

ORIGINAL INVESTIGATION

Open Access



Use of the ankle-brachial index combined with the percentage of mean arterial pressure at the ankle to improve prediction of all-cause mortality in type 2 diabetes mellitus: an observational study

Yu-Hsuan Li¹, Wayne Huey-Herng Sheu^{1,2,3} and I-Te Lee^{1,2,4,5*} 

Abstract

Background: Peripheral artery disease (PAD) in the lower extremities is a common complication of type 2 diabetes and has been shown to be associated with mortality. The ankle-brachial index (ABI) is a simple noninvasive method to screen PAD, but this method has limited sensitivity. We hypothesized that using the percentage of mean arterial pressure (%MAP) in combination with the ABI would improve the prediction of mortality.

Methods: We retrospectively collected data from patients with type 2 diabetes who had undergone ABI and %MAP measurements at our hospital. We separated the cohort into four groups according to their ABI and %MAP values, and we examined whether these indices were associated with mortality.

Results: A total of 5569 patients (mean age, 65 ± 11 years) were enrolled. During the follow-up period (median, 22.9 months), 266 (4.8%) of the enrolled patients died. The combination of ABI and %MAP was significantly more effective than ABI alone for predicting mortality (C index of 0.62, 95% confidence interval [CI] of 0.57 to 0.65 vs. C index of 0.57, 95% CI of 0.53 to 0.62; $P = 0.038$). In multivariate analysis (with a reference group defined by $ABI > 0.90$ and $\%MAP \leq 45\%$), the highest risk of mortality was seen in patients with $ABI \leq 0.90$ and $\%MAP > 45\%$ (hazard ratio = 2.045 [95% CI 1.420, 2.945], $P < 0.001$).

Conclusions: The use of %MAP alongside ABI appears to significantly improve the prediction of all-cause mortality in patients with type 2 diabetes.

Keywords: Ankle-brachial index, Diabetes, Lower extremity artery disease, Mortality, Percentage of the mean arterial pressure, Peripheral artery disease

Background

Diabetes mellitus (DM) has become a heavy health burden because of its high global prevalence [1]. Peripheral artery disease (PAD) of the lower extremities is a common complication of type 2 DM [2]. The mortality risk of PAD was reported to be between those of myocardial infarction and stroke in a cohort study with a mean follow-up of 5.9 years, and DM increased the risk of

*Correspondence: itlee@vghtc.gov.tw

¹ Division of Endocrinology and Metabolism, Department of Internal Medicine, Taichung Veterans General Hospital, No. 1650 Taiwan Boulevard, Section 4, Taichung 40705, Taiwan
Full list of author information is available at the end of the article



© The Author(s) 2020. This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

mortality by 1.4 times in patients with PAD [3]. Although PAD is clinically confirmed using noninvasive angiography (i.e., computed tomography angiography and magnetic resonance angiography) or invasive angiography for anatomical assessments, the use of the ankle-brachial index (ABI) as a simple screen for PAD in patients with DM and cardiovascular risk is recommended by the American Heart Association/American College of Cardiology (AHA/ACC) guidelines on the management of patients with lower extremity PAD [4].

However, the commonly used ABI value of <0.90 has been reported to have only 75% sensitivity for PAD diagnosis, and the sensitivity is even lower in patients with DM than in those without DM [5, 6]. Since borderline low ABI values between 0.91 and 0.99 are associated with a higher risk of PAD and mortality than $ABI \geq 1.00$ [7, 8], it has been suggested that sensitivity could be increased by raising the cutoff value for normal ABI to 1.00 [5, 9]. However, the specificity is markedly decreased when the cutoff value for normal ABI is raised [10]. Instead, an increase in diagnostic accuracy could be achieved by using other parameters in combination with ABI [5].

The combination of ABI and percentage of mean arterial pressure (%MAP) at the ankle has been reported to show better diagnostic accuracy than ABI alone [10]. The %MAP can be calculated from a pulse volume recording at the ankle and automatically reported by the ABI-measuring machine, and so it is a convenient index to use along with the ABI in screening for PAD [10–12]. A previous study has shown that $\%MAP > 45\%$ predicts a high mortality risk in patients with normal ABI [13].

In summary, %MAP is a useful biomarker and can be conveniently measured to detect PAD in patients with normal ABI, especially in patients with DM, for whom the sensitivity of ABI for PAD diagnosis is relatively low. However, the utility of %MAP in combination with ABI in predicting long-term mortality is still not clear in patients with type 2 DM. Therefore, in this study, we aimed to determine whether the combination of low ABI and high %MAP would be a better predictor of all-cause mortality than low ABI alone in patients with type 2 DM.

Materials and methods

Study design and population

This retrospective cohort study was conducted at Taichung Veterans General Hospital in Taiwan. According to our computer-interpretable guidelines from August 2016, ABI was suggested via the annual diabetes review program of the hospital information system if ABI data had not been available in patients who were older than 50 years and had participated in the diabetes pay-for-performance (P4P) program [14].

From the hospital database, we retrospectively identified all patients with DM who had undergone ABI assessment between August 01, 2016 and July 31, 2019. Moreover, each enrolled patient was required to fulfill at least one of the following inclusion criteria: (1) age ≥ 50 years, (2) diabetes duration ≥ 10 years, (3) current smoking, (4) a history of cardiovascular disease (CVD), (5) hypertension, (6) body mass index (BMI) ≥ 27 kg/m², (7) hemoglobin A1c (HbA1c) $\geq 7\%$, (8) total cholesterol ≥ 160 mg/dL (4.1 mmol/L), (9) high-density lipoprotein (HDL) cholesterol < 50 mg/dL (1.29 mmol/L) in women or < 40 mg/dL (1.03 mmol/L) in men, (10) triglycerides ≥ 150 mg/dL (1.69 mmol/L), (11) estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m², or (12) albuminuria. We excluded patients who met any of the following conditions: (1) incomplete laboratory data; (2) not type 2 DM; (3) incomplete ABI, brachial-ankle pulse wave velocity (baPWV), or %MAP data due to lack of a complete four-limb assessment; (4) unreliable ABI data due to previous lower-limb surgery, pregnancy, or hemodialysis treatment; or (5) $ABI > 1.40$.

ABI measurements were made using a validated device (VP-1000 Plus; Omron Healthcare Co. Ltd., Kyoto, Japan). After patients had rested in a supine position for at least 5 min, cuffs which were connected to both a plethysmographic sensor for detecting volume change and an oscillometric pressure sensor for detecting blood pressure were placed on the brachia and ankles. In addition to ABI, this device automatically reports the baPWV and %MAP of the ankle pulse volume waveform. These data, along with anthropometric data and results of laboratory tests performed within 3 months of the ABI assessment, were extracted from the electronic medical records. For patients who had undergone repeated assessments during this period, only the data from the first assessment were recorded. This research protocol was approved by the Institutional Review Board of Taichung Veterans General Hospital, and the need for informed consent was waived.

