Interarm Blood Pressure Difference in People With Diabetes: Measurement and Vascular and Mortality Implications

A Cohort Study

Diabetes Care 2014;37:1613–1620 | DOI: 10.2337/dc13-1576

Christopher E. Clark,[1] Anna M. Steele,[2] Rod S. Taylor,[1] Angela C. Shore,[2] Obioha C. Ukoumunne,[3] and John L. Campbell[1]

OBJECTIVE

Differences in blood pressure between arms are associated with vascular disease and increased mortality; this has not been reported in diabetes. We explored these associations, and assessed reference standard and pragmatic measurement techniques, in people with diabetes and in nondiabetic controls.

RESEARCH DESIGN AND METHODS

A prospective cohort study in Devon, England, recruited 727 people with type 1 or type 2 diabetes and 285 nondiabetic controls. Simultaneous repeated measurements of bilateral blood pressure were made at recruitment. Data were used to inform a pragmatic measurement strategy. Interarm differences were examined for cross-sectional associations with target organ disease and prospective mortality associations (median follow-up 52 months).

RESULTS

We found 8.6% of participants with diabetes and 2.9% of controls had systolic interarm differences ≥10 mmHg. Single pairs of blood pressure measurements had high negative predictive values (97–99%) for excluding interarm differences. Systolic interarm differences ≥10 mmHg in diabetes were associated with peripheral arterial disease (odds ratio [OR] 3.4 [95% CI 1.2–9.3]). Differences ≥15 mmHg were associated with diabetic retinopathy (OR 5.7 [1.5–21.6]) and chronic kidney disease (OR 7.0 [1.7–29.8]). Systolic interarm differences were associated prospectively with increased cardiovascular mortality: hazard ratios 3.5 (1.0–13.0) for ≥10 mmHg and 9.0 (2.0–41.0) for ≥15 mmHg.

CONCLUSIONS

Blood pressure should be measured in both arms during initial assessment in diabetes. Systolic interarm differences can be excluded with a single pair of measurements. In the population with diabetes, systolic differences may be associated with an increased risk of morbidity and mortality.

[1]Primary Care Research Group, Institute of Health Services Research, University of Exeter Medical School, Exeter, Devon, U.K.
[2]NIHR Exeter Clinical Research Facility, Royal Devon and Exeter Hospital and University of Exeter Medical School, Exeter, Devon, U.K.
[3]Peninsula Collaboration for Leadership in Applied Health Research and Care (PenCLAHRC), University of Exeter Medical School, Exeter, Devon, U.K.

Corresponding author: Christopher E. Clark, c.e.clark@exeter.ac.uk.

Received 4 July 2013 and accepted 2 February 2014.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc13-1576/-/DC1.

The views and opinions expressed in this article are those of the authors and not necessarily those of the National Health Service, the NIHR, or the Department of Health.

A systolic difference in blood pressures between arms is associated with peripheral arterial disease, cerebrovascular disease, and increased cardiovascular and all-cause mortality (1); these findings are mainly derived from populations at elevated cardiovascular risk. Studies that have examined the interarm difference in people with diabetes, who are also at elevated cardiovascular risk (2), report a prevalence of a systolic difference ≥10 mmHg between arms in type 2 diabetes of 9–10% (3,4). However, the associations of interarm difference in blood pressure with increased cardiovascular and all-cause mortality have not been reported in diabetes.

Failure to recognize an interarm difference in blood pressure may incorrectly classify the majority of subjects with such a difference as having controlled hypertension if the lower reading arm is measured (4). This can delay the diagnosis or confound the treatment of hypertension (5), a key component of effective diabetes care (6), if an interarm difference is not specifically looked for. Guidelines advise measuring both arms during initial assessment of high blood pressure (7,8), but this guidance is followed by less than one in five general practitioners in the U.K. (9), perhaps due, in part, to clinical inertia or to a lack of evidence directly relevant to primary care for the importance of measuring both arms (10).

Confirmation of an interarm difference requires a method of repeated simultaneous measurement, to avoid overestimation of prevalence (8,11). This technique, however, may not be practical in routine clinical care (12). It adds time to the clinical assessment of subjects in primary care, and we have found it to be a barrier to recruitment in our previous study in diabetes (4). Initially, a sequentially measured pair of readings may be sufficient to rule subjects out of further assessment for an interarm difference, but this requires further evaluation (13). Previous small studies that directly compared sequential and simultaneous measurement techniques have concluded that the reproducibility of an interarm difference measured by different techniques is poor (3,14), although we have found that repeated sequential measures can predict a systolic interarm difference ≥10 mmHg on repeated simultaneous measurement (15).

The current study examines the cross-sectional and prospective associations of an interarm difference with signs of vascular disease and increased mortality in a diabetic cohort demographically representative of the primary care population with diabetes and using an accepted reference standard method of repeated simultaneous blood pressure measurements. Concurrent measurement of a control (nondiabetic) group was included since we have not found any previous reports on the application of repeated simultaneous measurements to an unselected community cohort. Further assessment of the predictive value of a pragmatic sequential method of interarm blood pressure measurement for confirmed interarm differences was also planned as a study objective.

RESEARCH DESIGN AND METHODS

Study Participants

The Diabetes Alliance for Research in England (DARE; DRN082) is a community-wide collaboration between patients and professionals aiming to provide a platform to enable further study into the causes and complications of diabetes. It aims to establish a sample of all patients with diabetes within the regions included in the National Institute for Health Research (NIHR) Diabetes Research Network, part of the NIHR Clinical Research Network. By collecting DNA samples from all participants, which can be linked with clinical information, it provides a resource to look for gene/environment interaction in the development of type 1, type 2, and other forms of diabetes and their associated complications.

