





ORIGINAL RESEARCH

# Bidirectional Longitudinal Relationships Between Arterial Stiffness and Hypertension Are Independent of Those Between Arterial Stiffness and Diabetes: A Large-Scale Prospective Observational Study in Employees of a Japanese Company

Hiroki Nakano , MD, PhD; Kazuki Shiina , MD, PhD; Takamichi Takahashi, MD; Masatsune Fujii, MD; Yoichi Iwasaki, MD, PhD; Chisa Matsumoto , MD, PhD; Akira Yamashina, MD, PhD; Taishiro Chikamori, MD, PhD; Hirofumi Tomiyama , MD, PhD

**BACKGROUND:** Hypertension and diabetes frequently coexist; however, it has not yet been clarified if the bidirectional longitudinal relationships between arterial stiffness and hypertension are independent of those between arterial stiffness and diabetes.

**METHODS AND RESULTS:** In this 16-year prospective observational study, 3960 middle-aged employees of a Japanese company without hypertension/diabetes at the study baseline underwent annual repeated measurements of blood pressure, serum glycosylated hemoglobin A<sub>1c</sub> levels, and brachial-ankle pulse wave velocity. By the end of the study period, 664, 779, 154, and 406 subjects developed hypertension, prehypertension, diabetes, and prediabetes, respectively. Increased brachial-ankle pulse wave velocity at the baseline was associated with a significant odds ratio (per 1 SD increase) for new onset of prehypertension/hypertension with (2.45/3.28;  $P<0.001$ ) or without (2.49/2.76;  $P<0.001$ ) coexisting prediabetes/diabetes, but not for new onset of prediabetes/diabetes without coexisting hypertension. Analyses using the latent growth curve model confirmed the bidirectional relationships between brachial-ankle pulse wave velocity and hypertension, but no such relationship was observed between brachial-ankle pulse wave velocity and abnormal glucose metabolism.

**CONCLUSIONS:** In middle-aged employees of a Japanese company, while bidirectional relationships were found to exist between increased arterial stiffness and hypertension, such a relationship was not found between increased arterial stiffness and diabetes. Therefore, it appears that increased arterial stiffness may be associated with the development of hypertension but not with that of diabetes.

**Key Words:** arterial stiffness ■ diabetes ■ hypertension

Arterial stiffness is known as a risk marker for the development of cardiovascular disease, independent of conventional risk factors, such as hypertension and diabetes.<sup>1-4</sup> Recent studies have also identified arterial stiffness as a risk factor for the development of

hypertension and diabetes.<sup>5-11</sup> Conversely, hypertension and diabetes have been reported by several studies to be associated with increased arterial stiffness.<sup>12-16</sup> Thus, the existence of bidirectional relationships between increased arterial stiffness and hypertension/diabetes has

Correspondence to: Hirofumi Tomiyama, MD, PhD, FAHA, Department of Cardiology, Tokyo Medical University, 6-7-1 Nishi-Shinjuku, Shinjuku-ku, Tokyo 160-0023, Japan. Email: [tomiyaama@tokyo-med.ac.jp](mailto:tomiyaama@tokyo-med.ac.jp)

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## CLINICAL PERSPECTIVE

### What Is New?

- Arterial stiffness may be a risk factor for the development of hypertension/prehypertension, including that of hypertension/prehypertension coexisting with diabetes/prediabetes but not for the development of diabetes/prediabetes alone.
- Latent growth curve model analyses confirmed the existence of bidirectional longitudinal relationships between arterial stiffness and hypertension but not between arterial stiffness and diabetes.
- Increased arterial stiffness preceding the development of diabetes may represent that associated with the development of hypertension, as it is observed only in cases of diabetes coexisting with hypertension.

### What Are the Clinical Implications?

- Arterial stiffness may be a key element in the development of hypertension but not in the development of diabetes, so that its contribution to the cardiovascular risk associated with hypertension may be greater than that to the cardiovascular risk associated with diabetes.

## Nonstandard Abbreviations and Acronyms

<b>baPWV</b>	brachial-ankle pulse wave velocity
<b>HbA<sub>1c</sub></b>	glycosylated hemoglobin A <sub>1c</sub>
<b>LGCM</b>	latent growth curve model

been proposed,<sup>17–19</sup> and it has been suggested that arterial stiffness may be the key contributor to the increase in cardiovascular risk associated not only with hypertension but also with diabetes, even from the early pathophysiological stages of development.<sup>19</sup> However, only limited evidence is available yet for the existence of such bidirectional relationships, and the findings published so far are inconsistent.<sup>5,6,8,11,12</sup> Furthermore, despite the frequent coexistence of hypertension and diabetes,<sup>20</sup> it has not yet been clarified whether the contribution of arterial stiffness to the cardiovascular risk associated with hypertension might be independent of that to the cardiovascular risk associated with diabetes.

Based on repeated annual measurements of the arterial stiffness, blood pressure, and serum glycosylated hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) levels during annual medical checkups over a 16-year period in middle-aged employees of a Japanese company, the present prospective observational study was conducted to examine whether the bidirectional relationships between arterial stiffness and diabetes might be independent

of those known to exist between arterial stiffness and hypertension even from the early pathophysiological stages of development (ie, even before the criteria for clinical diagnosis are fulfilled).

