ORIGINAL PAPER

WILEY

Interarm blood pressure differences predict target organ damage in type 2 diabetes

Francesco Spannella MD[1,2] | Federico Giulietti MD[1,2] | Massimiliano Fedecostante MD[3] |
Maddalena Ricci MD[1,2] | Paolo Balietti MD[1,2] | Guido Cocci MD[1,2] |
Laura Landi MD[1,2] | Anna Rita Bonfigli MSc[4] | Massimo Boemi MD[5] |
Emma Espinosa MD[1,2] | Riccardo Sarzani MD PhD[1,2]

[1]Internal Medicine and Geriatrics, "Hypertension Excellence Centre" of the European Society of Hypertension, IRCCS-INRCA "U.Sestilli", Ancona, Italy

[2]Department of Clinical and Molecular Sciences, University "Politecnica delle Marche", Ancona, Italy

[3]Geriatrics and Geriatric Emergency Department, IRCCS-INRCA "U.Sestilli", Ancona, Italy

[4]Scientific Direction, IRCCS-INRCA "U.Sestilli", Ancona, Italy

[5]Metabolic Diseases and Diabetology Unit, IRCCS-INRCA "U.Sestilli", Ancona, Italy

Correspondence
Riccardo Sarzani, MD, PhD, Internal Medicine and Geriatrics, Department of Clinical and Molecular Sciences, University "Politecnica delle Marche", Italian National Research Centre on Aging, Hospital "U. Sestilli", IRCCS-INRCA, Ancona, Italy.
Email: r.sarzani@univpm.it

Patients with type 2 diabetes mellitus are at high risk for atherosclerotic disease, and proper blood pressure measurement is mandatory. The authors examined the prevalence of an interarm difference (IAD) in blood pressure and its association with cardiovascular risk factors and organ damage (nephropathy, retinopathy, left ventricular hypertrophy, and vascular damage) in a large diabetic population. A total of 800 consecutive patients with type 2 diabetes mellitus were evaluated with an automated simultaneous bilateral device (men: 422 [52.8%]; mean age: 68.1±12.2 years). Diabetic patients with systolic IAD ≥5 and systolic IAD ≥10 mm Hg showed an increased risk of having vascular damage (adjusted odds ratios: 1.73 and 2.49, respectively) and higher pulse pressure. IAD is highly prevalent in patients with diabetes, is associated with vascular damage, even for IAD ≥5 mm Hg, and should be accurately obtained to avoid underdiagnosis and undertreatment of hypertension.

1 | INTRODUCTION

High blood pressure (BP) is a leading risk factor for morbidity, mortality, and healthcare costs worldwide.[1] Hypertension, with its high incidence and prevalence, together with the low percentage of patients with controlled BP while taking therapy, is a major health problem. Indeed, with the recent findings of the landmark Systolic Blood Pressure Intervention Trial (SPRINT),[2] which reported that intensive control of BP in high-risk hypertensive patients reduces mortality and adverse outcomes, optimizing BP measurement is a high priority. Accurate measurement of BP is the first essential step for proper identification and management of hypertension. All major guidelines recommend BP measurement in both arms, at least during the first visit, and then the arm with the highest values should be used for subsequent measurements.[3,4] This guidance is infrequently followed in primary care and the main barrier may be healthcare providers' inertia. In fact, only about 13% of primary care physicians routinely perform bilateral BP measurement.[5] Therefore, patients may be underinvestigated or undertreated for hypertension if an interarm difference (IAD) in BP is not taken into account.[6] Indeed, the diagnosis of hypertension could be missed and BP control could be overestimated when only the arm with the lower readings is chosen by chance.