Assessments

The following laboratory data were recorded: total cholesterol, HDL cholesterol, triglycerides, glucose, HbA1c, and creatinine. The eGFR was calculated using the Modification of Diet in Renal Disease equation, i.e., $eGFR = 186 \times (\text{serum creatinine [mg/dL]})^{-1.154} \times (\text{age [years]})^{-0.203} (\times 0.742, \text{ if female})$ [15]. The urinary albumin-to-creatinine ratio (UACR) was calculated using the formula $UACR = \text{albumin (mg)}/\text{creatinine (g)}$, and albuminuria was defined as $UACR \geq 300$ mg/g [15]. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or current use of an antihypertensive drug.

The %MAP value was automatically determined based on the ankle pulse volume waveform during ABI measurement. The ABI was calculated as (systolic pressure of the ankle in each leg)/(the higher of the two arm systolic pressures) [16]. The %MAP was calculated as (average amplitude of pulse wave)/(maximal amplitude of pulse wave) \times 100%, and the average amplitude was calculated by dividing the area between a pulse volume curve and its initial base by duration of a pulse wave [12, 17]. The baPWV was calculated as (distance from the suprasternal notch to the brachium – distance from the suprasternal notch to the ankle)/(the time interval between waves detected at the brachium and ankle), where the distances from the suprasternal notch to the brachium and ankle were estimated based on the patient's body height [18]. The reproducibility of the ABI and %MAP has been demonstrated in our previous study [19], and the 95% confidence interval (CI) between repeated measurements of baPWV was 4.95 ± 46.46 cm/sec based on Bland–Altman plots. The lower ABI value and the higher %MAP and baPWV values between lower limbs in an individual were used for the analyses. $ABI \leq 0.90$ and $\%MAP > 45\%$ were defined as abnormal [13, 19].

Statistical analysis

Continuous data were summarized as the mean \pm standard deviation; differences among four study subgroups were analyzed using one-way analysis of variance, and the Scheffe post hoc test was conducted to examine the differences between the high %MAP and normal %MAP subgroups in patients with a normal ABI group or a low ABI group. Categorical data were summarized as numbers with percentages (%) and compared among groups using the Chi square test. Correlation was assessed using the Pearson correlation coefficient (r). The primary endpoint was all-cause mortality. Information on deaths registered up to August 31, 2019 was obtained from the Ministry of Health and Welfare, Executive Yuan, Taiwan. Causes of death were categorized according to the diagnosis codes of the International Classification of Disease 10, Clinical Modification.

The improvement in mortality prediction caused by considering the %MAP along with the ABI was assessed by examining the increases in the area under the receiver operating characteristic curve (AUC). The performance of the model containing both ABI and %MAP compared to the model with ABI alone was evaluated by the C index. The integrated discrimination improvement (IDI) and continuous net reclassification improvement (NRI) were also assessed to quantify the improvement in predictive ability by adding %MAP.

The cumulative risk of the all-cause mortality was assessed using Kaplan–Meier analysis; the log-rank test

was used to determine whether the differences between groups were significant. Multivariable Cox proportional hazards regression analysis was conducted to identify the independent predictors of mortality; hazard ratio (HR) and 95% CI were calculated. A two-sided P value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS v22.0 (IBM Corp., Armonk, NY, USA) and R software v3.4.

Results

A total of 5569 patients were enrolled in this study, and %MAP was inversely correlated with ABI ($r = -4.70$, $P < 0.001$). Based on the ABI value, all patients were first separated into two groups: a normal ABI group and a low ABI group. Each group was then separated into two subgroups according to the %MAP value. Thus, there were four subgroups: patients with normal ABI and normal %MAP ($n = 4601$); patients with normal ABI but high %MAP ($n = 500$); patients with low ABI but normal %MAP ($n = 130$); and patients with low ABI and high %MAP ($n = 338$, Fig. 1).

Table 1 shows the baseline characteristics of patients in the different subgroups. Patients with high %MAP were significantly older than patients with normal %MAP in both the normal ABI group (70 ± 12 vs. 64 ± 10 years, $P < 0.001$) and the low ABI group (73 ± 12 vs. 65 ± 12 years, $P < 0.001$). The baPWV was significantly higher in the high %MAP subgroup than in the normal %MAP subgroup in both the normal ABI group ($P < 0.001$) and the low ABI group ($P < 0.001$). BMI, ABI and eGFR were significantly lower in the high %MAP subgroup than in the normal %MAP subgroup in both the normal ABI group ($P = 0.027$, $P < 0.001$, and $P < 0.001$; respectively) and the low ABI group (all P values < 0.001). The prevalence rates of CVD, albuminuria and use of antiplatelet drugs were significantly higher in the high %MAP subgroup than in the normal %MAP subgroup in both the normal ABI group (all P values < 0.001) and the low ABI group ($P = 0.015$, $P = 0.004$, and $P < 0.001$; respectively). The proportion of patients using oral antihyperglycemic drugs was significantly lower in the high %MAP subgroup than in the normal %MAP subgroup in both the normal ABI group ($P < 0.001$) and the low ABI group ($P = 0.008$). Patients with high %MAP had a significantly higher proportion of females, a higher prevalence of hypertension, higher systolic blood pressure, higher prevalence rates of antihypertensive drug use and insulin therapy, and longer diabetes duration than those with normal %MAP in the normal ABI group (all $P < 0.001$), but the same was not true in the low ABI group.

Over a median follow-up of 22.9 months (interquartile range: 13.2–29.7 months), 266 (4.8%) of the 5569 enrolled