## METHODS

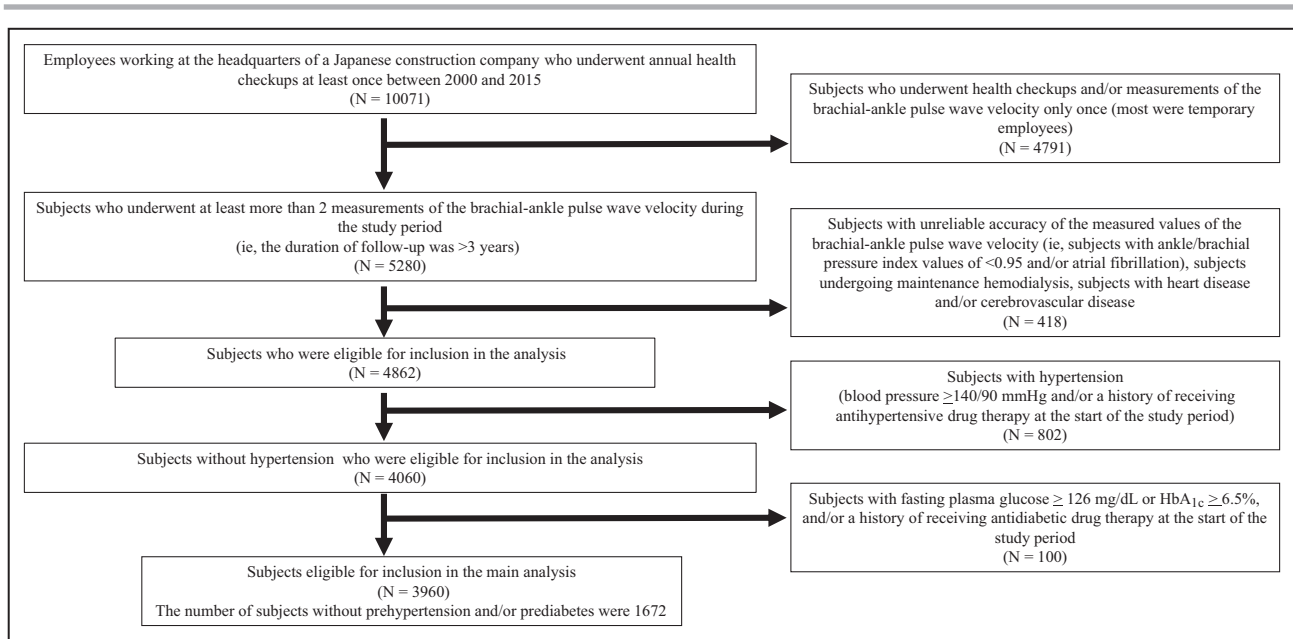
The authors declare that all supporting data are available within the article.

### Design and Subjects

The present study was conducted in the same cohort that we examined for our previously reported prospective observational study.<sup>5,21</sup> The cohort consisted of employees working at the headquarters of a large Japanese company located in downtown Tokyo (all the study participants had desk jobs). Informed consent for participation in this study was obtained from each of the study participants before their enrollment in this study. The study was conducted with the approval of the Ethical Guidelines Committee of Tokyo Medical University (No. 209 and No. 210 in 2003).

Annual health checkup data obtained from the year 2000 through the year 2015 were used for the present study. The flowchart of selection of the study subjects for this longitudinal study is shown in [Figure 1](#). Of the total of 10071 subjects working at the headquarters of the company, 5280 subjects who had undergone at least 2 measurements of the brachial-ankle pulse wave velocity (baPWV) were enrolled in the study. Of these, 418 subjects were excluded because they fulfilled at least 1 of the following exclusion criteria: unreliable accuracy of the measured baPWV values (ankle-brachial systolic blood pressure index <0.95 or presence of atrial fibrillation),<sup>22,23</sup> currently undergoing maintenance hemodialysis or presence of heart disease or cerebrovascular disease. A further 802 subjects who had a blood pressure of  $\geq 140/90$  mmHg or were receiving antihypertensive drug therapy at the start of the study period were also excluded. In addition, 100 subjects who had fasting plasma glucose levels of  $\geq 126$  mg/dL or HbA<sub>1c</sub>  $\geq 6.5\%$  or were receiving antidiabetic drug therapy at the start of the study period were also excluded.

Finally, the data of the remaining 3960 subjects without hypertension or diabetes at the start of the study period were included in the analyses conducted in this study to assess the relationships of increased arterial stiffness with hypertension and diabetes. In addition, the data of 1672 subjects (ie, after additionally excluding subjects with blood pressure in the range of 120–139/80–89 mmHg or fasting plasma glucose levels in the range of 100–125 mg/dL or HbA<sub>1c</sub> in the range of 5.7–6.4% at the study baseline) were analyzed for the development of prehypertension or prediabetes by the end of the study period.



**Figure 1. Flow diagram of subject enrollment for the study.**

The total study period was 16 years, and the minimum duration of follow-up was >3 years. Therefore, the start and end of the study for each study participant were individually determined during the study period (for each study participant, the first annual health checkup during the study was the study start, and the last annual health checkup during the study period was the study end).

### Blood Pressure Measurement

Brachial blood pressure was measured as the mean of 2 measurements obtained in an office setting by the conventional cuff method using a mercury sphygmomanometer. Both measurements were performed on the same occasion with the subjects in the seated position after they had rested for at least 5 minutes.

### Measurement of the baPWV

The baPWV was measured using a volume-plethysmographic apparatus (Form/ABI; Omron Healthcare Co., Ltd., Kyoto, Japan), as previously described.<sup>22</sup> The brachial and posttibial arterial pressures were measured with an oscillometric sensor. The measurements were conducted after the subjects had rested for at least 5 minutes in the supine position. Data of subjects with ankle-brachial systolic blood pressure index values of <0.95 and of those with atrial fibrillation were excluded from the analyses. The baPWV was measured once on each side, and the mean of the measured values on the right and left sides was used for the analyses. Acceptable reproducibility of baPWV measurement has been reported elsewhere.<sup>22</sup> All the measurements (ie, blood pressure and baPWV) were conducted by well-trained nurses.

### Laboratory Measurements

Serum concentrations of uric acid, triglyceride, total cholesterol, high-density lipoprotein cholesterol, and creatinine (except between 2000 and 2003), as well as the plasma glucose and serum HbA<sub>1c</sub> levels were measured using standard enzymatic methods (Falco Biosystems Co. Ltd, Tokyo), except between 2000 and 2003. All the blood samples for the measurements were obtained in the morning after the patients had fasted overnight.