In previous community-based cohort studies, the prevalence of IAD was nearly 10% for systolic IAD ≥10 mm Hg and slightly above 2% for systolic IAD ≥15 mm Hg,[7,8] while hypertensive patients may have a higher prevalence (24% and 9.1%, respectively).[9] Prevalence of IAD is also affected by the method of measurement. Published data clearly suggest that sequential measurement of BP overestimates the

prevalence of IAD and simultaneous measurement of both arms seems preferable.[10] Evidence also suggests that IAD, in particular systolic IAD ≥10 mm Hg or IAD ≥15 mm Hg, is associated with peripheral arterial disease (PAD) and increased mortality in different cohorts with high cardiovascular (CV) risk.[9,11–16] A recent study explored and identified this association in a cohort representative of a general population in the United Kingdom. In this study, authors found that in a cohort of patients without clinical evidence of vascular disease at recruitment, a systolic IAD ≥5 mm Hg based on a single pair of sequential measurements was associated with increased CV and all-cause mortality.[17]

The presence of IAD and its association with CV risk factors and organ damage has been studied in different populations.[18] Data in populations at higher CV risk, such as patients with diabetes, are scant; however, hazard ratios of CV events and mortality associated with IAD do increase with rising population CV risk.[19]

In patients with type 2 diabetes mellitus (DM2), proper hypertension management is essential to prevent CV diseases, the primary cause of mortality and morbidity.[3,20] Notwithstanding, only a few studies with small samples have evaluated the prevalence of IAD and its clinical implications. In this population with high CV risk, systolic IAD seems to be more frequent than in nondiabetic populations and is associated with microvascular/macrovascular damage and increased mortality.[21–23] Therefore, the aim of our study was to evaluate the prevalence of systolic and diastolic IAD and their associations with the main CV risk factors and organ damage in a large unselected sample of patients with DM2.

2 | METHODS

2.1 | Study population

We evaluated 800 consecutive patients with DM2 referred to the diabetes center of our clinical research Institution (IRCCS-INRCA, Ancona, Italy) between January 1, 2012, through December 31, 2012. Our sample is well representative of the general diabetic population, given that in Italy most diabetic patients refer to diabetes centers for evaluation and management of the disease. All participants gave informed written consent and clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki.

Fasting blood samples were obtained in the morning. We considered the following laboratory parameters: creatinine, estimated glomerular filtration rate (eGFR), urinary albumin excretion, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein cholesterol, triglycerides, glycemia, and glycated hemoglobin. Creatinine was determined in serum or plasma and the GFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration equation.[24] LDL cholesterol concentration was estimated using the method proposed by Martin and colleagues.[25]

According to the latest published European Society of Hypertension guidelines,[3] hypertension was defined as a recruitment BP ≥140/90 mm Hg in nontreated patients or the use of antihypertensive medications at baseline, while a threshold <140/85 mm Hg was considered the target for BP control by therapy. Pulse pressure

(PP), defined as the difference between systolic BP and diastolic BP readings, was also evaluated. We considered a glycated hemoglobin <7% as a target of well-controlled DM2.[20] Dyslipidemia was defined as total cholesterol ≥200 mg/dL and/or by use of lipid-lowering treatment. We considered LDL cholesterol values <100 mg/dL as a target for all patients with diabetes, and LDL cholesterol values <70 mg/dL as a target for diabetic patients with CV disease or chronic kidney disease or with other CV risk factors or markers of organ damage.[26] Smoking status was ascertained during recruitment and smoking habit was defined as current smoking or previous smoking of at least 100 cigarettes in a lifetime.[27,28] We considered the presence of anamnestic major CV events (previous stroke/transient ischemic attack [TIA] and coronary artery disease [CAD]) and main target organ damage: diabetic retinopathy (both proliferative and nonproliferative),[29] vascular damage (carotid and/or lower limbs arterial plaques evaluated by Doppler ultrasound), microalbuminuria or macroalbuminuria (defined as urinary albumin level >20 mg/L), reduced eGFR (eGFR <60 mL/min per 1.73 m^2), and left ventricular hypertrophy (LVH; concentric or eccentric, on the basis of indexed left ventricular mass estimated by echocardiography with thresholds of 95 g/m^2 for women and 115 g/m^2 [body surface area] for men).[3]

2.2 | IAD in BP measurement

During the clinical evaluation of patients with diabetes, we performed automatic BP measurements using a specifically designed device (Watch BP Office; Microlife, Taipei, Taiwan). It performs three consecutive simultaneous bilateral measurements 1 minute apart, returning the average value of BP for each arm. Repeated simultaneous measurement is the method used to avoid overestimation of prevalence, compared with other methods such as sequential measurements.[10] Correct cuff sizes (range 22–32 cm or 32–42 cm) were selected according to arm circumference and BP measurements were performed after at least 5 minutes of rest in the sitting position. The patient's arm was kept at the heart level during the measurement. We considered both systolic and diastolic IAD as an absolute value of the difference between the dominant and nondominant arm. Moreover, we grouped our patients based on the following cutoffs: 5, 10, and 15 mm Hg for systolic IAD and 5 and 10 mm Hg for diastolic IAD, respectively. We separately analyzed systolic and diastolic IAD. For the analysis, we selected the BP values of the arm with the higher average BP, from the three consecutive automatic measurements, and considered them the "real" BP values of the patient.