Within each region, the study aims to recruit all adult patients with diabetes with no exceptions other than the patient's being unable to understand the consent form. It thus seeks to be broadly representative of the English diabetic population. Nondiabetic controls are also recruited to permit genetic comparisons. Diabetic patients were identified from searches of primary and secondary care diabetes registers, and social-class-matched controls were identified where possible from spouses of patients.

Data Collection

People with diabetes and controls were recruited within primary and secondary care settings by trained research nurses who collected demographic and clinical data, including patient-reported cardiovascular and peripheral vascular events and/or interventions, and who performed a baseline clinical assessment including measurement of blood pressure. Specifically for the duration of this study, the nurses recruiting to the Exeter center (Devon, England) included within the baseline visit an assessment of blood pressure measured simultaneously in both arms with two automated sphygmomanometers using our previously piloted standard operating procedure (Supplementary Data) (4,15). This involved the participant sitting quietly for 5 min. A total of four pairs of bilateral blood pressures were then measured. Two pairs of bilateral blood pressure measurements were obtained by simultaneous activation of two automated sphygmomanometers (Omron 705IT; Omron Matsusaka, Japan). The cuffs and their associated machines were then swapped to the contralateral arms, and two further pairs of blood pressure readings were obtained. The order of application of machines to arms was randomized using a random number table. Flagging of diabetic patients' and controls' records on the National Health Service register with the National Health Service Information Centre permitted prospective collation of mortality data from information on death certificates.

Data Analysis

Baseline characteristics of diabetic and control participants, and cutoffs of interarm difference, were compared using t tests or χ^2 tests as appropriate. Systolic and diastolic interarm blood pressure differences were calculated as the mean of all right arm minus the mean of all left arm measurements. Hypertension was defined as the use at baseline of antihypertensive medication or a recruitment blood pressure ≥140/80 mmHg.

Interarm differences from individual simultaneous pairs of readings were compared with the reference standard, defined as the mean of differences from all four simultaneous pairs. Best and worst case scenarios, as pragmatic estimates of sequential data collection in routine clinical practice, were examined by calculating differences with the least

time separation (first right arm reading minus second left arm reading) and the greatest time separation (first right arm reading minus fourth left arm reading). Pairs of sequentially and simultaneously measured interarm difference measurements were examined for validity (sensitivity and specificity) using interarm difference greater or equal to prespecified cutoffs of 10 and 15 mmHg for the mean of the four pairs of readings as the reference standard. Receiver operating characteristic (ROC) plots were examined for the areas under the curve. Both patients with diabetes and controls were used in these analyses.

Cross-sectional analyses were undertaken for diabetic subjects to examine associations between interarm difference status (using cutoffs ≥10 mmHg and ≥15 mmHg based on previous findings [1]) and demographic factors, medication use, and markers of microvascular and macrovascular disease (any diabetic retinopathy on most recent screening, history of claudication and peripheral arterial disease, and medical history of cardiovascular and cerebrovascular events). Associations identified on univariate analysis were tested in a multivariate logistic regression; covariables were included in the analysis on clinical grounds and/or identification of an association on univariate analysis.

Participants were followed up for a period of up to 5 years. Cox proportional hazards regression models were used to compare all-cause and cardiovascular mortality between diabetic subjects with and without an interarm difference (based on cut points ≥10 mmHg and ≥15 mmHg) reporting hazard ratios (HRs). Deaths due to myocardial infarction, cardiac failure, or ischemic cerebrovascular events were defined as cardiovascular deaths. Since it is recommended that 10 or more events are required per covariate, we did not attempt to run multivariable models (16). We assessed proportionality of hazards by plotting $-\ln(-\ln(\text{survival}))$ versus ln(analysis time) and tested this using Schoenfeld residuals (17). Since the proportionality assumption was not always upheld, we also reported the log-rank test *P* value. Analyses were carried out using SPSS 20 (IBM, New York, NY).

RESULTS

Characteristics of Participants

Recruitment took place from 30 October 2007 to 12 February 2010; mortality data to 13 November 2013 were included in this analysis. During this period, a total of 727 people with diabetes and 285 control subjects were recruited. The diabetic cohort predominantly had type 2 diabetes (621/727; 85.4%); 89 (12.2%) were classified as type 1 diabetes, and the remainder were steroid related (2), gestational (1), maturity onset of diabetes in the young (1), or unclassified (13). Compared with controls, diabetic participants were older, with higher BMI, waist:hip ratio, arm circumference, systolic and diastolic blood pressures, and interarm differences. Cholesterol concentrations, sex, and smoking status also differed (Table 1). Participants were predominantly of British or other white origin (969/1,012; 95.8%).

In 116 (11.5%) subjects, no pairs of readings were successfully recorded. The main reasons for not obtaining any readings were machine errors (36) or arrhythmias (25) (Supplementary Table 1). No subjects with atrial fibrillation had four pairs of readings recorded with success. The four-pairs protocol was successfully completed in 514 (71%) people with diabetes and in 238 (84%) control subjects ($P < 0.001$). Compared with those not achieving four pairs of readings, those completing the protocol had lower systolic blood pressures (mean [SD] 140.1 [16.8] vs. 146.6 [21.4], BMI measurements 28.5 [4.9] vs. 31.0 [5.9], and waist:hip ratios 0.91 [0.10] vs. 0.94 [0.10]; all $P < 0.001$).