Between 2000 and 2003 alone, the serum concentrations of creatinine were measured by Jaffe's method and then converted to the values obtained by the enzymatic methods (value obtained by Jaffe's method minus 0.2). In regard to the serum HbA<sub>1c</sub> levels, from 2000 to 2012, the method proposed by the Japan Diabetes Society was adopted, while from 2013 to 2015, the method proposed by the National Glycohemoglobin Standardization Program was adopted. For this study, the value of HbA<sub>1c</sub> was unified to the National Glycohemoglobin Standardization Program value (ie, National Glycohemoglobin Standardization Program [%]=1.02×Japan Diabetes Society [%]+0.25 [%]).<sup>24</sup>

### Definitions of Hypertension/Prehypertension and Diabetes/Prediabetes and the Outcome Categories

#### Definition of Prehypertension

Prehypertension is defined as systolic blood pressure ≥120 mmHg or diastolic blood pressure ≥80 mmHg or a history of receiving antihypertensive drug therapy at the time of the annual health checkups.<sup>25</sup>

### Definition of Hypertension

Hypertension is defined as systolic blood pressure  $\geq 140$  mmHg or diastolic blood pressure  $\geq 90$  mmHg or a history of receiving antihypertensive drug therapy at the time of the annual health checkups.

### Definition of Prediabetes

Prediabetes is defined as fasting plasma glucose  $\geq 100$  mg/dL or HbA<sub>1c</sub>  $\geq 5.7\%$  or a history of receiving antidiabetic drug therapy at the time of the annual health checkups.<sup>26</sup>

### Definition of Diabetes

Diabetes is defined as fasting plasma glucose  $\geq 126$  mg/dL or HbA<sub>1c</sub>  $\geq 6.5\%$  or a history of receiving antidiabetic drug therapy at the time of the annual health checkups.<sup>26–28</sup>

For logistic regression analyses, the outcome categories were hypertension/prehypertension alone, diabetes/prediabetes alone, coexisting hypertension and diabetes, or coexisting prehypertension and prediabetes at the end of study for each study participant.

### Statistical Analysis

Data are expressed as means $\pm$ SD, unless otherwise indicated. Differences in the measured values between the baseline and final examinations were assessed by the paired *t* test for continuous variables, and by McNemar's nonparametric test for categorical variables. The differences among the groups were assessed by 1-way ANOVA.

Binomial (backward selection method) and multinomial logistic regression analyses (to examine the probability of dependence of an outcome category on a dependent variable based on multiple independent variables) were performed to identify the variables that were predictive of the development of each outcome by the end of the study period. To examine the association of the blood pressure and plasma glucose/serum HbA<sub>1c</sub> levels at the study baseline with the baPWV measured at the end of the study, multivariate linear regression analyses without and with adjustments were performed.

To analyze the bidirectional longitudinal associations among the variables, first, latent growth curve model (LGCM) analyses were performed to assess the significance of the unidirectional relationships (in both directions) between the mean blood pressure and baPWV. In the LGCM analyses, the time effect was entered as the interaction term between time (years from the baseline as a continuous variable) and each of the explanatory variables.<sup>29</sup> Then, we conducted LGCM analyses in the panel data to examine the significance

of the bidirectional relationships between the 2 growth processes with and without adjustments.<sup>30</sup> We also performed LGCM analyses to assess the significance of the bidirectional relationships between HbA<sub>1c</sub> and the baPWV.

Age, sex, body mass index, current smoking history, current daily alcohol intake, heart rate, serum levels of total cholesterol, high-density lipoprotein cholesterol, triglyceride, uric acid, and creatinine, and history of medication use for dyslipidemia (not receiving medication=0, receiving medication=1; for the medication) were used as the basic covariates for the adjustments in the logistic regression analyses and LGCM analyses. Additional covariates used in the logistic regression analyses were the mean blood pressure and HbA<sub>1c</sub> at the baseline. In the LGCM analyses, the measurement data available at each annual measurement were entered as the covariates including mean blood pressure or HbA<sub>1c</sub> levels.

The LGCM analysis to assess the significance of each growth process individually was conducted using the SPSS software (version 27.0; IBM/SPSS Inc., Armonk, NY), the LGCM analysis in panel data was conducted using Amos software (version 23.0; IBM/SPSS Inc., Tokyo Japan), and all other analyses were conducted using the SPSS software.  $P < 0.05$  was considered as being indicative of statistical significance in all the statistical tests.

## RESULTS

The clinical characteristics of the study participants (ie, subjects without hypertension or diabetes and subjects without prehypertension or prediabetes at the study baseline) are summarized in Table 1. Increases in the blood pressure, serum HbA<sub>1c</sub>, and baPWV values were observed by the end of study period in all the subjects. In 3960 subjects without hypertension or diabetes at the baseline, the mean follow-up period was 10.1 $\pm$ 4.2 years, and the measurements were repeated 8.0 $\pm$ 3.2 times. Of these, 655 subjects developed hypertension (16.5%) and 150 subjects developed diabetes (3.8%) by the end of the study period. Of the 655 who developed hypertension, 594 had hypertension alone (ie, without diabetes), 89 subjects had diabetes alone (ie, without hypertension), and 61 subjects had coexisting hypertension and diabetes. As shown in Figure 2, the prevalence of hypertension and diabetes and the mean baPWV value increased significantly with time ( $P < 0.001$  in 1-way ANOVA). By the 16th year of follow-up, data in 859 subjects were available, and 204/859 (23.7%) subjects had hypertension and 44/859 (5.1%) subjects had diabetes (Figure 2).

In the binomial logistic regression analyses conducted in crude models, increased baPWV at the