2.3 | Statistical analysis

Data were analyzed with the SPSS version 13 (SPSS Inc, Chicago, IL, USA). A P value <.05 was defined as statistically significant.

Continuous variables were checked for normality and were expressed as mean±standard deviation or as median and interquartile range for the variables markedly skewed.

Categorical variables were expressed as absolute number and percentage. Cross-sectional analyses were undertaken to examine

associations of IAD cutoffs with CV risk factors. Associations identified on univariate analyses with $P<.10$ were tested in multivariate logistic regressions. The χ^2 test was used to analyze the prevalence of organ damage between different IAD cutoffs. Logistic and linear regression analyses were used to create adjusted models.

3 | RESULTS

3.1 | General characteristics of the population

We studied 800 patients with DM2: 378 (47.2%) women and 422 (52.8%) men. The mean age of patients was 68.1±12.2 years. General characteristics of the population are shown in Table 1. The prevalence in the studied population was 43.8% for systolic IAD ≥5 mm Hg, 13.4% for IAD ≥10 mm Hg, and 4.6% for IAD ≥15 mm Hg and the prevalence for diastolic IAD ≥5 mm Hg was 26.1% and IAD ≥10 mm Hg was 6.5%. No statistical difference was found in BP readings between the dominant and nondominant arms.

Patients with systolic IAD ≥5 mm Hg showed higher glycated hemoglobin and longer duration of diabetes. Duration of diabetes was also associated with systolic IAD ≥10 mm Hg. Smoking status was associated with systolic IAD ≥15 mm Hg.

Higher systolic BP values were associated with systolic and diastolic IAD, regardless of the cutoff. Patients with diastolic IAD ≥5 and IAD ≥10 mm Hg showed higher diastolic BP and higher urinary albumin excretion values.

Regarding therapy, there were no differences in statin, antihypertensive, and antidiabetic treatment between cutoffs of IAD, while antiplatelet/antithrombotic therapy was associated with systolic and diastolic IAD ≥5 mm Hg. Moreover, there were no significant differences in prevalence of IAD when patients were divided into groups according to the classes of antihypertensive medications.

3.2 | Systolic IAD and CV risk factors: multivariate analysis

CV risk factors that showed at univariate analysis an association with the systolic IAD cutoffs with a $P<.10$ were included in logistic regression models to test their independent association and their relevance. Data are shown in Table 2. Systolic BP was the CV risk factor that remained associated with all systolic IAD cutoffs, while smoking habit remained associated with systolic IAD ≥15 mm Hg only. No associations were found between systolic IAD, duration of diabetes, diabetes control, and urinary albumin excretion.

3.3 | Systolic IAD and organ damage: multivariate analysis

Analyzing the association between systolic IAD and organ damage, patients with a systolic IAD showed higher prevalence of vascular damage, LVH, and TIA/stroke. There were no associations with CAD or retinopathy. The associations between systolic IAD cutoffs