Method of Interarm Difference Measurement Analysis

Data from the completed four-pairs protocol in 752 control or diabetic participants were used to examine the validity of different methods of initial measurement. Sensitivities calculated for individual pairs of simultaneous and sequential readings ranged from 63 to 78%, and from 54 to 77% for systolic interarm differences ≥10 and ≥15 mmHg, respectively; specificities for simultaneous readings were higher (87–88 and 95–96%, respectively) than for sequential measurements (67 and 84%, respectively, for best case; 54 and 74% for worst case). A similar pattern was seen for diastolic interarm differences ≥10 mmHg (Table 2). Insufficient cases with a diastolic difference ≥15 mmHg were identified to permit further analysis (3/752). For all analyses, the negative predictive values of individual pairs for the reference standard interarm difference were high (range 97–99%), and in all combinations, correlations with the reference

Table 1—Comparison of people with diabetes and without diabetes (controls)

	Diabetes *n* = 726	Control *n* = 285	*P* value
Discrete variables*			
Sex (male)	421 (58)	124 (44)	<0.001
Smoking status			
Never	292 (40)	146 (51)	
Previous	351 (48)	109 (38)	0.005
Present	80 (11)	26 (9)	
Prevalence of hypertension	645 (89)	183 (64)	<0.001
Continuous variables†			
Age (years)	63.0 (68.1)	56.9 (13.3)	0.02
BMI (kg/m^2)	29.8 (5.5)	27.3 (4.1)	<0.001
Waist:hip ratio	0.94 (0.10)	0.87 (0.09)	<0.001
Right arm circumference (cm)	26.2 (11.0)	12.4 (15.0)	<0.001
Left arm circumference (cm)	26.5 (17.8)	11.6 (14.8)	<0.001
Alcohol (units/week)	5.5 (9.9)	7.0 (10.8)	0.07
Exercise (sessions/week)	4.8 (7.4)	5.4 (4.5)	0.14
HbA_{1c} (%)	7.5 (3.6)	6.7 (2.8)	<0.001
HbA_{1c} (mmol/mol)	58.8 (15.4)	39.1 (6.0)	<0.001
Total cholesterol (mmol/L)	4.3 (0.9)	5.8 (1.2)	<0.001
HDL cholesterol (mmol/L)	1.5 (0.6)	1.6 (0.6)	0.24
Glomerular filtration rate (mL/min/1.73 m^2)	69.7 (56.0)	51.9 (8.2)	<0.001
Systolic blood pressure (mmHg)	144.5 (18.0)	134.9 (17.3)	<0.001
Diastolic blood pressure (mmHg)	79.1 (10.2)	81.6 (9.3)	<0.001
Pulse pressure (mmHg)	65.4 (16.2)	53.3 (13.0)	<0.001
Absolute systolic interarm difference (mmHg)	4.6 (3.9)	3.8 (3.0)	<0.001
Absolute diastolic interarm difference (mmHg)	3.0 (3.3)	2.5 (2.8)	0.03

*Data are *n* (%). *P* value from Pearson χ^2. †Data are mean (SD). *P* value from *t* test.

standard were significant (*P* for Pearson's correlations <0.001).

Analysis of ROC plots showed any single pair of systolic interarm differences (simultaneous or sequential) to be able to predict the reference standard interarm difference. Areas under the curve ranged from 0.67 to 0.79 for systolic pairs (Supplementary Fig. 1) but were not significant for any diastolic pair in predicting a diastolic difference ≥10 mmHg (Table 2).

Prevalence

Mean prevalences of interarm differences fell with increasing numbers of pairs of simultaneous measurements averaged (χ^2 for trend, $P < 0.001$) (Supplementary Fig. 2). Where four pairs of readings were obtained, the prevalences in people with diabetes were 8.6% (95% CI 3.8–13.3) for systolic differences ≥10 mmHg and 2.3% (0–4.9) for ≥15 mmHg; corresponding diastolic figures were 1.9% (0–4.3) for ≥10 mmHg difference and 0.4% (0–1.4) for ≥15 mmHg difference. For control subjects, the corresponding prevalences were systolic 2.9% (0–7.1) ≥10 mmHg and 0.4% (0–2.0) for ≥ 15 mmHg and diastolic 3.4% (0–7.8) for ≥10 mmHg and 0.4% (0–2.0) for ≥15 mmHg (Supplementary Fig. 4). Further analysis was restricted to subjects with diabetes and four successfully recorded pairs of simultaneous readings. Sensitivity analyses according to type of diabetes were explored.

Cross-sectional Analysis

Cross-sectional associations of interarm difference with vascular morbidity were examined for the diabetic participants. Baseline demographics for subjects with and without systolic interarm differences ≥15 mmHg were similar; subjects with a difference ≥10 mmHg showed

Table 2—Comparison of individual pairs of interarm difference measures with reference standard (the mean of four simultaneous pairs of readings)