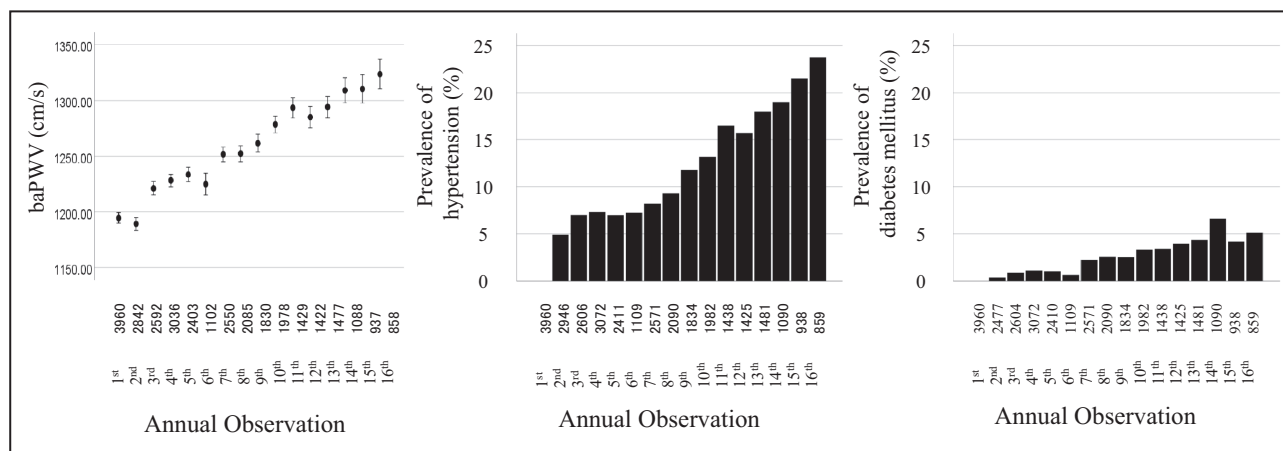
**Table 1. Clinical Characteristics of the Study Subjects Without Hypertension or Diabetes at the Start of the Study Period**

Parameter	Subjects without hypertension or diabetes at baseline			Subjects without prehypertension or prediabetes at baseline		
	Baseline	End	P value	Baseline	End	P value
Study subjects	3960	3960		1672	1672	
Men, n (%)	3264 (82)	3264 (82)		1187 (71)	1187 (71)	
Age, y	38±8	48±9		36±7	46±8	
BMI, kg/m <sup>2</sup>	22.9±3.0	23.5±3.2	<0.001	21.9±2.7	22.6±3.0	<0.001
Smoking (current), n (%)	1376 (35)	927 (23)	<0.001	531 (32)	348 (21)	<0.001
Daily alcohol intake (ethanol g/d)	10.2±10.1	13.0±11.8	<0.001	8.3±8.8	11.4±11.1	<0.001
Systolic BP, mmHg	118±11	122±13	<0.001	108±7	116±12	<0.001
Diastolic BP, mmHg	71±9	75±10	<0.001	66±7	71±10	<0.001
Mean BP, mmHg	87±9	91±11	<0.001	80±6	86±10	<0.001
Heart rate, beats/min	63±9	64±9	<0.001	66±7	71±10	<0.001
baPWV, cm/s	1195±154	1297±200	<0.001	1123±128	1222±168	<0.001
TC, mg/dL	193±33	208±33	<0.001	187±31	206±34	<0.001
HDL, mg/dL	59±14	63±16	<0.001	61±14	65±17	<0.001
Triglyceride, mg/dL	108±90	112±80	<0.001	89±64	101±75	<0.001
UA, mg/dL	5.6±1.3	5.7±1.3	<0.001	5.3±1.3	5.4±1.4	<0.001
BS, mg/dL	89±8	88±12	<0.001	86±6	85±8	<0.001
HbA <sub>1c</sub> , %	5.3±0.3	5.5±0.5	<0.001	5.2±0.3	5.5±0.3	<0.001
Serum creatinine, mg/dL	0.77±0.13	0.82±0.14	<0.001	0.75±0.13	0.79±0.14	<0.001
Medications						
For hypertension, n (%)	0 (0)	262 (6.6)	<0.001	0	27 (1.6)	<0.001
For diabetes, n (%)	0 (0)	65 (1.6)	<0.001	0 (0)	5 (0.3)	0.025
For dyslipidemia, n (%)	24 (0.6)	211 (5.3)	<0.001	8 (0.5)	51 (3.1)	<0.001

baPWV indicates brachial-ankle pulse wave velocity; BMI, body mass index; BP, blood pressure; BS, blood sugar; HbA<sub>1c</sub>, glycosylated hemoglobin A<sub>1c</sub>; HDL, serum high-density lipoprotein cholesterol; TC, serum total cholesterol; and UA, serum uric acid.

study baseline showed a significant odds ratio for the development of hypertension (including hypertension coexisting with diabetes) and prehypertension (including prehypertension coexisting with prediabetes); increased baPWV at the study baseline was associated

with a significant odds ratio for the development of diabetes (including coexisting with hypertension) but not prediabetes (including prediabetes coexisting with prehypertension) (Table 2). However, after the adjustments, the association remained significant only for



**Figure 2. The mean value of the brachial-ankle pulse wave velocity and prevalence rates of hypertension and diabetes during the observation period and the number of available data at each annual measurement.**

1st–16th indicates annual observation. baPWV indicates brachial-ankle pulse wave velocity; BP, blood pressure; MBP, mean blood pressure; and PWV, pulse wave velocity.

the development of hypertension (including hypertension coexisting with diabetes) and prehypertension (including prehypertension coexisting with prediabetes) (Table 2).

In addition, multinomial logistic regression analyses were conducted with adjustments to examine the association of the baPWV at the baseline with the outcome categories at the end of the study (the reference was subjects who did not have either hypertension/

prehypertension or diabetes/prediabetes at the end of the study period, and the outcome categories were as follows: [1] subjects with hypertension/prehypertension but not diabetes/prediabetes [hypertension alone/prehypertension alone] at the end of the study; [2] subjects with diabetes/prediabetes but not hypertension/prehypertension [diabetes alone/prediabetes alone] at the end of the study; [3] subjects with coexisting hypertension/prehypertension and diabetes/prediabetes

**Table 2. Results of Logistic Regression Analyses Performed to Examine the Predictive Value of Increased Brachial-Ankle Pulse Wave Velocity at the Study Baseline for the Development of Hypertension/Prehypertension or Diabetes/Prediabetes**