TABLE 1 Characteristics of the population

Clinical characteristics	
Age, y	68.1±12.2
Female/male sex	378 (47.2)/422 (52.8)
Duration of diabetes, y	15.2±11.6
BMI, kg/m^2	29.4±5.3
Systolic BP, mm Hg[a]	146.2±19.0
Diastolic BP, mm Hg[a]	79.5±11.2
PP, mm Hg[a]	66.8±16.1
Absolute systolic IAD, mm Hg	4 (25–75 pcs: 2–7)
Absolute diastolic IAD, mm Hg	3 (25–75 pcs: 1–5)
Smoking habit	385 (48.1)
Hypertension	617 (77.1)
Dyslipidemia	668 (83.5)
Diabetes control	331 (41.4)
BP control[b]	110 (17.8)
LDL cholesterol target (yes)	195 (25.1)
Laboratory parameters	
Glycemia, mg/dL	138 (25°–75°pcs: 117–160)
Creatinine, mg/dL	0.90 (25°–75°pcs: 0.79–1.10)
eGFR, mL/min per 1.73 m^2	79.1±26.0
Urinary albumin excretion, mg/L	6.6 (25–75 pcs: 3.5–24.3)
Glycated hemoglobin	7.2 (25–75 pcs: 6.6–8.1)
Total cholesterol, mg/dL	183.5±40.7
HDL cholesterol, mg/dL	50.8±15.1
Triglycerides, mg/dL	114 (25–75 pcs: 83–162)
LDL cholesterol, mg/dL	106.1±34.7
Organ damage	
Vascular damage	403 (51.5)
LVH	276 (35)
TIA/stroke	57 (7.2)
CAD	176 (22.3)
Diabetic retinopathy	226 (28.6)
Microalbuminuria or macroalbuminuria	175 (22.2)
Pharmacological therapy	
Insulin therapy	300 (37.5)
Antihypertensive therapy	493 (62.7)
Statin therapy	326 (41.4)
Antiplatelet/antithrombotic therapy	300 (38.0)

BP, blood pressure; BMI, body mass index; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; IAD, interarm difference; LDL, low-density lipoprotein; LVH, left ventricular hypertrophy; pcs, percentiles; PP, pulse pressure; TIA, transient ischemic attack. Continuous variables are expressed as mean±standard deviation, except skewed variables, which are expressed as median and interquartile range. Categorical variables are expressed as absolute number and percentage.
[a]Systolic BP, diastolic BP, and PP referred to the arm with the higher average BP reading from three consecutive automatic measurements.
[b]BP control was considered in patients with hypertension (n=617).

TABLE 2 Cardiovascular risk factors and systolic IAD

Variables[a]	Systolic IAD ≥5 mm Hg		Systolic IAD ≥10 mm Hg		Systolic IAD ≥15 mm Hg	
	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value
Duration of diabetes	1.01 (0.99–1.02)	.366	1.01 (0.99–1.03)	.201	1.02 (0.99–1.05)	.144
Diabetes control (Ref: controlled)	1.16 (0.86–1.57)	.327	0.94 (0.61–1.46)	.792	0.89 (0.44–1.79)	.747
Systolic BP[b]	1.01 (1.01–1.02)	**<.001**	1.02 (1.01–1.03)	**.001**	1.02 (1.00–1.03)	**.038**
Urinary albumin excretion	/	/	1.00 (1.00–1.00)	.474	/	/
Smoking habit	/	/	/	/	2.64 (1.28–5.45)	**.008**

Bold values indicate significance. BP, blood pressure; CI, confidence interval; IAD, interarm difference; OR, odds ratio; /, variables not associated with the systolic IAD cutoffs considered with a P<.10 at univariate analysis.
[a]For continuous variables OR was for a 1-unit increase.
[b]Systolic BP referred to the arm with the higher average BP reading from three consecutive automatic measurements.

and organ damage, that were statistically significant at the univariate analysis, were adjusted for cofactors (Table 3).

Systolic IAD ≥5 and IAD ≥10 mm Hg remained associated with vascular damage even after adjusting for covariates (adjusted ORs 1.73 and 2.49, respectively), while the associations with LVH and TIA/stroke did not remain significant after adjusting for age and sex. We also evaluated the associations between systolic IAD cutoffs and PP. All systolic IAD cutoffs were significantly associated with higher PP values even after adjusting for covariates (age, sex, hypertension, smoking habit, dyslipidemia, duration of diabetes, diabetes control) (β=.08; P=.011 for systolic IAD ≥5 mm Hg; β=.11; P<.001 for systolic IAD ≥10 mm Hg; β=.09; P=.006 for systolic IAD ≥15 mm Hg).

3.4 | Diastolic IAD and CV risk factors: multivariate analysis

Logistic regression models showed that diastolic IAD ≥5 mm Hg was associated with higher diastolic BP values (odds ratio [OR], 1.07; 95% confidence interval [CI], 1.05–1.09 [P<.001]), older age (OR, 1.02; 95% CI, 1.00–1.04 [P=.024]), and longer duration of diabetes (OR, 1.02; 95% CI, 1.00–1.04 [P=.014]). Higher diastolic BP values (OR, 1.07; 95% CI, 1.04–1.11 [P<.001] and older age (OR, 1.04; 95% CI, 1.01–1.07 [P=.023]) were also associated with diastolic IAD ≥10 mm Hg.