Pair of readings	Sensitivity	Specificity	Positive predictive value	Positive likelihood ratio	Negative predictive value	Negative likelihood ratio	Area under ROC curve	*P* value
Systolic interarm difference ≥10 mmHg								
Systolic difference (right–left) pair 1	0.76	0.87	0.30	5.96	0.98	0.27	0.73 (0.62–0.83)	<0.001
Systolic difference (right–left) pair 2	0.69	0.88	0.29	5.66	0.97	0.36	0.68 (0.57–0.79)	<0.001
Systolic difference (right–left) pair 3	0.63	0.87	0.26	4.73	0.97	0.43	0.67 (0.56–0.78)	<0.001
Systolic difference (right–left) pair 4	0.69	0.88	0.30	5.94	0.97	0.35	0.70 (0.60–0.81)	<0.001
Systolic right pair 1–left pair 2	0.76	0.67	0.14	2.33	0.98	0.35	0.70 (0.60–0.80)	<0.001
Systolic right pair 1–left pair 4	0.78	0.54	0.11	1.72	0.97	0.40	0.67 (0.58–0.77)	<0.001
Systolic interarm difference ≥15 mmHg								
Systolic difference (right–left) pair 1	0.62	0.95	0.18	12.63	0.99	0.40	0.79 (0.60–0.99)	<0.001
Systolic difference (right–left) pair 2	0.54	0.95	0.15	10.20	0.99	0.49	0.67 (0.45–0.88)	0.04
Systolic difference (right–left) pair 3	0.54	0.95	0.16	10.75	0.99	0.49	0.68 (0.46–0.89)	0.03
Systolic difference (right–left) pair 4	0.69	0.96	0.22	15.99	0.99	0.32	0.72 (0.51–0.93)	0.006
Systolic right pair 1–left pair 2	0.69	0.84	0.07	4.30	0.99	0.37	0.75 (0.58–0.93)	0.002
Systolic right pair 1–left pair 4	0.77	0.74	0.05	2.98	0.99	0.31	0.75 (0.57–0.93)	0.002
Diastolic interarm difference ≥10 mmHg								
Diastolic difference (right–left) pair 1	0.56	0.94	0.20	9.95	0.99	0.47	0.56 (0.36–0.76)	0.38
Diastolic difference (right–left) pair 2	0.33	0.96	0.19	9.41	0.98	0.69	0.54 (0.37–0.71)	0.59
Diastolic difference (right–left) pair 3	0.44	0.95	0.19	9.32	0.99	0.58	0.60 (0.42–0.78)	0.14
Diastolic difference (right–left) pair 4	0.33	0.95	0.14	6.61	0.98	0.70	0.63 (0.46–0.81)	0.06
Diastolic right pair 1–left pair 2	0.67	0.90	0.14	6.70	0.99	0.37	0.58 (0.39–0.77)	0.25
Diastolic right pair 1–left pair 4	0.72	0.86	0.12	5.30	0.98	0.32	0.59 (0.38–0.80)	0.20

differences in age, sex distribution, waist:hip ratio, and smoking habits. Drug history was similar apart from higher rates of use of calcium channel blockers and angiotensin-2 receptor antagonists with systolic interarm differences ≥10 mmHg; there was no overall difference in prevalence of hypertension with and without an interarm difference (Table 3). No differences were observed in the type of diabetes or in the handedness of subjects.

On univariate analysis, a systolic interarm difference ≥10 mmHg was associated with a greater prevalence of claudication and peripheral arterial disease at recruitment (odds ratio [OR] 3.1 [1.2–8.0]; $P = 0.03$). A systolic interarm difference ≥15 mmHg was associated with the presence of diabetic retinopathy (OR 6.5 [1.7–24.4]; $P = 0.003$) and a higher prevalence of chronic kidney disease (OR 5.4 [1.4–21.1]; $P = 0.03$). These associations remained on multivariate analysis, including terms for age, sex, waist:hip ratio, smoking status, and systolic blood pressure (OR for peripheral arterial disease with systolic interarm difference ≥10 mmHg was 3.4 [1.2–9.3], $P = 0.02$; ORs for retinopathy and chronic kidney disease with systolic interarm difference ≥15 mmHg were 5.7 [1.5–21.6], $P = 0.01$, and 7.0 [1.7–29.8], $P = 0.008$, respectively). Smoking, in association with peripheral arterial disease was the only significant covariable identified in the analyses. Additional analyses indicated that for differences ≥10 mmHg, the association with peripheral arterial disease was seen in type 2 diabetes (OR 4.4 [1.6–12.0]; $P = 0.008$) but not type 1 diabetes (no cases with condition and interarm difference ≥10 mmHg; therefore, OR could not be calculated). The association of retinopathy with differences ≥15 mmHg was also consistent for type 2 diabetes (OR 7.0 [1.4–35.0]; $P = 0.01$) but not type 1 diabetes (OR 4.1 [0.4–41.7]; $P = 0.31$). Conversely, chronic kidney disease remained more prevalent with an interarm difference ≥15 mmHg in type 1 diabetes (OR 11.8 [1.4–102.5]; $P = 0.05$) but not type 2 diabetes (OR 2.4 [0.3–20.4]; $P = 0.38$). Little evidence was found of associations between diastolic interarm difference status and morbidity. The SDs of the four right and left arm systolic and diastolic blood pressure measurements, one measure of blood pressure variability, showed some correlation with systolic and diastolic absolute interarm differences, respectively ($r = 0.29$ [$P < 0.05$] for left systolic pressures; $r = 0.09$–0.37 [$P < 0.01$] for other Pearson's correlations).