Outcomes	Odds ratio of baPWV/1 SD (95% CI) in the crude model 1 SD of baPWV=154 cm/s	P value	Odds ratio of baPWV/1 SD (95% CI) in adjusted model 1 SD of baPWV=154 cm/s	P value
Binominal logistic regression analyses				
Subjects without hypertension or diabetes at baseline (n=3960)				
No hypertension (n=3305)	Reference	...	Reference	...
Hypertension (n=655)	2.77 (2.46–3.12)	<0.001	1.92 (1.67–2.20)	<0.001
No diabetes (n=3810)	Reference	...	Reference	...
Diabetes (n=150)	1.63 (1.35–1.97)	<0.001	1.11 (0.83–1.48)	0.492
Subjects without prehypertension or prediabetes at baseline (n=1672)				
No prehypertension (n=941)	Reference	...	Reference	...
Prehypertension (n=731)	2.56 (2.15–3.05)	<0.001	1.92 (1.57–2.35)	<0.001
No prediabetes (n=1277)	Reference	...	Reference	...
Prediabetes (n=395)	0.97 (0.81–1.17)	0.761	...	...
Multinomial logistic regression analyses				
Subjects without hypertension or diabetes at baseline (n=3960)				
No hypertension or diabetes (n=3216)	Reference	...	Reference	...
Hypertension alone (n=594)	2.76 (2.44–3.12)	<0.001	1.87 (1.60–2.18)	<0.001
Diabetes alone (n=89)	1.47 (1.10–1.97)	0.010	0.86 (0.58–1.27)	0.447
Coexisting hypertension and diabetes (n=61)	3.28 (2.47–4.37)	<0.001	2.18 (1.43–3.32)	<0.001
Subjects without prehypertension or prediabetes at baseline (n=1672)				
No prehypertension or prediabetes (n=737)	Reference	...	Reference	...
Prehypertension alone (n=540)	2.49 (2.05–3.03)	<0.001	1.85 (1.46–2.33)	<0.001
Prediabetes alone (n=204)	0.85 (0.65–1.12)	0.247	...	...
Coexisting prehypertension and prediabetes (n=191)	2.45 (1.87–3.20)	<0.001	1.57 (1.13–2.17)	0.007

Adjustments: the covariates used for the adjustment were the basic variable for adjustment (age, sex, body mass index, current smoking history, current daily alcohol intake, heart rate, serum levels of total cholesterol, high-density lipoprotein cholesterol, triglyceride, uric acid, creatinine, history of medication use for dyslipidemia [not receiving medication=0, receiving medication=1; for each medication]), mean blood pressure and HbA<sub>1c</sub> levels. Coexisting hypertension and diabetes: subjects with coexistent hypertension and diabetes mellitus at the end of study period; Coexisting prehypertension and prediabetes: subjects with prehypertension coexisting with prediabetes at the end of study period; diabetes alone: subjects with diabetes but not hypertension at the end of study period; diabetes, subjects with diabetes including coexisting with hypertension at the end of study period; hypertension alone, subjects with hypertension but not diabetes at the end of study period; hypertension, subjects with hypertension including coexisting with diabetes at the end of study period; no diabetes, subjects who did not have diabetes at the end of study period; no hypertension or diabetes, subjects who did not have either hypertension or diabetes at the end of study period; no hypertension, subjects who did not have hypertension at the end of study period; no prediabetes, subjects who did not have prediabetes at the end of study period; no prehypertension or prediabetes, subjects who did not have either prehypertension or prediabetes at the end of study period; no prehypertension, subjects who did not have prehypertension at the end of study period; odds of baPWV/1SD, odds ratio for every 1 standard deviation; outcomes, outcome variables; prediabetes alone, subjects with prediabetes excluding coexisting with prehypertension at the end of study period; prediabetes, subjects with prediabetes at the end of study period; prehypertension alone, subjects with prehypertension excluding coexisting with prediabetes at the end of study period; and prehypertension, subjects with prehypertension at the end of study period. baPWV indicates brachial-ankle pulse wave velocity; and HbA<sub>1c</sub>, glycosylated hemoglobin A<sub>1c</sub>.

[coexisting hypertension and diabetes/coexisting prehypertension and prediabetes] at the end of the study). In these analyses, increased baPWV at the study baseline had significant odds ratios for the development of hypertension alone/prehypertension alone and also for the development of coexisting hypertension and diabetes/coexisting prehypertension and prediabetes (Table 2). On the other hand, increased baPWV at the study baseline was not associated with a significant odds ratio for the development of diabetes alone after the adjustments or even for the development of prediabetes alone in the crude models (Table 2).

Not only in subjects without hypertension or diabetes at the baseline ( $n=3960$ ) but also in those without prehypertension or prediabetes at the baseline ( $n=1672$ ), the mean blood pressure, but not the plasma glucose/serum HbA<sub>1c</sub> level at the baseline showed a significant relationship, even after adjustments, with the baPWV at the end of the study (Table 3). However, when subjects with hypertension or diabetes at the baseline were also included the analyses ( $n=4862$ ), not only the mean blood pressure but also the serum HbA<sub>1c</sub> level at the baseline showed a significant relationship, even after adjustments, with the baPWV at the end of the study period (Table 3).

The number of available data from the annual measurements are shown in Figure 2. Then, LGCM analyses, which were conducted in subjects without hypertension or diabetes at the study baseline, revealed the significant bidirectional longitudinal relationships between the baPWV and the mean blood pressure even after the adjustments. However, in the

relationships between baPWV and the serum HbA<sub>1c</sub> levels, both growth processes were not significant (Table 4). Moreover, after the adjustments, higher mean blood pressure at baseline accelerated the increases in the baPWV over follow-up (unstandardized coefficient [B]=0.39, standard error [SE]= $0.05 \times 10^{-1}$ ,  $P < 0.001$ ). Similarly, higher baPWV at baseline accelerated the increases in mean blood pressure over follow-up ( $B=0.02 \times 10^{-1}$ ,  $SE=0.01 \times 10^{-1}$ ,  $P < 0.001$ ) (Figure 3). On the other hand, higher HbA<sub>1c</sub> levels at baseline accelerated the increases in the baPWV over follow-up ( $B=0.43$ ,  $SE=0.05 \times 10^{-1}$ ,  $P < 0.001$ ), but higher baPWV at baseline did not accelerate the increases in HbA<sub>1c</sub> levels over follow-up ( $B < 0.01$ ,  $SE < 0.01$ ,  $P=0.521$ ) (Figure 4).

## DISCUSSION

To the best of our knowledge, the present study was the first to examine whether the bidirectional longitudinal relationships between arterial stiffness and diabetes were independent of the longitudinal relationships between arterial stiffness and hypertension even from the early pathophysiological stages of development, in our middle-aged Japanese study subjects.

