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Cardiovascular Diabetology

RESEARCH

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Relationships between ankle blood pressure indices and major adverse cardiovascular events in people with and without type 2 diabetes

Kamel Mohammedi[1,2*], Marie Pigeyre[1], Jackie Bosch[1,3], Salim Yusuf[1] and Hertzel C. Gerstein[1]

Abstract

Background The relationship between ankle blood pressure (BP) and cardiovascular disease remains unclear. We examined the relationships between known and new ankle BP indices and major cardiovascular outcomes in people with and without type 2 diabetes.

Methods We used data from 3 large trials with measurements of ankle systolic BP (SBP), ankle-brachial index (ABI, ankle SBP divided by arm SBP), and ankle-pulse pressure difference (APPD, ankle SBP minus arm pulse pressure). The primary outcome was a composite of cardiovascular mortality, myocardial infarction, hospitalization for heart failure, or stroke. Secondary outcomes included death from cardiovascular causes, total (fatal and non-fatal) myocardial infarction, hospitalization for heart failure, and total stroke.

Results Among 42,929 participants (age 65.6 years, females 31.3%, type 2 diabetes 50.1%, 53 countries), the primary outcome occurred in 7230 (16.8%) participants during 5 years of follow-up (19.4% in people with diabetes, 14.3% in those without diabetes). The incidence of the outcome increased with lower ankle BP indices. Compared with people whose ankle BP indices were in the highest fourth, multivariable-adjusted hazard ratios (HRs, 95% CI) of the outcome for each lower fourth were 1.05 (0.98–1.12), 1.17 (1.08–1.25), and 1.54 (1.54–1.65) for ankle SBP; HR 1.06 (0.99–1.14), 1.26 (1.17–1.35), and 1.48 (1.38–1.58) for ABI; and HR 1.02 (0.95–1.10), 1.15 (1.07–1.23), and 1.48 (1.38–1.58) for APPD. The largest effect size was noted for ankle SBP (HRs 1.05 [0.90–1.21], 1.21 [1.05–1.40], and 1.93 [1.68–2.22]), and APPD (HRs 1.08 [0.93–1.26], 1.30 [1.12–1.50], and 1.97 [1.72–2.25]) with respect to hospitalization for heart failure, while only a marginal association was observed for stroke. The relationships were similar in people with and without diabetes (all p for interaction > 0.05).

Conclusions Inverse and independent associations were observed between ankle BP and cardiovascular events, similarly in people with and without type 2 diabetes. The largest associations were observed for heart failure and the smallest for stroke. Including ankle BP indices in routine clinical assessments may help to identify people at highest risk of cardiovascular outcomes.

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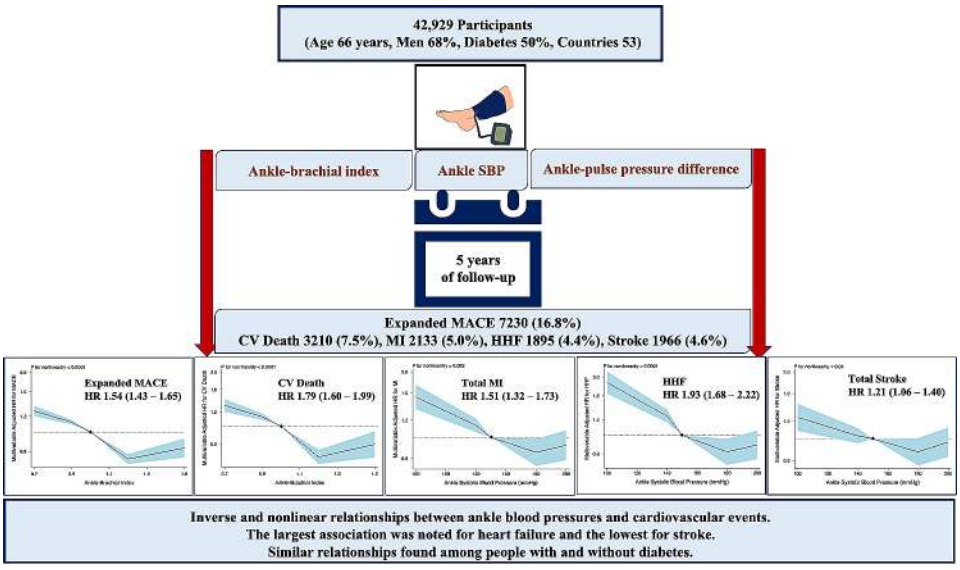
Graphical abstract Ankle blood pressure indices and incidence of major cardiovascular outcomes. Expanded MACE, a composite of death from cardiovascular causes, myocardial infarction,hospitalization for heart failure, or stroke. BP, blood pressure; CV, cardiovascular; HHF, hospitalization for heart failure; HR, Hazard ratio (for the lowest fourth of blood pressure indice compared to the highest); MACE, major adverse cardiovascular events; MI, myocardial infarction; Total, fatal and non-fatal MI or stroke.