Survival Analysis

During the study period, median follow-up was 52.4 months (interquartile range 48.1–56.7). There were 12 (2.3%) cardiovascular deaths and 41 (8.0%) deaths from all causes. In crude analysis, cardiovascular mortality was higher with a systolic interarm difference ≥10 mmHg (HR 3.5 [1.0–13.0]; $P = 0.04$) and ≥15 mmHg (HR 9.0 [2.0 to 40.1]; $P = 0.001$) (Supplementary Fig. 3). There was no

Table 3—Baseline comparison in subjects with diabetes and systolic interarm differences ≥10 and ≥15 mmHg

	Interarm difference			Interarm difference		
	<10 mmHg $n = 470$	≥10 mmHg $n = 44$	*P* value	<15 mmHg $n = 502$	≥15 mmHg $n = 12$	*P* value
Characteristic						
Sex (female)	198 (42.1)	8 (18.2)	0.001†	205 (40.8)	1 (8.3)	0.31†
Age (years)	65.2 ± 12.0	60.1 ± 13.9	0.041*	64.9 ± 12.2	60.9 ± 13.0	0.28*
Systolic blood pressure (mmHg)	142.6 ± 16.1	146.0 ± 17.0	0.22*	142.8 ± 16.2	148.1 ± 15.9	0.87*
Diastolic blood pressure (mmHg)	78.7 ± 9.1	80.3 ± 10.8	0.34*	78.8 ± 9.2	79.4 ± 12.7	0.82*
Pulse pressure (mmHg)	63.9 ± 14.8	65.6 ± 14.5	0.47*	64.0 ± 14.8	68.7 ± 15.5	0.28*
BMI (kg/m^2)	29.1 ± 5.2	29.9 ± 4.3	0.23*	29.1 ± 5.1	30.5 ± 5.4	0.40*
Waist:hip ratio	0.93 ± 0.10	0.98 ± 0.11	0.003*	0.93 ± 0.10	0.99 ± 0.06	0.06*
Right midarm circumference (cm)	26.7 ± 9.9	24.5 ± 12.2	0.29*	26.4 ± 10.3	28.1 ± 3.7	0.62*
Left midarm circumference (cm)	27.4 ± 19.6	24.2 ± 12.4	0.17*	27.0 ± 19.3	28.3 ± 4.0	0.84*
HbA_{1c} (%)	7.4 ± 3.4	8.2 ± 4.3	0.75*	7.5 ± 3.5	8.3 ± 4.0	0.22*
HbA_{1c} (mmol/mol)	57.6 ± 13.7	65.9 ± 23.4	0.75*	58.2 ± 15.0	66.6 ± 19.7	0.22*
Current smoker	48 (10.2)	6 (13.6)	0.05†	53 (10.6)	1 (8.3)	0.56†
Previous smoker	212 (45.1)	28 (63.6)	0.05†	232 (46.2)	8 (66.7)	0.56†
Never smoked	206 (43.8)	10 (22.7)	0.05†	213 (42.4)	3 (25.0)	0.56†
Medication use§						
Angiotensin-2 receptor antagonist	24 (5.1)	8 (18.2)	0.003‡	30 (6.0)	2 (16.7)	0.17‡
Calcium channel blocker	77 (16.4)	16 (36.4)	0.001†	88 (17.6)	5 (41.7)	0.05‡
Antiplatelet	238 (50.6)	19 (43.2)	0.34†	250 (49.8)	7 (58.3)	0.56†
Fibrate	1 (0.2)	1 (2.3)	0.16‡	1 (0.2)	1 (8.3)	0.05‡
Statin	327 (69.7)	36 (81.8)	0.09†	252 (70.5)	10 (83.3)	0.52‡
Medical history‖						
Hypertension	409 (91.0)	39 (88.6)	0.76†	438 (87.3)	10 (83.3)	0.66‡
Chronic renal disease	28 (6.0)	4 (9.1)	0.34‡	29 (5.8)	3 (25.0)	0.03‡
Retinopathy	147 (31.3)	20 (45.5)	0.06†	158 (31.5)	9 (75.0)	0.003‡
PVD or claudication	23 (4.9)	6 (13.6)	0.03‡	29 (5.8)	0 (0)	0.49‡

Continuous variables presented as mean ± SD. Dichotomous variables presented as *n* (%). PVD, peripheral vascular disease. †*P* value from Pearson χ^2. **P* value from *t* test. §No differences were observed for use of ACE inhibitors, α-blockers, β-blockers, diuretics, nitrates, corticosteroids, or warfarin. ‡*P* value from Fisher's exact test. ‖No differences were observed for preexisting microalbuminuria, proteinuria, ischemic heart disease, coronary interventions, stroke, transient ischemic attack, amputations, or peripheral vascular interventions.

clear evidence that all-cause mortality was higher with systolic interarm differences, and no mortality differences were observed with diastolic interarm difference analyses.

CONCLUSIONS

Summary of Main Findings

This is the largest study of interarm differences in a population with diabetes. The prevalence of interarm differences suggested by previous reports (3,4) is confirmed (9% for systolic interarm difference ≥10 mmHg, 2.3% ≥15 mmHg); prevalences were significantly lower in the nondiabetic control population. The importance of repeated measurements to accurately define an interarm difference, and the utility of a single sequentially or simultaneously measured pair of blood pressure measurements in excluding a difference, are also demonstrated.

Systolic interarm differences were associated with presence of retinopathy, peripheral arterial disease, and chronic kidney disease in cross-sectional analysis. Preliminary prospective analyses suggest that systolic interarm differences ≥10 and ≥15 mmHg are also associated with increased cardiovascular mortality at an average of 4.5 years follow-up.