Although the Framingham study failed to identify elevated blood pressure as a risk factor for the progression of arterial stiffness,<sup>6</sup> several studies have demonstrated elevated blood pressure as a risk factor for the progression of arterial stiffness.<sup>12-14</sup> Conversely, increased arterial stiffness is also reported as a risk

**Table 3. Results of Multivariate Linear Regression Analyses Performed to Examine the Relationship of the Mean Blood Pressure and Serum HbA<sub>1c</sub> Level at the Baseline With the Brachial-Ankle Pulse Wave Velocity at the End of the Study Period**

Explained variable	Model	R-squared	B (95% CI)	Beta	P value
Subjects without hypertension or diabetes at baseline ( $n=3960$ )					
Mean BP	Crude	0.15	8.79 (8.13 to 9.47)	0.38	<0.001
Mean BP	Adjusted	0.30	4.92 (4.22 to 5.62)	0.21	<0.001
HbA <sub>1c</sub>	Crude	0.01	75.03 (54.63 to 95.44)	0.11	<0.001
HbA <sub>1c</sub>	Adjusted	0.27	7.24 (-11.86 to 26.33)	0.11	0.457
Subjects without prehypertension or prediabetes at baseline ( $n=1672$ )					
Mean BP	Crude	0.06	6.84 (5.53 to 8.16)	0.24	<0.001
Mean BP	Adjusted	0.25	3.15 (1.87 to 4.44)	0.11	<0.001
HbA <sub>1c</sub>	Crude	0.01	20.25 (-11.44 to 59.94)	0.03	0.210
HbA <sub>1c</sub>	Adjusted	...	...	...	...
Subjects including hypertension or diabetes at baseline ( $n=4862$ )					
Mean BP	Crude	0.24	9.57 (9.10 to 10.05)	0.49	<0.001
Mean BP	Adjusted	0.40	5.28 (4.73 to 5.82)	0.27	<0.001
HbA <sub>1c</sub>	Crude	0.05	96.54 (84.11 to 108.93)	0.21	<0.001
HbA <sub>1c</sub>	Adjusted	0.35	28.92 (17.91 to 39.93)	0.07	<0.001

Adjustments: age, sex, body mass index, current smoking history, current daily alcohol intake, heart rate, serum levels of total cholesterol, high-density lipoprotein cholesterol, triglyceride, uric acid, creatinine, and history of medication use for dyslipidemia (not receiving medication=0, receiving medication=1; for the medication) at the baseline. Adjusted indicates adjusted model; B, unadjusted coefficient; beta, adjusted coefficient; BP, blood pressure; and HbA<sub>1c</sub>, glycosylated hemoglobin A<sub>1c</sub>.

**Table 4. Results of Latent Growth Curve Model Analyses Performed to Examine the Significance of Longitudinal Relationships Among the Variables in Subjects Without Hypertension or Diabetes at the Baseline**

Explained variable	Model	Estimate (95% CI)	P value
For baPWV			
Mean BP	Crude	0.22 (0.20 to 0.25)	<0.001
Mean BP	Adjusted	0.20 (0.18 to 0.22)	<0.001
For mean BP			
baPWV	Crude	0.04×10 <sup>-2</sup> (0.03×10 <sup>-2</sup> to 0.05×10 <sup>-2</sup> )	<0.001
baPWV	Adjusted	0.12×10 <sup>-2</sup> (0.11×10 <sup>-2</sup> to 0.13×10 <sup>-2</sup> )	<0.001
For baPWV			
HbA <sub>1c</sub>	Crude	0.17 (-0.47 to 0.82)	0.604
HbA <sub>1c</sub>	Adjusted	...	...
For HbA <sub>1c</sub>			
baPWV	Crude	2.90×10 <sup>-7</sup> (-4.99×10 <sup>-6</sup> to 5.57×10 <sup>-9</sup> )	0.914
baPWV	Adjusted	...	...

Adjustments: age, sex, body mass index, current smoking history, current daily alcohol intake, heart rate, serum levels of total cholesterol, high-density lipoprotein cholesterol, triglyceride, uric acid, creatinine, and history of medication use for dyslipidemia (not receiving medication=0, receiving medication=1; for the medication) and mean BP or HbA<sub>1c</sub>. baPWV indicates brachial-ankle pulse wave velocity; BP, blood pressure; and HbA<sub>1c</sub>, glycosylated hemoglobin A<sub>1c</sub>.

factor for the development of hypertension.<sup>5-7</sup> In the present study, the blood pressure, HbA<sub>1c</sub>, and baPWV levels increased, and factors related to atherosclerosis such as the BMI, serum triglyceride level, alcohol intake, and serum creatinine also increased. On the other hand, the smoking rate decreased. After adjustment for these background factors, multinomial logistic regression analyses identified only increased baPWV at the baseline as a significant predictor of new onset of prehypertension/hypertension, including that with coexisting prediabetes/diabetes. Conversely, the mean blood pressure at the baseline showed a significant relationship with the baPWV value at the end of study. In addition, LGCM analyses demonstrated the existence of significant bidirectional longitudinal relationships between the baPWV and the mean blood pressure. Thus, significant bidirectional longitudinal relationships between the arterial stiffness and hypertension may exist even from the early pathophysiological stages of development, in middle-aged Japanese subjects.

Abnormal glucose metabolism has been reported as a risk factor for the progression of arterial stiffness.<sup>15,16</sup> Conversely, some prospective studies have reported that increased arterial stiffness is a risk factor for the development of diabetes.<sup>10,11</sup> On the other hand, in Zheng's prospective study conducted in a Chinese

population, arterial stiffness preceded the development of diabetes, but elevated blood glucose failed to be identified as a risk factor for the progression of arterial stiffness.<sup>11</sup> These inconsistencies in the relationships of the arterial stiffness with hypertension and diabetes might be derived, at least in part, from the ethnicity or age of the study subjects. In the present study, multinomial logistic regression analyses demonstrated that increased baPWV at the baseline was a significant predictor of the new onset of prediabetes/diabetes with coexisting prehypertension/hypertension, but not for new onset of prediabetes/diabetes without coexisting prehypertension/hypertension. Conversely, the serum HbA<sub>1c</sub> level at the baseline showed a significant relationship with the baPWV value at the end of study period, but only in subjects who had hypertension or diabetes at the baseline. In addition, the LGCM analyses demonstrated no significant bidirectional longitudinal relationships between the baPWV and the serum HbA<sub>1c</sub> level. Thus, no significant bidirectional longitudinal relationships may exist between arterial stiffness and diabetes.