3.5 | Diastolic IAD and organ damage: multivariate analysis

After adjusting for covariates (age, sex, hypertension, smoking habit, dyslipidemia, systolic BP, duration of diabetes, diabetes control), no significant associations emerged between diastolic IAD cutoffs and vascular damage, retinopathy, LVH, or TIA/stroke. We found no association between diastolic IAD and PP.

4 | DISCUSSION

This trial represents the largest cross-sectional study on IAD in DM2 patients, using a specifically designed device for simultaneous bilateral BP measurements. We found that IAD was highly prevalent in our sample. The prevalence of systolic IAD was 43.8% for IAD ≥5 mm Hg, 13.4% for IAD ≥10 mm Hg, and 4.6% for IAD ≥15 mm Hg. The prevalences were slightly higher than those reported in the most relevant previous study on diabetic patients (8.6% and 2.3% for systolic IAD ≥10 and IAD ≥15 mm Hg, respectively).[22] These differences between the two studies may be due to the older age and the higher prevalence of vascular damage in our population of 800 DM2 patients. Importantly, the wide prevalence of IAD in DM2 might contribute to

TABLE 3 Organ damage and systolic IAD

Organ Damage	Systolic IAD Cutoffs	Model 1[a] OR (95% CI)	Model 2[b] OR (95% CI)	Model 3[c] OR (95% CI)
Vascular damage	≥5 mm Hg	1.65 (1.24–2.19)*	1.61 (1.20–2.16)*	1.73 (1.25–2.41)*
	≥10 mm Hg	2.44 (1.57–3.79)**	2.49 (1.58–3.93)**	2.49 (1.48–4.17)*
	≥15 mm Hg	2.02 (1.00–4.09)*	2.19 (1.06–4.53)*	1.86 (0.84–4.12)
LVH	≥5 mm Hg	1.35 (1.01–1.81)*	1.28 (0.94–1.75)	1.30 (0.94–1.80)
TIA/stroke	≥10 mm Hg	2.03 (1.05–3.91)*	1.95 (0.99–3.81)	1.72 (0.86–3.46)

CI, confidence interval; IAD, interarm difference; LVH, left ventricular hypertrophy; OR, odds ratio; TIA, transient ischemic attack.
[a]Model 1: univariate analysis.
[b]Model 2: adjusted for age and sex.
[c]Model 3: fully adjusted (age, sex, hypertension, smoking habit, dyslipidemia, systolic blood pressure, duration of diabetes, diabetes control).
*P<.05. **P<.001.

an altered perception of the "real" BP values, resulting in a significant impact on CV risk classification and management.

Our study was not the only one in which a dedicated device to identify IAD in diabetic patients has been used. Okada and colleagues[30] performed simultaneous four-limb measurements of BP, finding that a difference in systolic BP ≥10 mm Hg between arms and a difference in systolic BP ≥15 mm Hg between lower limbs correlated with the risk of albuminuria (OR, 12.23 and 4.291, respectively). These investigators suggested a relationship between PAD and renal damage as the link between systolic IAD and diabetic nephropathy.

No associations were found between renal function and IAD in our population. As well as in the study performed by Okada and colleagues,[30] the presence of systolic IAD in diabetic patients in our study did not appear related to the duration and severity of diabetes. In our study, systolic IAD was associated with systolic BP values in the higher reading arm, even for values ≥5 mm Hg, while smoking habit was associated with systolic IAD only for the highest cutoff (≥15 mm Hg).

Peripheral vascular disease with arterial stenosis, a recognized risk factor for future CV events and mortality, has been assumed to be one of the pathological bases for IAD,[31] although there is no direct radiological evidence to confirm that PAD is the anatomical cause of an IAD.[11] The IADs observed may result from more diffuse stiffening in the arteries, since structural changes in large arteries as a result of hypertension and diabetes begin early in the course of the condition and are insidious. Symptomatic CV and peripheral vascular disease are late sequelae of a process of gradual arterial stiffening as a result of damage to the elastic fibers under sustained elevated BP.[32] In our study, higher BP values in addition to smoking were shown to compromise the vascular bed, thus reflecting a possible development of IAD in this high CV risk population. It is well known that atherosclerotic plaques appear in specific localized tracts of the arteries and it is also likely that arterial stiffening might be localized, being more accentuated in one arm because of anatomical reasons.