Strengths and Limitations of Study

We believe this to be the largest reported series of interarm difference measurements in people with diabetes; it uses a robust simultaneous measurement protocol and also presents the first prevalence data for an unselected community population using this methodology. This study presents early evidence of reduced cardiovascular survival in association with an interarm difference in diabetes. We observed a relatively small number of deaths in this period of follow-up, and nonfatal outcome data were not collected within the study protocol. These limitations precluded us from undertaking multivariate analyses in order to adjust for risk factors that might confound the comparison of those with and without an interarm blood pressure difference (e.g., mean blood pressure, smoking status, and prevalence of hypertension). The CIs around our estimated HRs are wide, and these prospective findings will require future reanalysis and confirmation.

The study protocol did not collect the same breadth of data for control subjects; therefore, the analyses for control subjects were limited to estimation of their prevalence of interarm differences. The failure rate of collection of pairs of blood pressure measurements was higher than we have previously experienced (4,15). Arrhythmias, predominantly atrial fibrillation, were a frequent cause of failure. This is a recognized problem with automated sphygmomanometers (7,18), and interarm difference studies often therefore list atrial fibrillation as an exclusion criterion, whereas the DARE protocol does not exclude subjects with arrhythmias; however, an adequate sample size was still achieved.

Baseline recording of participant cardiovascular and peripheral vascular medical history was based on self-reported events and may therefore have suffered from recall bias.

The ethnicity of the cohort recruited reflects the relative underrepresentation of ethnic minority groups in Devon compared with the U.K. population; therefore, some caution may be needed with generalization of these results to other diabetic cohorts.

Relationship to Existing Literature

The prevalences of interarm differences in people with diabetes reported here agree closely with previous reports of smaller cohorts (9% [*n* = 169] and 10% [*n* = 101] for systolic interarm differences ≥10 mmHg) (3,4). The prevalences reported for control subjects were lower than those from the diabetic recruits. Reports using simultaneous repeated measures in unselected general populations have not previously been published; four studies, all of convenience samples drawn from hospital inpatients and outpatients and visitors provide the closest comparison (19–22). The pooled prevalence of a systolic interarm difference ≥10 mmHg for these cohorts is 4.2% (3.0–5.3), which is comparable to the 2.9% control prevalence reported here. Two large community-based series using a four-limb device (VP-1000; Colin Co. Ltd, Komaki, Japan) to measure a single simultaneous interarm difference have reported prevalences for a systolic interarm difference ≥10 mmHg of 9.1% (*n* = 1,090, mean age 62.1 [11.1]) and 6.4% (*n* = 3,133, all subjects aged 60 years or over, mean age 69.0 [7.7]) (23,24); the use of a single simultaneous reading from devices of this type has not, however, been validated against simultaneous repeated measures (11,25). The prevalences of interarm differences were noted in this study to be higher where four pairs of readings were not obtained. Successful completion of the protocol was associated with lower systolic blood pressure and measures of obesity, which may also be relevant to the recorded prevalences; however, the findings do support previous evidence that a simultaneous repeated measurement protocol, such as that used here, is necessary for accurate identification of interarm differences in epidemiological study (11,26). Eguchi et al. (14) have previously demonstrated the correlation of interarm differences measured by simultaneous and sequential techniques, which corresponds with the findings presented here.

Prevalences are higher in the presence of hypertension (26) and in older age groups (22). These two factors may account for the differences in prevalences observed with and without diabetes in this study; without age- and blood-pressure-matched cohorts, it is not possible to determine whether diabetes per se is associated with an increased prevalence of interarm differences.

The cross-sectional association of a systolic interarm difference ≥10 mmHg with peripheral arterial disease is in keeping with the findings of our recent systematic review (1), and pooled analysis of the current findings with previous community-based studies using the same measurement techniques (4,15,27) gives ORs of 3.0 (1.5–6.2; I^2 = 0%) for a systolic interarm difference ≥10 mmHg and 3.6 (1.7–7.3; I^2 = 0%) for ≥15 mmHg. We found an association of a systolic interarm difference ≥15 mmHg with chronic kidney disease; increased levels of albuminuria have also recently been associated with a systolic interarm difference ≥10 mmHg in a smaller cohort (*n* = 314) with type 2 diabetes (28).

The preliminary mortality findings are based on small numbers of events up to the time of analysis but are also in keeping with our previous published findings and support the evidence that

an interarm difference is a marker of increased cardiovascular mortality (1,25). Peripheral arterial disease, a recognized risk factor for future cardiovascular events and mortality, has been assumed to be the pathological basis for an interarm difference in blood pressure (29). There is no direct radiological evidence from a general population such as that in the current study to confirm that this is the anatomical cause of an interarm difference (1). The differences observed may result from more diffuse stiffening in the arteries since structural changes in large arteries as a result of hypertension begin early in the course of the condition and are insidious, whereas symptomatic cardiovascular 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 blood pressure (30). Unevenly distributed stiffness could produce a measurable interarm difference; Su et al. have recently shown an association of a systolic difference ≥10 mmHg with elevated brachial-ankle pulse wave velocity, suggesting increased arterial stiffness (31). Increased blood pressure variability is a potential confounder of interarm difference and is associated with increased arterial stiffness (32). Different methods of measurement of blood pressure variability exist (33); however, the SD of blood pressure measurements is one simple method that correlates independently with mortality differences (34). The modest correlation of SDs of unilateral systolic and diastolic blood pressure measurements with interarm differences in the current study is in keeping with these findings.