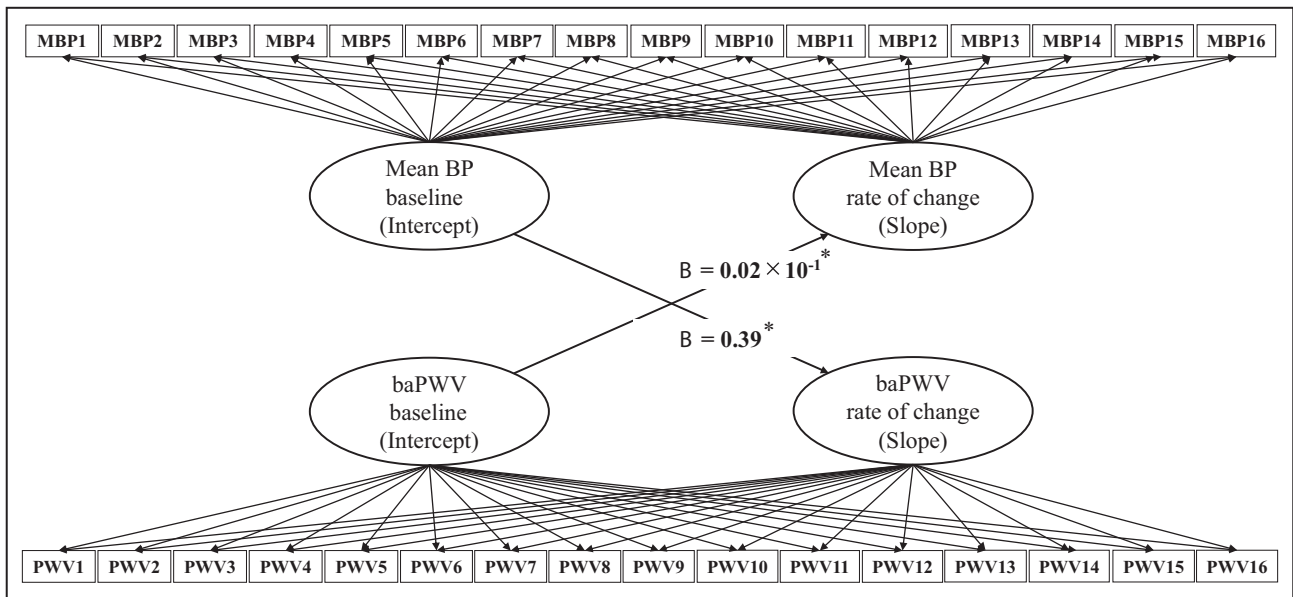
In the present study, we demonstrated that increased arterial stiffness precedes the development of clinical hypertension, including hypertension coexisting with diabetes, or even the development of elevated blood pressure in the prehypertensive range; on the other hand, increased arterial stiffness was not associated with the development of diabetes or impaired glucose tolerance without coexisting prehypertension/hypertension. Therefore, arterial stiffness preceding the development of diabetes may represent an epiphenomenon, as it is only observed in cases of diabetes with coexisting hypertension.

We could not examine the mechanisms underlying the differences in the interrelationships among arterial stiffness, hypertension, and diabetes. As a plausible common mechanism underlying the 3 pathophysiological abnormalities, endothelial dysfunction,<sup>4,31</sup> microvascular dysfunction,<sup>19,31</sup> or impaired activity of the renin-angiotensin system and sympathetic nervous system or elastin peptide and elastin receptor activity have been proposed.<sup>32-34</sup> However, considering the results of the present study, the mechanisms underlying these abnormalities might be different.

## Clinical Implications

Elevated blood pressure and abnormal glucose metabolism have been reported as risk factors, even from the early pathophysiological stages of their development, for future cardiovascular events.<sup>35</sup> Furthermore, the risk levels increase further with advancing severity of hypertension and diabetes. On the other hand, increased baPWV has been demonstrated as a risk marker for the development of cardiovascular