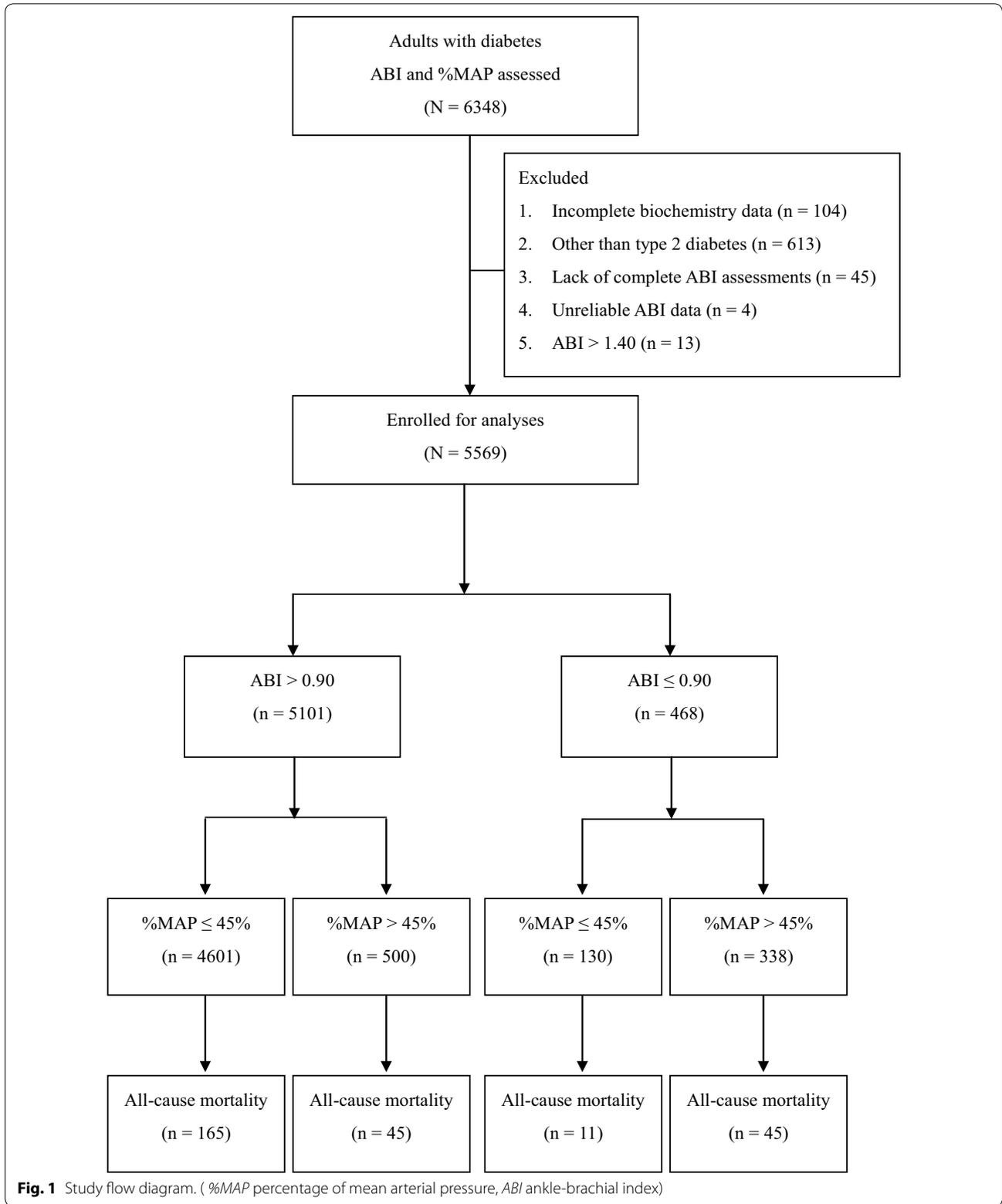


Table 1 Characteristics of enrolled patients categorized based on a combination of ABI and %MAP*

Group	Normal ABI (n = 5101)			Low ABI (n = 468)			P [#]
	Normal % MAP (n = 4601)	High %MAP (n = 500)	P [†]	Normal %MAP (n = 130)	High %MAP (n = 338)	P [‡]	
Subgroup	Mean ± SD	Mean ± SD		Mean ± SD	Mean		
Age (year)	64 ± 10	70 ± 12	<0.001	65 ± 12	73 ± 12	<0.001	<0.001
Male, n (%)	2559 (55.6%)	203 (40.6%)	<0.001	66 (50.8%)	196 (58.0%)	0.192	<0.001
Diabetes duration (year)	11 ± 7	14 ± 8	<0.001	14 ± 8	15 ± 8	0.4	<0.001
Currently smoking, n (%)	415 (9.0%)	32 (6.4%)	0.06	11 (8.5%)	26 (7.7%)	0.932	0.197
CVD history, n (%)	357 (7.8%)	72 (14.4%)	<0.001	22 (16.9%)	96 (28.4%)	0.015	<0.001
BMI (kg/m ²)	25.9 ± 4.1	25.3 ± 4.2	0.027	28.0 ± 5.0	25.0 ± 4.0	<0.001	<0.001
Systolic BP (mmHg)	135 ± 19	144 ± 24	<0.001	140 ± 20	145 ± 25	0.139	<0.001
Diastolic BP (mmHg)	77 ± 12	76 ± 13	0.519	75 ± 15	74 ± 16	0.584	<0.001
Fasting glucose (mmol/L)	8.2 ± 3.6	8.2 ± 3.4	0.999	8.3 ± 2.9	8.7 ± 3.8	0.76	0.066
HbA1c (%)	7.5 ± 1.6	7.6 ± 1.6	0.99	7.9 ± 2.0	7.8 ± 1.9	0.997	0.001
Total cholesterol (mmol/L)	4.1 ± 0.9	4.1 ± 1.0	0.966	4.1 ± 0.9	4.0 ± 1.0	0.881	0.188
HDL cholesterol (mmol/L)	1.3 ± 0.4	1.3 ± 0.4	0.999	1.2 ± 0.3	1.2 ± 0.3	0.915	<0.001
Triglycerides (mmol/L)	1.6 ± 1.3	1.5 ± 1.2	0.637	2.0 ± 1.9	1.7 ± 1.1	0.193	0.004
eGFR (mL/min/1.73 m ²)	81 ± 28	70 ± 34	<0.001	73 ± 34	53 ± 32	<0.001	<0.001
UACR ≥ 300 mg/g	498 (10.8%)	88 (17.6%)	<0.001	19 (14.6%)	94 (27.8%)	0.004	<0.001
ABI	1.11 ± 0.09	1.07 ± 0.09	<0.001	0.83 ± 0.08	0.68 ± 0.21	<0.001	<0.001
baPWV (cm/sec)	1823 ± 433	2087 ± 671	<0.001	1867 ± 690	2176 ± 1143	<0.001	<0.001
Ankle %MAP (%)	39.4 ± 3.1	47.2 ± 1.8	<0.001	40.9 ± 3.1	50.4 ± 3.5	<0.001	<0.001
Antiplatelet, n (%)	1212 (26.3%)	178 (35.6%)	<0.001	64 (49.2%)	273 (80.8%)	<0.001	<0.001
Statins, n (%)	3253 (70.7%)	351 (70.2%)	0.855	97 (74.6%)	250 (74.0%)	0.979	0.446
Hypertension, n (%)	3466 (75.3%)	414 (82.8%)	<0.001	115 (88.5%)	317 (93.8%)	0.081	<0.001
Antihypertensive drugs, n (%)	2397 (52.1%)	307 (61.4%)	<0.001	87 (66.9%)	257 (76.0%)	0.06	<0.001
ACE inhibitors or ARBs, n (%)	1714 (37.3%)	213 (42.6%)	0.022	58 (44.6%)	168 (49.7%)	0.377	<0.001
α-blockers, n (%)	255 (5.5%)	74 (14.8%)	<0.001	11 (8.5%)	64 (18.9%)	0.009	<0.001
β-blockers, n (%)	949 (20.6%)	138 (27.6%)	<0.001	38 (29.2%)	135 (39.9%)	0.041	<0.001
Calcium channel blockers, n (%)	217 (4.7%)	28 (5.6%)	0.443	12 (9.2%)	37 (10.9%)	0.708	<0.001
Diuretics, n (%)	396 (8.6%)	88 (17.6%)	<0.001	24 (18.5%)	95 (28.1%)	0.043	<0.001
Insulin therapy, n (%)	1032 (22.4%)	159 (31.8%)	<0.001	42 (32.3%)	132 (39.1%)	0.213	<0.001
Oral antihyperglycemic drugs	4175 (90.7%)	424 (84.8%)	<0.001	113 (86.9%)	254 (75.1%)	0.008	<0.001
Insulin secretagogues, n (%)	1638 (35.6%)	190 (38.0%)	0.311	45 (34.6%)	96 (28.4%)	0.23	0.028
Metformin, n (%)	1838 (39.9%)	174 (34.8%)	0.029	54 (41.5%)	69 (20.4%)	<0.001	<0.001
Thiazolidinediones, n (%)	2737 (59.5%)	287 (57.4%)	0.393	72 (55.4%)	191 (56.5%)	0.908	0.469
α-Glucosidase inhibitors, n (%)	530 (11.5%)	40 (8.0%)	0.022	17 (13.1%)	17 (5.0%)	0.005	<0.001
DPP4 inhibitors, n (%)	1046 (22.7%)	95 (19.0%)	0.065	30 (23.1%)	51 (15.1%)	0.056	0.002
SGLT2 inhibitors, n (%)	415 (9.0%)	57 (11.4%)	0.096	8 (6.2%)	31 (9.2%)	0.384	0.212
Mortality, n (%)	165 (3.6%)	45 (9.0%)	<0.001	11 (8.5%)	45 (13.3%)	0.197	<0.001
CVD, n (%)	40 (0.9%)	19 (3.8%)		4 (3.1%)	27 (8.0%)		
Cancer, n (%)	87 (1.9%)	12 (2.4%)		2 (1.5%)	2 (0.6%)		
Others, n (%)	38 (0.8%)	14 (2.8%)		5 (3.8%)	16 (4.7%)		
Incidence of mortality (deaths/100 person-years)	2.0	5.0		4.8	8.3		