Keywords Ankle, Blood pressure, Cardiovascular disease, Cardiovascular mortality, Diabetes, Heart failure, Myocardial infarction, Stroke

Background

High blood pressure is a major modifiable risk factor for incident cardiovascular disease (CVD) and mortality [1–6]. The vast majority of blood pressure research has focused on arm measurements of systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse pressure (i.e., the difference between SBP and DBP), which have been reported to predict CVD [2, 7, 8] Pulse pressure may provide additional prognostic information beyond SBP [9], it reflects arterial compliance, cardiac output and peripheral vascular resistance [10]. The ankle BP is not commonly measured, and the optimal ankle BP measurement as well as the link of ankle BP to cardiovascular outcomes remains poorly understood. Moreover, most of research related to ankle BP has focused on the ankle brachial index (ABI, the ratio of ankle SBP to arm SBP). Although this index is recommended as a screening test for peripheral artery disease (PAD) [11–14], it has also been associated with CVD and mortality [12, 15, 16].

We have recently used data from three large studies to assess the relationship between various ankle BP indices and PAD (non-traumatic lower-limb amputation due to vascular disease, or lower-extremity arterial revascularization), and identified that three indices, ankle SBP, ABI, and the ankle-pulse pressure difference (APPD, calculated as the difference between ankle SBP and arm pulse pressure), were the best predictors of PAD, total mortality, or the composite of either PAD or death, with lower values predicting a higher incidence [17]. In the present study, we sought to examine the relationships between those ankle BP indices and the incidence of major cardiovascular outcomes, a composite of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure, using the same pooled population study including people with and without type 2 diabetes.

Methods

Participants

This is a cohort analysis of participants from three trials: the ONgoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), the Telmisartan Randomised AssessmeNt Study in ACE intolerant subjects with cardiovascular disease (TRANSCEND) trial (ClinicalTrials.gov, number NCT00153101), and the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial (ClinicalTrials.gov number, NCT00069784). The details of participants in the three studies have been previously published [18–21]. Briefly, ONTARGET and TRANSCEND trials

enrolled participants with a history of CVD, PAD, or type 2 diabetes with evidence of end organ damage (e.g., kidney or retinal complication). In ONTARGET trial, 25,620 participants tolerant to angiotensin-converting enzyme (ACE)-inhibitors were randomly assigned to ramipril 10 mg daily, telmisartan 80 mg daily, or the combination of both. Whereas, 5926 patients who could not tolerate ACE-inhibitors were assigned to either telmisartan 80 mg daily or matching placebo in the parallel TRANSCEND trial. ORIGIN was a 2-by-2 factorial randomized controlled trial, which tested the effect of titrated basal insulin glargine versus standard care, and of n–3 fatty-acid supplements versus placebo on cardiovascular outcomes in 12,537 participants with dysglycemia. ORIGIN involved people aged 50 years or older with either prediabetes (impaired glucose tolerance or impaired fasting glucose) or early type 2 diabetes, with use of no more than one oral glucose-lowering drug, in addition to other CVD or cardiovascular risk factors.

The 3 study protocols were approved by the ethics committee at each study site, and all participants provided written informed consent. The protocols and results of the 3 trials have been published previously [18–21]. The present study was conducted according to the STROBE guidelines.

Among a total of 44,083 participants, 1154 participants without data regarding ankle BP at baseline (or other missing values) were excluded, with 42,929 participants included in the present analysis (ORIGIN, 12,306; ONTARGET, 24853; and TRANSCEND, 5770 participants). Characteristics of participants with missing and available data are shown in Additional file Table S1.