Implications for Clinical Practice

The number of failed attempts to measure pairs of blood pressures brings into question the practicality of repeated simultaneous measures in clinical practice. Newer sphygmomanometers are equipped with algorithms to detect atrial fibrillation (35), which was a common reason for failure. However, time was evidently a factor during data collection, and this has been observed before (4). Machines that measure two (e.g., Microlife WatchBP Office) or four (e.g., Omron Colin VP-1000) limbs are now more readily available and may permit more practical assessment of interarm differences. They are, however, more costly than standard clinical sphygmomanometers. The findings presented here suggest that a single pair of measurements that can be feasibly made within routine practice can reliably rule subjects out of the need for further paired measurements; this may be a more practical first approach than resourcing simultaneous bilateral arm measurements for all subjects (12). Interpretation of ROC curves assumes that the sensitivity and specificity of a test are constant, whereas they may vary with population characteristics such as age or disease severity (36). The observed ROC curves displayed a nonconvex shape, which could imply caution is required in recommending a single pair of measurements for initial detection of an interarm difference (37). Therefore, prospective assessment of this approach is required.

The associations of interarm difference with peripheral arterial disease and with increased cardiovascular mortality suggest that detection of an interarm difference may define a subpopulation at high risk of vascular events (38). In therapeutic terms, there is no evidence to support any different intervention on detection of a difference, but in a health service of finite and shrinking resources, this may help to identify subjects who can most benefit from intensive lifestyle interventions.

Implications for Future Research

Southwest England has relatively low ethnic minority representation; therefore, these findings cannot be extrapolated to other diabetic populations such as South Asians, who are known to be at higher cardiovascular risk than the population studied here (39). Further studies of the measurement and implications of an interarm difference are therefore needed in such populations. The effect of the full protocol in reducing apparent prevalence suggests that future epidemiological studies of interarm difference must adopt a similar robust repeated simultaneous measurements approach to avoid overestimation of prevalence (40).

The mortality findings presented here are based on small numbers of events and should therefore be regarded as preliminary. We intend to review the prospective mortality implications after a longer period of follow-up to confirm the associations demonstrated.

We only have anecdotal evidence as to why clinicians do not measure both arms (4). Why primary care practitioners do not follow current guidance to measure blood pressure in both arms is also unknown, and no existing research has explored the barriers and facilitators of bilateral blood pressure measurement. The practicality of any protocol for interarm difference measurement will influence its degree of implementation; the findings presented here suggest that a pragmatic sequential pair of measurements could be a simple first test. This needs to be assessed in future measurement studies, and we also recognize the need to undertake a detailed qualitative exploration of barriers and facilitators of measurement of both arms.

There is also a need for a health economic assessment of the costs and benefits of identifying interarm differences in terms of improving detection and management of hypertension.

Acknowledgments. The authors thank Anita Hill and Gillian Baker (NIHR Exeter Clinical Research Facility, Royal Devon and Exeter Hospital and University of Exeter Medical School, Exeter, Devon, U.K.) for their assistance and support with the DARE data and project management. The authors are also indebted to research nurses, Danielle Cox, Gayle Githens-Mazer, Kirsty Wensley, Stephanie Estcourt, Lorraine Scaiffe, and Jane Rowley (NIHR Exeter Clinical Research Facility, Royal Devon and Exeter Hospital and University of Exeter Medical School, Exeter, Devon, U.K.) who recruited the patients and undertook the blood pressure measurements and Andrew Hattersley, DARE principal investigator (University of Exeter Medical School, Exeter, Devon, U.K.) for his advice and encouragement. The study was approved by the North and East Devon Local Research Ethics Committee (study no. 2002/7/118).

Funding. DARE is supported by the National Institute for Health Research through the NIHR Exeter Clinical Research Facility and the Diabetes Research Network. Initially, DARE in Exeter was grant funded by the Wellcome Trust. C.E.C. was supported by grants from the Scientific Foundation Board of the Royal College of General Practitioners (grant SFB-2009-06) and from the South West GP Trust. O.C.U. received funding from the NIHR Collaboration for Leadership in Applied Health Research and Care (CLAHRC) South West Peninsula.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. C.E.C. conceived the study, designed the blood pressure data collection protocol, and undertook the analysis. A.M.S. supervised and participated in the data collection.

R.S.T. advised on the study design, supervised the analysis, and gave expert medical statistical advice. A.C.S. and J.L.C. advised on study design and supervised the work. O.C.U. supervised the analysis and gave expert medical statistical advice. All authors contributed to the manuscript. All authors agreed on the final manuscript. C.E.C. is the guarantor of this work and, as such, 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.

Prior Presentation. These findings were presented orally at the 23rd Scientific Meeting of the European Society of Hypertension, Milan, Italy, 14–17 June 2013 (abstract in *J Hypertens* 2013;31[Suppl. A]:e92) and at the British Hypertension Society Annual Scientific Meeting, London, U.K., 9–10 September 2013 (abstract in *J Hum Hypertens* 2013;27[Suppl. 1]:s11).