The association between IAD and documented vascular disease is already known in diabetic populations. In a recent study on 206 diabetic patients, investigators found a correlation between systolic IAD and intima-media thickness, proposing IAD as a novel risk marker for subclinical atherosclerosis in patients with DM2.[23] In a longitudinal study with a median follow-up of 52.4 months in a diabetic population, Clark and colleagues showed that a systolic IAD ≥10 mm Hg was associated with a greater prevalence of claudication and PAD, while a systolic IAD ≥15 mm Hg was associated with the presence of diabetic retinopathy and a higher prevalence of chronic kidney disease. Moreover, in the survival analysis, a systolic IAD ≥10 and ≥15 mm Hg was associated with higher CV mortality.[22]

In our study, the association between systolic IAD and vascular damage emerged even for IAD ≥5 mm Hg and it was confirmed for all systolic IAD cutoffs even after adjusting for cofactors. We found no relationship between systolic IAD cutoffs and renal or retinal damage, while the association with LVH and cerebrovascular events lost significance after adjusting for the other main CV risk factors.

Moreover, we evaluated diastolic IAD and its possible associations with CV risk factors and organ damage, given that it is still a poorly investigated area. In our population, prevalence of diastolic IAD ≥5 and IAD ≥10 mm Hg was 26.1% and 6.5%, respectively, slightly higher than those reported by Clark and colleagues.[22] Diastolic IAD appears to be associated with different CV risk factors compared with systolic IAD; therefore, different underlying pathophysiological causes are possible. Higher diastolic BP values, older age, and longer duration of diabetes were associated with diastolic IAD in our study. Previous studies have shown an association between diastolic IAD and BP variability,[22] and the association between short-term BP variability and arterial stiffness is well recognized.[33] Older age and longer duration of diabetes may be precisely the factors responsible for arterial calcification, leading to arterial stiffness that may be different between arms. However, in our study, we found no significant association between diastolic IAD and target organ damage, nor an association with PP, an indirect index of generalized arterial stiffness. The limited accuracy of the oscillometric method in the measurement of diastolic BP in atherosclerotic patients might also have contributed to the lack of association between diastolic IAD and organ damage in our study, due to the fact that more than half of our patients (51.5%) had documented atherosclerotic lesions.

The mechanisms of the observed pathophysiological aspects go beyond the focus of our report and further studies are needed, especially regarding diastolic IAD.

The relationship between systolic IAD and arterial stiffness, however, is well documented. Recent cross-sectional studies have found an association between systolic IAD ≥10 mm Hg with elevated ankle-brachial pulse wave velocity, an indicator of increasing vascular stiffness, demonstrating that part of the association between systolic IAD and CV risk could be mediated by arterial stiffness.[27,34] In agreement with previous reports, we have found an association between systolic IAD and PP, an indirect index of reduced arterial elasticity, even for systolic IAD ≥5 mm Hg and after adjusting for confounding factors. These findings support the close relationship between IAD and vascular damage.

5 | STUDY STRENGTHS AND LIMITATIONS

The strengths of our study are the use of a simultaneous measurement technique to evaluate BP and the large sample analyzed. However, this study has limitations that require consideration. First, the study used a cross-sectional design that did not permit the determination of a cause-effect nature of relationships. Second, IAD was measured in a single clinical evaluation, which did not take into account the small differences due to cuff positioning and did not permit us to evaluate the reproducibility of IAD measurement. However, cuffs were positioned by well-trained physicians of our hypertension center and three consecutive simultaneous dual-arm measurements were performed. The association between IAD, risk factors for atherosclerosis, and vascular damage, even for IAD ≥5 mm Hg, further strengthens and supports our results. Third, we cannot ignore the low reproducibility of IAD. Previous studies have reported varying degrees of IAD reproducibility.[35–37] Finally, this study was not designed to assess atherosclerosis

in the upper limb arteries systematically using ultrasound evaluation; therefore, we had no direct evidence of the relationship between IAD and upper limb atherosclerosis. Moreover, a systematic evaluation of arterial stiffness, such as pulse wave velocity measurement, was not performed at the time of patient recruitment.