Measurements of arm and ankle blood pressures

Both right and left arm SBP and DBP were measured in the same way in all three trials after 5 min of rest in a sitting position, using a validated automated BP monitors (*OMRON HEM-711DLXCAN, OMRONHEALTHCARE Inc.*, Lake Forrest, Illinois, USA in ORIGIN; and *OMRON model HEM 757, OMRON Kyoto*, Japan in ONTARGET and TRANSCEND) [22, 23]. Arm BP was measured once in ONTARGET and TRANSCEND, and twice (at least 5 min apart) in ORIGIN, and the average of the 2 values were used. Then, the highest measures of the 2 arms were used for statistical analyses, and for computation of pulse pressure and ankle-brachial indices. The pulse pressure was computed as arm SBP minus arm DBP. Right and left ankle SBP were measured once using the same device (within each study), with the appropriate cuff size, in a supine position for more than 5 min, after removing shoes and stockings so that the ankles were bared to mid-calf. We used the average value of the BP measures in the two ankles for statistical analyses, and to calculate ankle-brachial indices. The ABI was calculated as ankle SBP divided by arm SBP, and the APPD as ankle SBP minus arm pulse pressure.

Outcomes

The primary outcome was expanded major adverse cardiovascular events (MACE), a composite of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure. The secondary outcomes included death from cardiovascular causes, total (fatal and non-fatal) myocardial infarction, hospitalization for heart failure, and total stroke. All outcomes were adjudicated by independent endpoint committees for each trial using standard definitions.

Statistical analysis

We used pooled individual patient-level data from the 3 studies for all analyses, with systematic adjustment for study. Continuous variables were expressed as means ± standard deviations (SD), or as medians with the 25^{th} and 75^{th} percentiles for those with a skewed distribution. Categorical variables were expressed as the number of patients with the corresponding percentage. Characteristics of participants at baseline were compared using the chi-square test, ANOVA, or Wilcoxon tests. Correlations between BP indices were assessed using Pearson test.

The association between ankle BP indices and outcomes were assessed using Cox proportional hazards survival regression models. The proportional hazards assumption was checked by visual inspection of log-log survival plots.

Hazard ratios (HRs) and 95% confidence intervals (CI), were computed for outcomes according to splines of ankle BP indices using the following knots as previously reported [17]: 100, 140, 180 and 200 mmHg for ankle SBP (with 150 mmHg as the reference value); 0.7, 0.9, 1.2, and 1.5 for ABI (with 1.0 as the reference value); and 40, 60, 100 and 140 mmHg for APPD (with 80 mmHg as the reference value). Nonlinearity was tested by comparing the spline models with the linear models, using likelihood ratio tests.

HRs (95% CI) were also computed for outcomes by ankle BP indices categorized into four groups (i.e., fourths) using quartiles: ankle SBP (<140, 140–156, 156–172, and ≥172 mmHg), ABI (<1, 1–1.1, 1.1–1.2, and ≥1.2), and APPD (<80, 80–95, 95–110, and ≥110 mmHg). HRs (95% CI) were computed for the lowest groups compared to the highest fourth. Associations between ankle BP indices and outcomes were performed in the whole cohort (3 pooled studies), and in people with and without type 2 diabetes. We tested the interaction between ankle BP indices and the baseline history of type 2 diabetes in their associations with the outcomes,

by including the multiplicative interaction terms into the multivariable Cox models.

We also compute HRs (95% CI) of outcomes by the highest fourths compared to the lowest of arm SBP (<130, 130–142, 142–155, and ≥155 mmHg), DBP (<75, 75–82, 82–90, and ≥90 mmHg), and pulse pressure (<50, 50–60, 60–70, and ≥70 mmHg).

HRs were adjusted for sex, age, study membership, ethnic group, history of type 2 diabetes (except for analyses in people with and without diabetes), hypertension, CVD, and PAD, current and former smoking, LDL cholesterol, HDL cholesterol, estimated glomerular filtration rate (eGFR, computed using the Chronic Kidney Disease Epidemiology Collaboration equation), the number of used antihypertensive drugs, the use of statin, acetylsalicylic acid or antiplatelet treatments, as well as arm SBP (for ankle SBP analyses) or ankle SBP (for arm BP analyses).

Statistics were calculated by using SAS software version 9.4 (SAS Institute; www.sas.com), and Stata software version 15 (StataCorp; www.stata.com). Two-sided *p* values < 0.05 were considered significant.

Results

Characteristics of participants at baseline

Among 42,929 participants of mean age 65.6 ± 7.5 years, 31.3% were female, and 67.2% were white (Additional file Table S1). A history of hypertension, CVD, and PAD was present at baseline in 72.8%, 61.2%, and 5.1% of participants, respectively.