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

*: low ABI was defined as an ABI value ≤ 0.90 and normal ABI > 0.90; high %MAP was defined as a %MAP > 45% and normal %MAP ≤ 45%

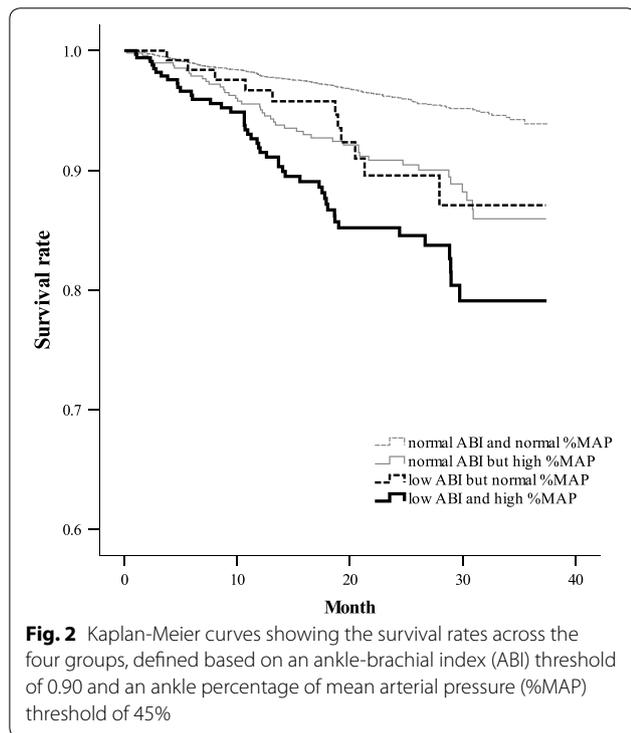
P: denotes a significant difference across the four subgroups

† P: post hoc comparison between two subgroups in patients with normal ABI; ‡P: post hoc comparison between two subgroups in patients with low ABI

%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

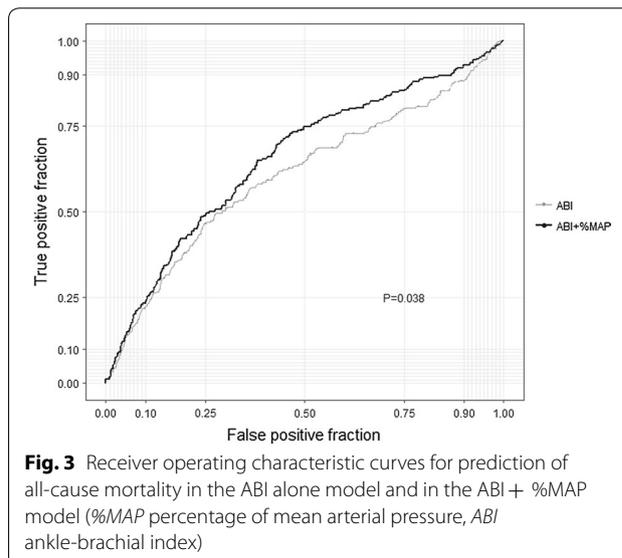
Table 1 (continued)

rate, *HbA1c* hemoglobin A1c, *HDL* high-density lipoprotein, *SD* standard deviation, *SGLT2* sodium glucose cotransporter 2, *UACR* urine albumin-to-creatinine ratio



patients died. The incidence rates of mortality were 2.0 deaths/100 person-years in the normal ABI and normal %MAP subgroup, 5.0 deaths/100 person-years in the normal ABI but high %MAP subgroup, 4.8 deaths/100 person-years in the low ABI but normal %MAP subgroup, and 8.3 deaths/100 person-years in the low ABI and high %MAP subgroup, respectively; the survival rates were significantly different across these four subgroups (log-rank test $P < 0.001$, Fig. 2).

To evaluate how the inclusion of the %MAP along with ABI affected the prediction of all-cause mortality, we analyzed the increases in the AUC. We used ABI as the standard risk factor; the AUC increased significantly from 0.57 (95% CI 0.53–0.62) for the ABI alone model to 0.62 (95% CI 0.57–0.65) for the ABI plus %MAP model ($P = 0.038$; Fig. 3). Furthermore, the use of %MAP along with ABI yielded a significant IDI of 0.006 (95% CI 0.002–0.014, $P < 0.001$) and a significant NRI of 0.119 (95% CI 0.045–0.183, $P < 0.001$). The predictive model with %MAP and ABI was still significantly better than the model with ABI alone after adjusting for age, sex, diabetes duration, smoking, CVD history, BMI, hemoglobin A1c, total cholesterol, HDL cholesterol, triglycerides, eGFR, albuminuria, baPWV, systolic blood pressure, use