6 | CONCLUSIONS

We found that IAD is highly prevalent in patients with diabetes, in which diagnosis and treatment of hypertension may be compromised if IAD is not accurately obtained. Diabetic patients with systolic IAD ≥5 mm Hg showed an increased risk of having vascular damage compared with diabetic patients with systolic IAD <5 mm Hg, a risk that even doubled for systolic IAD ≥10 mm Hg. IAD is not only an epiphenomenon of the BP level, but it may represent the evidence of underlying acquired vascular damage. We conclude that, especially in patients with high CV risk, such as diabetics, the need and benefit of implementing BP measurement in both arms in current clinical practice should be a high priority, keeping in mind that IAD is associated with significant target organ damage in this population. Moreover, IAD could develop at any time with aging and may worsen as a result of atherosclerosis progression. Therefore, repeated measurements over time might help to confirm the presence/absence of IAD and to assess its possible evolution. Given the importance of a correct BP measurement in an age of more intensive BP control and proper hypertension management, especially in patients with diabetes, physicians' adherence to this practice should be strongly encouraged, starting from primary care.

FINANCIAL DISCLOSURE

REFERENCES

1. Ng M, Fleming T, Robinson M, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2014;384:766–781.
2. Wright JT Jr, Williamson JD, Whelton PK, et al. SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2015;373:2103–2116.
3. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens*. 2013;31:1281–1357.
4. Weber MA, Schiffrin EL, White WB, et al. Clinical practice guidelines for the management of hypertension in the community: a statement by the American Society of Hypertension and the International Society of Hypertension. *J Clin Hypertens (Greenwich)*. 2014;16:14–26.
5. Parati G, Zanchetti A. Diabetes: measuring interarm blood pressure differences in diabetes. *Nat Rev Endocrinol*. 2014;10:387–388.
6. Giles TD, Egan P. Inter-arm difference in blood pressure may have serious research and clinical implications. *J Clin Hypertens (Greenwich)*. 2012;14:491–492.
7. White J, Mortensen LH, Kivimäki M, Gale CR, Batty GD. Interarm differences in systolic blood pressure and mortality among US army veterans: aetiological associations and risk prediction in the Vietnam Experience Study. *Eur J Prev Cardiol*. 2014;21:1394–1400.
8. Weinberg I, Gona P, O'Donnell CJ, Jaff MR, Murabito JM. The systolic blood pressure difference between arms and cardiovascular disease in the Framingham Heart Study. *Am J Med*. 2014;127:209–215.
9. Clark CE, Taylor RS, Shore AC, Campbell JL. The difference in blood pressure readings between arms and survival: primary care cohort study. *BMJ*. 2012;20:e1327.
10. Verberk WJ, Kessels AG, Thien T. Blood pressure measurement method and inter-arm differences: a meta-analysis. *Am J Hypertens*. 2011;24:1201–1208.
11. Clark CE, Taylor RS, Shore AC, Ukoumunne OC, Campbell JL. Association of a difference in systolic blood pressure between arms with vascular disease and mortality: a systematic review and meta-analysis. *Lancet*. 2012;379:905–914.
12. Kim J, Song TJ, Song D, et al. Interarm blood pressure difference and mortality in patients with acute ischemic stroke. *Neurology*. 2013;16:80.
13. Sheng CS, Liu M, Zeng WF, Huang QF, Li Y, Wang JG. Four-limb blood pressure as predictors of mortality in elderly Chinese. *Hypertension*. 2013;61:1155–1160.
14. Quiroga B, Galán I, García de Vinuesa S, Goicoechea M, Verdalles Ú, Luño J. Interarm systolic blood pressure as a predictor of cardiovascular events in patients with chronic kidneydisease. *Nephrol Dial Transplant*. 2015;30:801–806.
15. Cao K, Xu J, Shangguan Q, et al. Association of an inter-arm systolic blood pressure difference with all-cause and cardiovascular mortality: an updated meta-analysis of cohort studies. *Int J Cardiol*. 2015;189:211–219.
16. Singh S, Sethi A, Singh M, Khosla K, Grewal N, Khosla S. Simultaneously measured inter-arm and inter-leg systolic blood pressure differences and cardiovascular risk stratification: a systemic review and meta-analysis. *J Am Soc Hypertens*. 2015;9:640–650.
17. Clark CE, Taylor RS, Butcher I, et al. Inter-arm blood pressure difference and mortality: a cohort study in an asymptomatic primary care population at elevated cardiovascular risk. *Br J Gen Pract*. 2016;66:e297–e308.
18. Clark CE. Difference in blood pressure measurements between arms: methodological and clinical implications. *Curr Pharm Des*. 2015;21:737–743.
19. Clark CE, Shore A, Taylor R, Campbell J. The inter-arm difference in blood pressure and mortality: systematic review and meta-analysis. *J Hypertens*. 2015;33(suppl1):e11.
20. Rydén L, Grant PJ, Anker SD, et al. ESC Guidelines on diabetes, prediabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J*. 2013;34:3035–3087.
21. Okada H, Fukui M, Tanaka M, et al. A difference in systolic blood pressure between arms and between lower limbs is a novel risk marker for diabetic nephropathy in patients with type 2 diabetes. *Hypertens Res*. 2013;36:403–407.
22. Clark CE, Steele AM, Taylor RS, Shore AC, Ukoumunne OC, Campbell JL. Interarm blood pressure difference in people with diabetes: measurement and vascular and mortality implications: a cohort study. *Diabetes Care*. 2014;37:1613–1620.
23. Tanaka Y, Fukui M, Tanaka M, et al. The inter-arm difference in systolic blood pressure is a novel risk marker for subclinical atherosclerosis in patients with type 2 diabetes. *Hypertens Res*. 2014;37:548–552.
24. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–612.

