.001
β-blocker													0.990	(0.812, 1.208)		0.923
Calcium channel blocker													1.036	(0.746, 1.437)		0.834
Diuretics													1.490	(1.173, 1.891)		0.001

ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor antagonist; CI: confidence interval; CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate; HbA1c: haemoglobin A1c; HDL: high-density lipoprotein; OR: odds ratio; SD: standard deviation: BP: blood pressure.

Low HDL-cholesterol is defined as a serum HDL level less than 40 mg/dL (1.03 mmol/L) in men or 50 mg/dL (1.29 mmol/L) in women.

*p denotes a significant difference in comparison with the low mean/low SD group.

Table 5. Mean and interquartile range (IQR) of annual HbA1c mean and annual HbA1c standard deviation (SD) in patients grouped based on HbA1c trajectories.

	Mean of annual HbA1c			SD of annual HbA1c		
	Mean	IQR	*p*	Mean	IQR	*p*
Stable group	8.1	(7.6, 8.3)	<0.001	0.5	(0.4, 0.7)	<0.001
Improving group	8.6	(7.9, 9.1)		1.8	(1.1, 2.2)	
Worsening group	8.7	(7.9, 9.2)		1.5	(1.0, 1.7)	

SD: standard deviation; HbA1c: haemoglobin A1c.

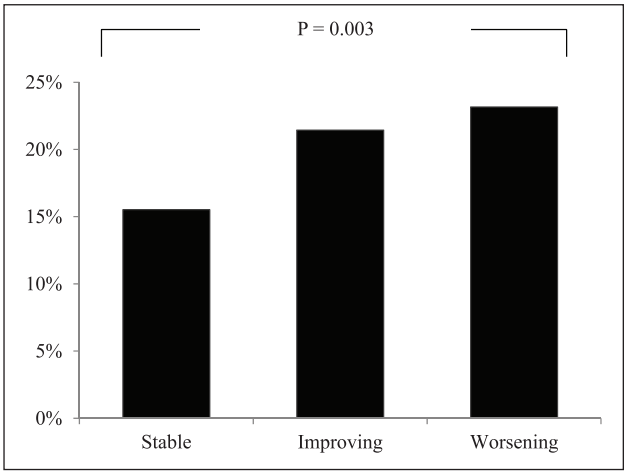

Figure 3. Percentage of patients with high-risk peripheral artery disease across three patterns of HbA1c trajectory in patients with a mean annual HbA1c ⩾7.4%.

diagnosed type 2 DM. In our trending analysis for the subgroup of high mean HbA1c, a high SD of annual HbA1c was associated with a high risk of PAD, regardless of a worsening or improving trend of glucose control. However, the causal effect is unclear because of the cross-sectional design of this study.

Furthermore, there are some limitations in this study. First, high annual HbA1c variability might reflect poor adherence to regular medication. Although several PAD-associated risk factors have been adjusted in the multivariate regression model, the variabilities of other PAD-associated risk factors were not assessed in this study. It has been reported that high variability in cholesterol, body weight and blood pressure are predictors of cardiovascular events.[43–46] Second, only the annual HbA1c data were collected instead of all available HbA1c data, which are usually reported in previous studies.[4,23–25] Although the use of annual HbA1c weakened the ability to detect variations in HbA1c and yielded results towards a null hypothesis, annual HbA1c was selected to avoid the skewed contribution to the mean and SD of HbA1c from frequent detections over a short-term period. Third, a low total cholesterol level was observed in patients with ABI ⩽0.90 or %MAP ⩾45% in this study. Despite a similar proportion of patients using statins, I did not analyse the intensity of statins which might be aggressively used in the high-risk PAD group. Fourth, a higher HbA1c variability might be associated with a higher hypoglycaemic risk,[47,48] which is predictive of CVD. However, hypoglycaemia data were not collected in this study.[49,50] Finally, patients with ABI >1.4 were excluded because the association of the %MAP with a PAD diagnosis or long-term mortality is still unclear in this high-ABI population.[14,15]

Conclusion

A high variability of annual HbA1c was observed in patients with ABI ⩽0.90 or with %MAP ⩾45%. High variability and high mean of annual HbA1c were significantly associated with high-risk PAD. A low and stable HbA1c might be important for the PAD-associated prognosis of type 2 DM in patients with poor glucose control.

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Author contributions

I.-T.L. is the only author and guarantor.

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ORCID iD

I-Te Lee https://orcid.org/0000-0003-2665-3635

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