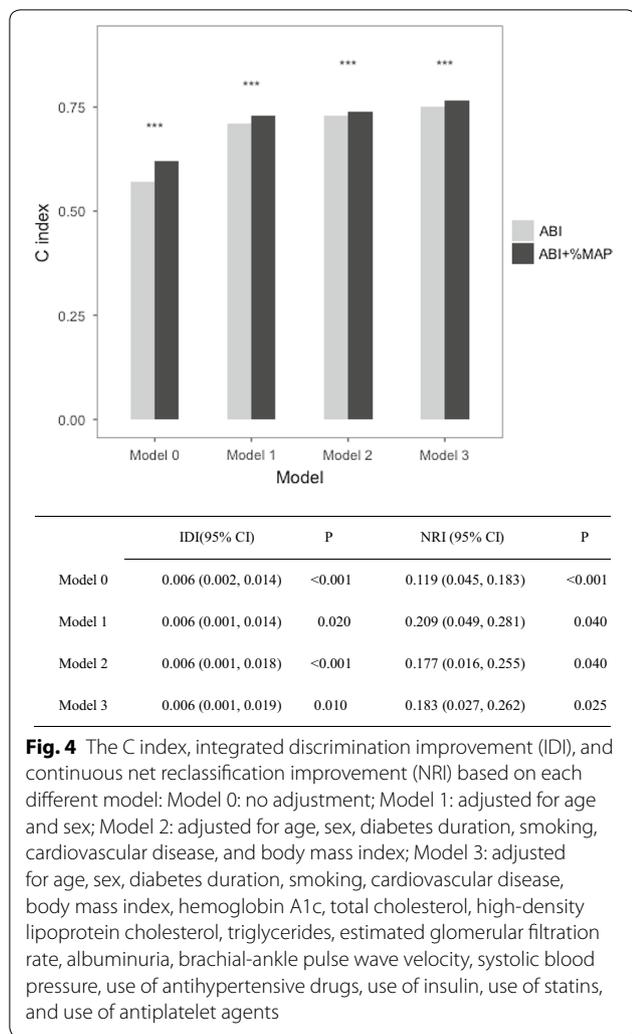


of antihypertensive drugs, use of insulin, use of statins, and use of antiplatelet agents (Fig. 4).

Multivariate Cox regression analysis was performed using the patients with normal ABI and normal %MAP as the reference group. The highest risk for mortality was observed in patients with low ABI and high %MAP (HR = 2.045, 95% CI 1.420 to 2.945, $P < 0.001$), followed by patients with low ABI but normal %MAP (HR = 1.730, 95% CI 0.932 to 3.209) and patients with normal ABI but high %MAP (HR = 1.579, 95% CI 1.120 to 2.226). Furthermore, high %MAP was found to be a significant predictor of all-cause mortality in patients with normal ABI ($P = 0.009$, Table 2).

Discussion

The main finding of our study was that high ankle %MAP acted synergistically with low ABI to improve the prediction of all-cause mortality in patients with type 2 DM. When these two indices were used in combination, $ABI \leq 0.90$ and $\%MAP > 45\%$, predicted an approximately two-fold higher mortality risk than $ABI > 0.90$ and $\%MAP \leq 45\%$. These results corroborate our previous study, which showed that high %MAP was a significant predictor of all-cause mortality [13]. The strength of the present study is that we demonstrated the synergy of ABI and %MAP for the prediction of mortality in a large sample of more than 5000 patients with type 2 DM. Furthermore, we used NRI and IDI to quantify the improvement of prediction. Because of the limitation to use only



AUC or C-index for the risk prediction model, NRI and IDI were recommended to give complementary information for model performance [20]. Thus, a combination of %MAP and ABI appears to be more effective than ABI alone in predicting the risk of death, and this finding is important because global mortality from PAD is continually increasing [21].

PAD is associated with several atherosclerotic morbidities and is predictive of long-term cardiovascular events [3]. An occluded artery in a lower extremity will result in decreased blood flow, reflected by a decrease in systolic blood pressure and a flattened pulse volume waveform at the ankle [16, 17]. However, the ankle systolic blood pressure will be elevated in a noncompressible artery, and a false negative PAD diagnosis may occur when ABI alone is used for screening [22, 23]. Zahner et al. [24] reported that measuring the augmentation index of pulse waves in the radial artery helps improve PAD diagnosis. DM is closely associated with arterial stiffness [25, 26], and

reportedly increases the risk of arterial stiffness by 1.8 times in a Chinese population [27]. In a study by Wukich et al., 42.7% of patients with DM and confirmed PAD had normal ABI values [28]. In contrast, a flattened pulse volume waveform in patients with DM was more closely associated with PAD than a low ABI value was, regardless of ankle arterial stiffness [29, 30]. The %MAP represents the percentage difference between the mean and maximum amplitude of the ankle pulse volume waveform [12]. A flattened waveform resulting from an occluded artery will increase the %MAP value, which is not strongly affected by noncompressible arteries [11, 30]. Therefore, the ankle %MAP might be a sensitive indicator of an occlusive artery with a noncompressible pattern, which is frequently observed in patients with DM [31]. The advantage of %MAP measurement in detecting arterial occlusion may explain why CVD-related mortality is markedly increased in patients with low ABI and high %MAP in the present study. In line with our study, %MAP was associated with CVD-related mortality in hemodialysis patients [32].

Arterial stiffness may involve extracellular destruction and cellular dysfunction of the vessel wall [33]. There are several potential mechanisms involved in the association between DM and arterial stiffness. First, glycation reactions during hyperglycemia can stiffen the arterial wall by inducing irreversible collagen cross-links [34]. Second, an overabundance of advanced glycation end products binding to their receptors on the vessel inner wall can activate a series of responses involving oxidation and inflammation [35]. An inflammatory process including the accumulation of macrophage and the activation of cell adhesion molecules can induce matrix metalloproteases to degrade the extracellular matrix and increase smooth muscle migration and proliferation [35, 36]. Oxidative stress can increase the vessel tone by impairing endothelial nitric oxide production and proliferating vascular smooth muscle cells [37–39]. Third, insulin resistance can increase the vessel tone by activating endothelin-1 and angiotensin II type 1 receptors [40, 41], and the Atherosclerosis Risk in Communities Study reported that insulin resistance was associated with arterial stiffness in patients with type 2 DM [42]. Arterial stiffness with high baPWV was also reported to be associated with new-onset DM [43]. Furthermore, a high prevalence of medial arterial calcification was reported in patients with DM [44, 45]. Noncompressible arteries are reportedly associated with mortality even in patients with high ABI [45, 46]. Therefore, the influence of noncompressible arteries on ABI must be considered in patients with type 2 DM.