References

1. 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
2. Davidson MH. Global risk management in patients with type 2 diabetes mellitus. Am J Cardiol 2007;99(4A):41B–50B
3. Kleefstra N, Houweling ST, Meyboom-de Jong B, Bilo HJ. [Measuring the blood pressure in both arms is of little use; longitudinal study into blood pressure differences between both arms and its reproducibility in patients with diabetes mellitus type 2]. Ned Tijdschr Geneeskd 2007;151:1509–1514
4. Clark CE, Greaves CJ, Evans PH, Dickens A, Campbell JL. Inter-arm blood pressure difference in type 2 diabetes: a barrier to effective management? Br J Gen Pract 2009;59:428–432
5. Kuwajima I, Hoh E, Suzuki Y, Matsushita S, Kuramoto K. Pseudohypertension in the elderly. J Hypertens 1990;8:429–432
6. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998;317:703–713
7. National Institute for Health and Clinical Excellence. *Hypertension: The clinical management of primary hypertension in adults, CG127*. London, National Institute for Health and Clinical Excellence, 2011
8. Mancia G, Fagard R, Narkiewicz K, et al.; Task Force Members. 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
9. Heneghan C, Perera R, Mant D, Glasziou P. Hypertension guideline recommendations in general practice: awareness, agreement, adoption, and adherence. Br J Gen Pract 2007;57:948–952
10. Parker E, Glasziou P. Use of evidence in hypertension guidelines: should we measure in both arms? Br J Gen Pract 2009;59:e87–e92
11. Verberk WJ, Kessels AGH, Thien T. Blood pressure measurement method and inter-arm differences: a meta-analysis. Am J Hypertens 2011;24:1201–1208
12. Clark CE. Inter-arm blood pressure measurement needs to be practical and accurate. Am J Hypertens 2011;24:1189–1190
13. 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
14. 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
15. Clark CE, Campbell JL, Powell RJ, Thompson JF. The inter-arm blood pressure difference and peripheral vascular disease: cross-sectional study. Fam Pract 2007;24:420–426
16. Tabachnick BG, Fidell LS. *Using multivariate statistics*. Boston, Allyn and Bacon, 2001
17. Schoenfeld D. Partial residuals for the proportional hazards regression model. Biometrika 1982;69:239–241
18. Stergiou GS, Kollias A, Destounis A, Tzamouranis D. Automated blood pressure measurement in atrial fibrillation: a systematic review and meta-analysis. J Hypertens 2012;30:2074–2082
19. Karagiannis A, Tziomalos K, Krikis N, Sfikas G, Dona K, Zamboulis C. The unilateral measurement of blood pressure may mask the diagnosis or delay the effective treatment of hypertension. Angiology 2005;56:565–569
20. Orme S, Ralph SG, Birchall A, Lawson-Matthew P, McLean K, Channer KS. The normal range for inter-arm differences in blood pressure. Age Ageing 1999;28:537–542
21. Harrison EG Jr, Roth GM, Hines EA Jr. Bilateral indirect and direct arterial pressures. Circulation 1960;22:419–436
22. Fotherby MD, Panayiotou B, Potter JF. Age-related differences in simultaneous interarm blood pressure measurements. Postgrad Med J 1993;69:194–196
23. Kimura A, Hashimoto J, Watabe D, et al. Patient characteristics and factors associated with inter-arm difference of blood pressure measurements in a general population in Ohasama, Japan. J Hypertens 2004;22:2277–2283
24. 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
25. Clark CE. Four-limb blood pressure measurement: a research tool looking for clinical use. Hypertension 2013;61:1146–1147
26. Clark CE, Campbell JL, Evans PH, Millward A. Prevalence and clinical implications of the interarm blood pressure difference: A systematic review. J Hum Hypertens 2006;20:923–931
27. Igarashi Y, Chikamori T, Tomiyama H, et al. Clinical significance of inter-arm pressure difference and ankle-brachial pressure index in patients with suspected coronary artery disease. J Cardiol 2007;50:281–289
28. 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
29. Clark CE. Difference in blood pressure between arms might reflect peripheral vascular disease. BMJ 2001;323:399–400
30. Williams B. Hypertension in the young: preventing the evolution of disease versus prevention of clinical events. J Am Coll Cardiol 2007;50:840–842
31. Su HM, Lin TH, Hsu PC, et al. Association of interarm systolic blood pressure difference with atherosclerosis and left ventricular hypertrophy. PLoS ONE 2012;7:e41173
32. Fukui M, Ushigome E, Tanaka M, et al. Home blood pressure variability on one occasion is a novel factor associated with arterial stiffness in patients with type 2 diabetes. Hypertens Res 2013;36:219–225
33. Parati G, Ochoa JE, Lombardi C, Bilo G. Assessment and management of blood-pressure variability. Nat Rev Cardiol 2013;10:143–155
34. Dawson SL, Manktelow BN, Robinson TG, Panerai RB, Potter JF. Which parameters of beat-to-beat blood pressure and variability best predict early outcome after acute ischemic stroke? Stroke 2000;31:463–468
35. Verberk WJ, de Leeuw PW. Accuracy of oscillometric blood pressure monitors for the detection of atrial fibrillation: a systematic review. Expert Rev Med Devices 2012;9:635–640
36. Bewick V, Cheek L, Ball J. Statistics review 13: receiver operating characteristic curves. Crit Care 2004;8:508–512
37. Pesce LL, Metz CE, Berbaum KS. On the convexity of ROC curves estimated from radiological test results. Acad Radiol 2010;17:960–968, e4
38. Clark CE, Taylor RS, Shore AC, Campbell JL. The difference in blood pressure readings between arms and survival: primary care cohort study. BMJ 2012;344:e1327
39. Chaturvedi N, Fuller JH. Ethnic differences in mortality from cardiovascular disease in the UK: do they persist in people with diabetes? J Epidemiol Community Health 1996;50:137–139
40. Verberk WJ, Kessels AG, Thien T. Blood pressure measurement method and inter-arm differences: a meta-analysis. Am J Hypertens 2011;24:1201–1208