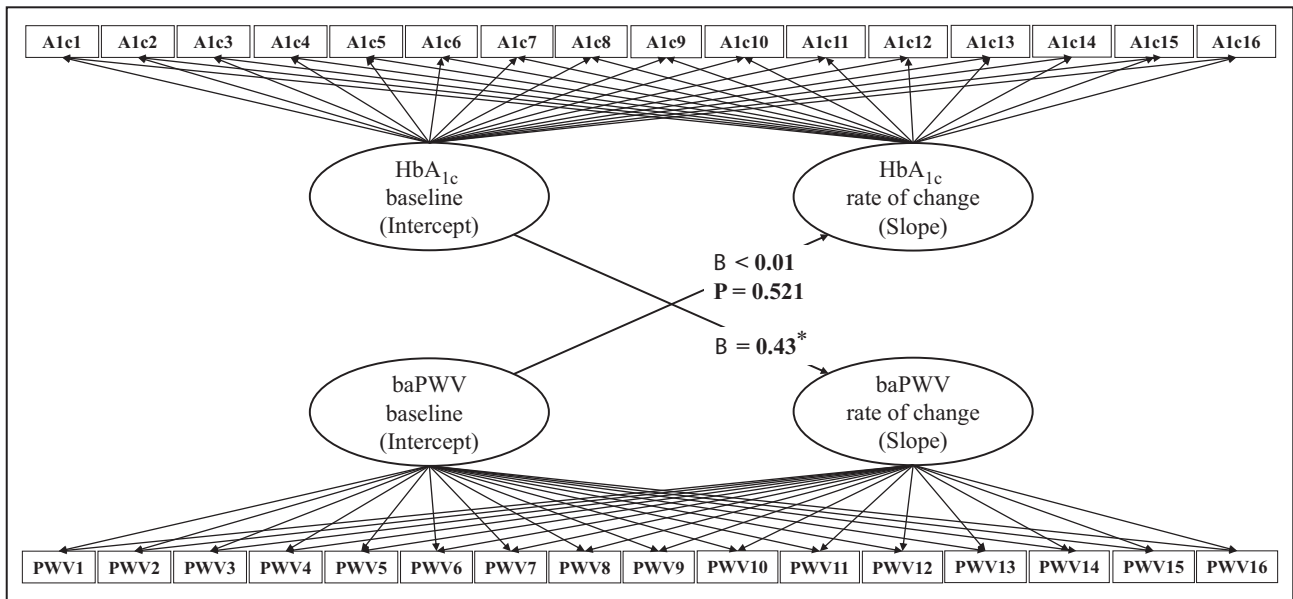




**Figure 3. Results of latent growth curve model analyses between mean blood pressure and brachial-ankle pulse wave velocity.** Single-headed arrows (B) represent unstandardized regression coefficients. To facilitate interpretation only the latent variables (intercept and slope) are shown. Intercepts and slopes were also regressed on covariates though this is not shown in the model. MBP X indicates mean blood pressure measured in the Xth year; and PWV X, brachial-ankle pulse wave velocity measured in the Xth year. \* $P < 0.001$ . baPWV indicates brachial-ankle pulse wave velocity; BP, blood pressure; MBP, mean blood pressure; and PWV, pulse wave velocity.

disease.<sup>3,4</sup> The findings of the present study suggest that there could be differences in the longitudinal associations of increased baPWV with the development

of hypertension and diabetes. Further study is needed to clarify whether increased baPWV might be a more reliable risk marker of future cardiovascular events in



**Figure 4. Results from the multivariable latent growth curve model analyses between serum hemoglobin A<sub>1c</sub> levels and brachial-ankle pulse wave velocity.** Single-headed arrows (B) represent un-standardized regression coefficients. To facilitate interpretation only the latent variables (intercept and slope) are shown. Intercepts and slopes were also regressed on covariates though this is not shown in the model. A1c X indicates hemoglobin A1c levels measured in the Xth year; and PWV X, brachial-ankle pulse wave velocity measured in the Xth year. \* $P < 0.001$ . baPWV indicates brachial-ankle pulse wave velocity; HbA<sub>1c</sub>, glycosylated hemoglobin A<sub>1c</sub>; and PWV, pulse wave velocity.

cases of early-stage hypertension as compared with cases of early-stage diabetes.

### Strengths and Limitations of the Study

The strengths of the present study were as follows: Several factors, such as smoking, alcohol intake, obesity, dyslipidemia, and hyperuricemia are known to affect the arterial stiffness, blood pressure, or glucose metabolism.<sup>1,2,4,19,20</sup> To minimize the influence of such confounding variables on the results of our study, the analyses in the present study were conducted on annually repeated measurements of the data over a 16-year follow-up period (the mean follow-up period was 10.1±4.2 years, and the measurements were repeated an average of 8.0±3.2 times in the subjects).

The limitations of the present study were as follows:

1. The incidence rate of diabetes in the present study was relatively low as compared with that of hypertension. As the prevalence of diabetes is known to increase with advancing age,<sup>20</sup> the findings of the present study, especially the association between arterial stiffness and diabetes, also needs to be confirmed in elderly subjects.
2. The present study was conducted on the employees of a Japanese company, which implies a specific population. Thus, it may be difficult to extrapolate these results to different populations or demographic/socioeconomic groups. Furthermore, ethnic and sex differences in the values of the baPWV have been demonstrated.<sup>36</sup> Therefore, the influence of ethnic/sex differences on the differential nature of the bidirectional relationships between increased arterial stiffness and hypertension/diabetes need to be clarified. In particular, most of the female subjects in the present study were presumably in a premenopausal state, so that further study is needed to examine the relationships in other subject groups, including women in the postmenopausal state, in whom the cardiovascular risk is higher.
3. baPWV primarily reflects the stiffness of the large to middle-sized arteries<sup>22</sup>; however, it is also known to show a close relationship with the carotid-femoral pulse wave velocity, a marker of large-arterial stiffness.<sup>22,37</sup>
4. While habitual exercising is known to be beneficial for patients with hypertension, diabetes, and also increased arterial stiffness,<sup>38</sup> we did not determine the daily physical activity level of the subjects in the present study.
5. The brachial blood pressure used for the analyses in the present study were the mean of 2 measurements in the study subjects, but both measurements were obtained on the same occasion (ie, at the time of the annual health checkups).
6. In the present study, no data were available on the waist circumference, which is also known to be related to increase in the arterial stiffness.<sup>39</sup>
7. As with previous traditional epidemiological studies, it was difficult to fully establish a causal relation in this study between increased arterial stiffness and the development of diabetes or hypertension because of various biases, confounding factors, or reverse causation. Recently, several studies have established an association between glucose metabolism and arterial stiffness using Mendelian randomization.<sup>40,41</sup> However, no genetic information was available in the present study, and we could not use this statistical method.
8. Significant associations in the clinical characteristics are likely a result of the study being overpowered and the large number of subjects included in the analysis. Moreover, we did not fully evaluate the effects of newly initiated medications on the hypertension and diabetes in this study.
9. In the multiple testing, we could not fully control type 1 error inflation.

### CONCLUSIONS

In middle-aged employees of a Japanese company, while bidirectional relationships were found to exist between increased arterial stiffness and hypertension, such a relationship was not found between increased arterial stiffness and diabetes. Therefore, it appears that increased arterial stiffness may be associated with the development of hypertension but not with that of diabetes.

### ARTICLE INFORMATION

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#### Affiliations

Department of Cardiology (H.N., K.S., T.T., M.F., Y.I., C.M., T.C., H.T.); and Division of Preemptive Medicine for Vascular Damage (K.S., H.T.), Tokyo Medical University, Tokyo, Japan; and Department of Nursing, Kiryu University, Gunma, Japan (A.Y.).

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#### Disclosures

The sponsor (Omron Health Care Company) assisted in the data formatting (ie, the data of the brachial-ankle pulse wave velocity stored in the hard disc of the equipment used for measurement of the brachial-ankle pulse wave velocity were transferred to an Excel file). The authors have no other disclosures to make.

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