In a previous study that enrolled 3004 Japanese participants, including 2598 (86%) with diabetes, the criterion of ABI<0.9 predicted 20.4% of deaths within a

Table 2 Cox regression analysis for all-cause mortality*

	Crude			Model 1			Model 2			Model 3		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Normal ABI and normal %MAP [#]	1.000			1.000			1.000			1.000		
Normal ABI but high %MAP	2.510	(1.805, 3.490)	<0.001	2.231	(1.597, 3.116)	<0.001	2.018	(1.443, 2.823)	<0.001	1.579	(1.120, 2.226)	0.009
Low ABI but normal %MAP	2.390	(1.298, 4.400)	0.005	2.171	(1.178, 4.000)	0.013	1.965	(1.063, 3.631)	0.031	1.730	(0.932, 3.209)	0.082
Low ABI and high %MAP	4.167	(2.997, 5.795)	<0.001	3.076	(2.199, 4.305)	<0.001	2.539	(1.801, 3.578)	<0.001	2.045	(1.420, 2.945)	<0.001

*The cumulative mortality rate was 4.8% in a total of 5569 enrolled patients

[#] Low ABI was defined as an ABI value ≤ 0.90 and normal ABI > 0.90 ; high %MAP was defined as %MAP $> 45\%$ and normal %MAP $\leq 45\%$

%MAP percentage of mean arterial pressure, ABI ankle-brachial index, CI confidence interval, HR hazard ratio

Model 1: adjusted for age and sex; Model 2: adjusted for age, sex, diabetes duration, smoking, cardiovascular disease, and body mass index; Model 3: adjusted for age, sex, diabetes duration, smoking, cardiovascular disease, body mass index, hemoglobin A1c, total cholesterol, high-density lipoprotein cholesterol, triglycerides, estimated glomerular filtration rate, albuminuria, brachial-ankle pulse wave velocity, systolic blood pressure, use of antihypertensive drugs, use of insulin, use of statins, and use of antiplatelet agents

mean follow-up duration of 4.4 years [47]. Notably, in the present study, the prediction of all-cause mortality was 21.1% with ABI alone and 38.0% with the combination of ABI and %MAP criteria. Although the C index was only 0.62 for predicting all-cause mortality in the combined ABI and %MAP model, it was still significantly higher than in the ABI alone model. Besides, the C index can reach to 0.72 by adding the common variables including age and sex in the model containing ABI and %MAP. Furthermore, Cox regression analysis confirmed that ABI accompanied by %MAP was superior to ABI alone in predicting the mortality of patients with type 2 DM.

The prevalence of PAD is increasing worldwide [48, 49]. Most patients with PAD are asymptomatic, but they have an elevated risk of mortality [48–50]. In Taiwan, annual screening for foot complications is recommended in the clinical guidelines and in the P4P program for patients with DM [14, 51]. In previous studies that have used the cutoff value of $ABI \leq 0.90$, the prevalence of PAD in type 2 DM was approximately 10.0% in patients with a mean age of 63 years in Taiwan, 10.4% in Malay patients (mean age, 63 years) who lived in Singapore, and 9.5% in patients aged >40 years in the US [52–54]. According to database of real-world clinical diagnosis, PAD was reported in 18.7% of patients with type 2 DM (mean age, 65 years) in the UK and in 13.6% of patients with type 2 DM (mean age, 66 years) in the US [55, 56]. In the present cohort, the prevalence of PAD was 8.4% when $ABI \leq 0.90$ was the only criterion used, but the rate increased to 17.4% when the combination of $ABI \leq 0.90$ and $\%MAP > 45\%$ was used. In the Taiwan National Health Insurance database, under 2.2% of patients with DM and age ≥ 65 years have a diagnosis of PAD, indicating that the condition is greatly underdiagnosed in clinical practice [57]. Thus, the use of ABI along with the automatically reported ankle %MAP is an effective and convenient method for PAD screening and for prediction of mortality [10, 13].

The risk factors for abnormal ABI have been extensively investigated, but the specific risk factors for high %MAP are still not clear [58, 59]. In the present study, the risk factors significantly associated with %MAP at both ABI levels included age, CVD history, BMI, HbA1c, eGFR, UACR, baPWV, use of antiplatelet agents, type of oral antihyperglycemic drug taken, and type of hypertensive drug taken (Table 1). However, we did not include all cardiovascular risk factors in the present study; for example, it has previously been reported that higher HbA1c variability is associated with a higher %MAP [19]. Furthermore, this study has several limitations. First, all participants were from a single teaching hospital, and the results may not be generalizable to all populations with type 2 DM. Second, this was a retrospective study, and so we could not control the risk factors and treatments

received during the follow-up period. Third, we did not apply anatomical assessments to confirm the lesions of PAD in the present study with a primary endpoint of all-cause mortality. Finally, the cutoff value of 45% for %MAP is based on the findings of previous studies [13]; we did not assess the normal range of %MAP in the present study.

In conclusion, the use of %MAP along with ABI appears to improve the prediction of all-cause mortality in patients with type 2 DM. The %MAP is automatically reported during ABI measurement and therefore can be conveniently used to improved prognostic prediction in clinical practice.

Abbreviations

%MAP: Percentage of the mean arterial pressure; ABI: Ankle-brachial index; AUC: Area under the receiver operating characteristic curve; baPWV: Brachial-ankle pulse wave velocity; CI: Confidence interval; CVD: Cardiovascular disease; DM: Diabetes mellitus; eGFR: Estimated glomerular filtration rate; HbA1c: Hemoglobin A1c; HDL: High-density lipoprotein; HR: Hazard ratio; IDI: Integrated discrimination improvement; NRI: Net reclassification improvement; P4P: Pay-for-performance; PAD: Peripheral artery disease; SD: Standard deviation; UACR: Urinary albumin-to-creatinine ratio.

Acknowledgements

Statistical analysis was performed by the Biostatistics Task Force of Taichung Veterans General Hospital.

Authors' contributions

YL participated in the data collection and the writing of the manuscript. WS contributed to the study design. IL contributed to the study design, data collection, data interpretation, and manuscript revision. IL, the guarantor of this work, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

Funding

This work was supported by Grants from Taichung Veterans General Hospital, Taichung, Taiwan (TCVGH-1093505D), and from the National Health Research Institute (Grant number NHRI-EX109-10927HT). The funding bodies had no role in the decision to submit the manuscript for publication.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study complied with the Declaration of Helsinki and was approved by the Institutional Review Board of Taichung Veterans General Hospital, with a waiver of the need for informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

¹ Division of Endocrinology and Metabolism, Department of Internal Medicine, Taichung Veterans General Hospital, No. 1650 Taiwan Boulevard, Section 4, Taichung 40705, Taiwan. ² School of Medicine, National Yang-Ming University, Taipei 11221, Taiwan. ³ Rong Hsing Research Center For Translational Medicine, College of Life Sciences, National Chung Hsing University, Taichung, Taiwan. ⁴ School of Medicine, Chung Shan Medical University, Taichung 40201, Taiwan. ⁵ College of Science, Tunghai University, Taichung 40704, Taiwan.