25. Martin SS, Blaha MJ, Elshazly MB, et al. Comparison of a novel method vs the Friedewald equation for estimating low-density lipoprotein cholesterol levels from the standard lipid profile. *JAMA*. 2013;310:2061–2068.

26. Reiner Z, Catapano AL, De Backer G, et al. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Eur Heart J*. 2011;32:1769–1818.

27. Canepa M, Milaneschi Y, Ameri P, et al. Relationship between inter-arm difference in systolic blood pressure and arterial stiffness in community-dwelling older adults. *J Clin Hypertens (Greenwich)*. 2013;15:880–887.

28. Centers for Disease Control and Prevention. MMWR. 2009;58: 1227–1258.

29. American Academy of Ophthalmology Retina/Vitreous Panel. PPP® Guidelines. Diabetic Retinopathy. San Francisco, CA: American Academy of Ophthalmology; 2016. www.aao.org/ppp. Accessed January 2016.

30. Okada H, Fukui M, Tanaka M, et al. A difference in systolic blood pressure between arms and between lower limbs is a novel risk marker for diabetic nephropathy in patients with type 2 diabetes. *Hypertens Res*. 2013;36:403–407.

31. Clark CE. Difference in blood pressure between arms might reflect peripheral vascular disease. *BMJ*. 2001;323:399–400.

32. Williams B. Hypertension in the young: preventing the evolution of disease versus prevention of clinical events. *J Am Coll Cardiol*. 2007;50:840–842.

33. Schillaci G, Bilo G, Pucci G, et al. Relationship between short-term blood pressure variability and large-artery stiffness in human hypertension: findings from 2 large databases. *Hypertension*. 2012;60:369–377.

34. Clark CE, Casanova F, Gooding K, et al. Inter-arm blood pressure difference and arterial stiffness. *J Hypertens*. 2014;1:e30.

35. Singh S, Khosla S. Inter-arm blood pressure difference and all-cause or cardiovascular mortality. *Int J Cardiol*. 2015;191:50–51.

36. Clark CE, Campbell JL, Evans PH, Shore A, Taylor R. Detection of an interarm blood pressure difference in primary care diabetes care. *Diabetic Med*. 2009;26(suppl. 1):128.

37. Eguchi K, Yacoub M, Jhalani J, Gerin W, Schwartz JE, Pickering TG. Consistency of blood pressure differences between the left and right arms. *Arch Intern Med*. 2007;167:388–393.