Received: 14 July 2020 Accepted: 1 October 2020
Published online: 09 October 2020

References

- Ogurtsova K, da Fernandes JD, Huang Y, Linnenkamp U, Guariguata L, Cho NH, Cavan D, Shaw JE, Makaroff LE. IDF Diabetes Atlas: global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes Res Clin Pract*. 2017;128:40–50.
- American Diabetes Association: 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2020. *Diabetes Care* 2020, 43(Suppl 1):S111–S134.
- Caro J, Migliaccio-Walle K, Ishak KJ, Proskorovsky I. The morbidity and mortality following a diagnosis of peripheral arterial disease: long-term follow-up of a large database. *BMC Cardiovasc Disord*. 2005;5:14.
- Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, Fleisher LA, Fowkes FG, Hamburg NM, Kinlay S, et al. 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: a Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2017;135(12):e726–79.
- Aboyans V, Ricco JB, Bartelink MEL, Björck M, Brodmann M, Cohnert T, Collet JP, Czerny M, De Carlo M, Debus S, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries Endorsed by the European Stroke Organization (ESO) The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). *Eur Heart J*. 2018;39(9):763–816.
- Xu D, Zou L, Xing Y, Hou L, Wei Y, Zhang J, Qiao Y, Hu D, Xu Y, Li J, et al. Diagnostic value of ankle-brachial index in peripheral arterial disease: a meta-analysis. *Can J Cardiol*. 2013;29(4):492–8.
- Natsuaki C, Inoguchi T, Maeda Y, Yamada T, Sasaki S, Sonoda N, Shimabukuro M, Nawata H, Takayanagi R. Association of borderline ankle-brachial index with mortality and the incidence of peripheral artery disease in diabetic patients. *Atherosclerosis*. 2014;234(2):360–5.
- Tanaka S, Kaneko H, Kano H, Matsuno S, Suzuki S, Takai H, Otsuka T, Uejima T, Oikawa Y, Nagashima K, et al. The predictive value of the borderline ankle-brachial index for long-term clinical outcomes: an observational cohort study. *Atherosclerosis*. 2016;250:69–76.
- Kithcart AP, Beckman JA. ACC/AHA Versus ESC Guidelines for Diagnosis and Management of Peripheral Artery Disease: JACC Guideline Comparison. *J Am Coll Cardiol*. 2018;72(22):2789–801.
- Lin HW, Lee IT. Combination of the ankle-brachial index and percentage of mean arterial pressure to improve diagnostic sensitivity for peripheral artery disease: an observational study. *Medicine (Baltimore)*. 2018;97(39):e12644.
- Hashimoto T, Ichihashi S, Iwakoshi S, Kichikawa K. Combination of pulse volume recording (PVR) parameters and ankle-brachial index (ABI) improves diagnostic accuracy for peripheral arterial disease compared with ABI alone. *Hypertens Res*. 2016;39(6):430–4.
- Shirasu T, Hoshina K, Akagi D, Miyahara T, Yamamoto K, Watanabe T. Pulse volume recordings to identify falsely elevated ankle brachial index. *Asian Cardiovasc Thorac Ann*. 2016;24(6):517–22.
- Li YH, Lin SY, Sheu WH, Lee IT. Relationship between percentage of mean arterial pressure at the ankle and mortality in participants with normal ankle-brachial index: an observational study. *BMJ Open*. 2016;6(3):e010540.
- Chen YC, Lee CT, Lin BJ, Chang YY, Shi HY. Impact of pay-for-performance on mortality in diabetes patients in Taiwan: a population-based study. *Medicine (Baltimore)*. 2016;95(27):e4197.
- Inker LA, Astor BC, Fox CH, Isakova T, Lash JP, Peralta CA, Kurella Tamura M, Feldman HI. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. *Am J Kidney Dis*. 2014;63(5):713–35.
- Hiatt WR. Medical treatment of peripheral arterial disease and claudication. *N Engl J Med*. 2001;344(21):1608–21.
- Watanabe Y, Masaki H, Yunoki Y, Tabuchi A, Morita I, Mohri S, Tanemoto K. Ankle-brachial index, toe-brachial index, and pulse volume recording in healthy young adults. *Ann Vasc Dis*. 2015;8(3):227–35.
- Munakata M. Brachial-ankle pulse wave velocity in the measurement of arterial stiffness: recent evidence and clinical applications. *Curr Hypertens Rev*. 2014;10(1):49–57.
- Lee IT. Mean and variability of annual haemoglobin A1c are associated with high-risk peripheral artery disease. *Diab Vasc Dis Res*. 2020;17(3):1479164120909030.
- Pencina MJ, D'Agostino RB, Pencina KM, Janssens AC, Greenland P. Interpreting incremental value of markers added to risk prediction models. *Am J Epidemiol*. 2012;176(6):473–81.
- Sampson UK, Fowkes FG, McDermott MM, Criqui MH, Aboyans V, Norman PE, Forouzanfar MH, Naghavi M, Song Y, Harrell FE Jr, et al. Global and regional burden of death and disability from peripheral artery disease: 21 world regions, 1990 to 2010. *Global Heart*. 2014;9(1):145–58.
- Osmundson PJ, Chesebro JH, Fallon WM, Zimmerman BR, Kazmier FJ, Palumbo PJ. A prospective study of peripheral occlusive arterial disease in diabetes. II. Vascular laboratory assessment. *Mayo Clin Proc*. 1981;56(4):223–32.
- Toth-Vajna Z, Toth-Vajna G, Gombos Z, Szilagyi B, Jarai Z, Berczeli M, Sotonyi P. Screening of peripheral arterial disease in primary health care. *Vascular Health Risk Manag*. 2019;15:355–63.
- Zahner GJ, Gruendl MA, Spaulding KA, Schaller MS, Hills NK, Gasper WJ, Grenon SM. Association between arterial stiffness and peripheral artery disease as measured by radial artery tonometry. *J Vasc Surg*. 2017;66(5):1518–26.
- Taniwaki H, Kawagishi T, Emoto M, Shoji T, Kanda H, Maekawa K, Nishizawa Y, Morii H. Correlation between the intima-media thickness of the carotid artery and aortic pulse-wave velocity in patients with type 2 diabetes Vessel wall properties in type 2 diabetes. *Diabetes Care*. 1999;22(11):1851–7.
- Schram MT, Henry RM, van Dijk RA, Kostense PJ, Dekker JM, Nijpels G, Heine RJ, Bouter LM, Westerhof N, Stehouwer CD. Increased central artery stiffness in impaired glucose metabolism and type 2 diabetes: the Hoorn Study. *Hypertension*. 2004;43(2):176–81.
- Wang JW, Zhou ZQ, Hu DY. Prevalence of arterial stiffness in North China, and associations with risk factors of cardiovascular disease: a community-based study. *BMC Cardiovasc Disord*. 2012;12:119.
- Wukich DK, Shen W, Raspovic KM, Suder NC, Baril DT, Avgerinos E. Noninvasive arterial testing in patients with diabetes: a guide for foot and ankle surgeons. *Foot Ankle Int*. 2015;36(12):1391–9.
- Lewis JE, Owens DR. The pulse volume recorder as a measure of peripheral vascular status in people with diabetes mellitus. *Diabetes Technol Ther*. 2010;12(1):75–80.
- Cao P, Eckstein HH, De Rango P, Setacci C, Ricco JB, de Donato G, Becker F, Robert-Ebadi H, Diehm N, Schmidli J, et al. Chapter II: diagnostic methods. *Eur J Vasc Endovasc Surg*. 2011;42(Suppl 2):S13–32.
- Eslahpazir BA, Allemang MT, Lakin RO, Carman TL, Trivonovich MR, Wong VL, Wang J, Baele HR, Kashyap VS. Pulse volume recording does not enhance segmental pressure readings for peripheral arterial disease stratification. *Ann Vasc Surg*. 2014;28(1):18–27.
- Lee WH, Hsu PC, Huang JC, Chen YC, Chen SC, Wu PY, Lee MK, Lee CS, Yen HW, Su HM. Association of pulse volume recording at ankle with total and cardiovascular mortality in hemodialysis patients. *J Clin Med*. 2019;8(12):2045.
- Zieman SJ, Melenovsky V, Kass DA. Mechanisms, pathophysiology, and therapy of arterial stiffness. *Arterioscler Thromb Vasc Biol*. 2005;25(5):932–43.
- Bailey AJ. Molecular mechanisms of ageing in connective tissues. *Mech Ageing Dev*. 2001;122(7):735–55.
- Negre-Salvayre A, Salvayre R, Auge N, Pamplona R, Portero-Otin M. Hyperglycemia and glycation in diabetic complications. *Antioxid Redox Signal*. 2009;11(12):3071–109.
- Wang M, Spinetti G, Monticone RE, Zhang J, Wu J, Jiang L, Khazan B, Telljohann R, Lakatta EG. A local proinflammatory signalling loop facilitates adverse age-associated arterial remodeling. *PLoS ONE*. 2011;6(2):e16653.
- Stewart AD, Millasseau SC, Kearney MT, Ritter JM, Chowienczyk PJ. Effects of inhibition of basal nitric oxide synthesis on carotid-femoral pulse wave velocity and augmentation index in humans. *Hypertension*. 2003;42(5):915–8.

38. Schmitt M, Avolio A, Qasem A, McEniery CM, Butlin M, Wilkinson IB, Cockcroft JR. Basal NO locally modulates human iliac artery function in vivo. *Hypertension*. 2005;46(1):227–31.
39. Lloyd-Jones DM, Bloch KD. The vascular biology of nitric oxide and its role in atherogenesis. *Annu Rev Med*. 1996;47:365–75.
40. Yki-Jarvinen H, Westerbacka J. Insulin resistance, arterial stiffness and wave reflection. *Adv Cardiol*. 2007;44:252–60.
41. Stehouwer CD, Henry RM, Ferreira I. Arterial stiffness in diabetes and the metabolic syndrome: a pathway to cardiovascular disease. *Diabetologia*. 2008;51(4):527–39.
42. Salomaa V, Riley W, Kark JD, Nardo C, Folsom AR. Non-insulin-dependent diabetes mellitus and fasting glucose and insulin concentrations are associated with arterial stiffness indexes. The ARIC Study. *Atherosclerosis Risk in Communities Study*. *Circulation*. 1995;91(5):1432–43.
43. Zhang Y, He P, Li Y, Zhang Y, Li J, Liang M, Wang G, Tang G, Song Y, Wang B, et al. Positive association between baseline brachial-ankle pulse wave velocity and the risk of new-onset diabetes in hypertensive patients. *Cardiovasc Diabetol*. 2019;18(1):111.
44. Reaven PD, Sacks J. Investigators for the V: coronary artery and abdominal aortic calcification are associated with cardiovascular disease in type 2 diabetes. *Diabetologia*. 2005;48(2):379–85.
45. Everhart JE, Pettitt DJ, Knowler WC, Rose FA, Bennett PH. Medial arterial calcification and its association with mortality and complications of diabetes. *Diabetologia*. 1988;31(1):16–23.
46. Potier L, Abi Khalil C, Mohammedi K, Roussel R. Use and utility of ankle brachial index in patients with diabetes. *Eur J Vasc Endovasc Surg*. 2011;41(1):110–6.
47. Yokoyama H, Sone H, Honjo J, Okizaki S, Yamada D, Shudo R, Shimizu H, Moriya T, Haneda M. Relationship between a low ankle brachial index and all-cause death and cardiovascular events in subjects with and without diabetes. *J Atheroscler Thromb*. 2014;21(6):574–81.
48. Fowkes FG, Aboyans V, Fowkes FJ, McDermott MM, Sampson UK, Criqui MH. Peripheral artery disease: epidemiology and global perspectives. *Nat Rev Cardiol*. 2017;14(3):156–70.
49. Tapp RJ, Shaw JE, de Courten MP, Dunstan DW, Welborn TA, Zimmet PZ, AusDiab Study G. Foot complications in Type 2 diabetes: an Australian population-based study. *Diabet Med*. 2003;20(2):105–13.
50. Aponte J. The prevalence of asymptomatic and symptomatic peripheral arterial disease and peripheral arterial disease risk factors in the U.S. population. *Holist Nurs Pract*. 2011;25(3):147–61.
51. Diabetes Association Of The Republic Of China T: Executive summary of the DAROC clinical practice guidelines for diabetes care- 2018. *J Formos Med Assoc* 2020, 119(2):577–586.
52. Tseng CH. Prevalence and risk factors of peripheral arterial obstructive disease in Taiwanese type 2 diabetic patients. *Angiology*. 2003;54(3):331–8.
53. Tavintharan S, Ning C, Su Chi L, Tay W, Shankar A, Shyong Tai E, Wong TY. Prevalence and risk factors for peripheral artery disease in an Asian population with diabetes mellitus. *Diab Vasc Dis Res*. 2009;6(2):80–6.
54. Gregg EW, Sorlie P, Paulose-Ram R, Gu Q, Eberhardt MS, Wolz M, Burt V, Curtin L, Engelgau M, Geiss L, et al. Prevalence of lower-extremity disease in the US adult population ≥ 40 years of age with and without diabetes: 1999–2000 national health and nutrition examination survey. *Diabetes Care*. 2004;27(7):1591–7.
55. Lautsch D, Wang T, Yang L, Rajpathak SN. Prevalence of established cardiovascular disease in patients with type 2 diabetes mellitus in the UK. *Diabetes Ther*. 2019;10(6):2131–7.
56. Arnold SV, Kosiborod M, Wang J, Fenici P, Gannedahl G, LoCasale RJ. Burden of cardio-renal-metabolic conditions in adults with type 2 diabetes within the Diabetes Collaborative Registry. *Diabetes Obes Metab*. 2018;20(8):2000–3.
57. Lee CH, Wu YL, Kuo JF, Chen JF, Chin MC, Hung YJ. Prevalence of diabetic macrovascular complications and related factors from 2005 to 2014 in Taiwan: a nationwide survey. *J Formos Med Assoc*. 2019;118(Suppl 2):S96–102.
58. Fowkes FG, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, Norman PE, Sampson UK, Williams LJ, Mensah GA, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet*. 2013;382(9901):1329–40.
59. Nativel M, Potier L, Alexandre L, Baillet-Blanco L, Ducasse E, Velho G, Marre M, Roussel R, Rigalleau V, Mohammedi K. Lower extremity arterial disease in patients with diabetes: a contemporary narrative review. *Cardiovasc Diabetol*. 2018;17(1):138.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