A history of type 2 diabetes was noted at baseline in 21,484 (50.1%) participants. The Additional file Table S2 shows baseline characteristics of participants with and without type 2 diabetes. Arm and ankle BP indices (except ABI) were statistically higher in people with type 2 diabetes compared with those without diabetes. The mean (±SD) arm SBP, DBP, pulse pressure, ankle SBP, APPD, and ABI were 141 ± 18 mmHg, 82 ± 11 mmHg, 58 ± 14 mmHg, 152 ± 25 mmHg, 94 ± 25 mmHg, and 1.09 ± 0.17, respectively in people without diabetes. They were 145 ± 19 mmHg, 83 ± 11 mmHg, 62 ± 15 mmHg, 156 ± 27 mmHg, 95 ± 28 mmHg, and 1.09 ± 0.19, respectively in people with diabetes.

Correlations between arm and ankle blood pressure indices

The correlations between different arm and ankle BP indices are shown in the Additional file Table S3. The correlations between arm and ankle BP indices were weak. The highest correlations were observed among the ankle BP indices. APPD shows the highest correlation with ankle SBP (r^2 0.72, 95% CI 0.71–0.73), and with ABI (r^2 0.78, 95% CI 0.77–0.79).

Incidence of expanded MACE

During a median (25^{th}, 75^{th} percentiles) follow-up of 5.0 (4.5, 5.7) years (i.e., 201,107 person-years), expanded MACE occurred in 7230 (16.8%) participants, corresponding to an incidence rate of 3.60 (95% CI 3.51–3.68) per 100 person-years (Additional file Table S1). The incidence rate of expanded MACE was 3.17 (95% CI 3.06–3.28) per 100 person-years in people without type 2 diabetes, and 4.0 (95% CI 3.87–4.11) per 100 person-years in those with type 2 diabetes (Additional file Table S2). Characteristics of participants at baseline according to the incidence of expanded MACE during follow-up are summarized in Table 1 for people with and without type 2 diabetes. Participants who experienced expanded MACE during follow-up had a higher arm SBP and pulse pressure, and a lower arm DBP, ankle SBP, ABI and APPD than those who remained free of this outcome.

Arm blood pressure indices and the incidence of primary and secondary outcomes

The relationships between arm BP indices and outcomes are shown for the whole cohort in the Additional file Fig. S1 and S2. High arm SBP and pulse pressure were associated with a higher incidence of expanded MACE. Thus, compared to people whose arm BP indices were in the lowest fourth, multivariable adjusted HRs (95% CI) for each higher fourth were 1.07 (95% CI 0.99–1.14), HR 1.16 (95% CI 1.08–1.24), and HR 1.39 (95% CI 1.29–1.49) for SBP, and HR 1.03 (95% CI 0.96–1.10), HR 1.14 (95% CI 1.06–1.22), and HR 1.29 (95% CI 1.20–1.38) for pulse pressure, respectively. The strongest associations were noted for stroke (Additional file Fig. S2, Panel D).

Ankle blood pressure indices and the incidence of primary outcome

The relationships between splines of ankle BP indices and the incidence of expanded MACE are illustrated in the whole cohort (Additional file Fig. S3) and in people with and without type 2 diabetes (Fig. 1). Each ankle BP indice had a nonlinear inverse relationship with incident expanded MACE (all *p* for nonlinearity ≤ 0.0001). Significant relationships were also observed for categories of ankle BP indices, with lower levels associated with higher HRs (Additional file Fig. S4). Thus, compared to people whose ankle BP indices were in the highest fourth, multivariable adjusted HR (95% CI) for each lower fourth were 1.05 (95% CI 0.98–1.12), HR 1.17 (95% CI 1.08–1.25), and HR 1.54 (95% CI 1.43–1.65) for ankle SBP; HR 1.06 (95% CI 0.99–1.14), HR 1.26 (95% CI 1.17–1.35), and HR 1.48 (95% CI 1.38–1.58) for ABI; and HR 1.02 (95% CI, 0.95–1.10), HR 1.15 (95% CI, 1.07–1.23), and HR 1.48 (95% CI, 1.38–1.58) for APPD (Additional file Fig. S4). As shown in Figs. 1 and 2, the shape and magnitude of the relationships between ankle BP indices and expanded MACE

Table 1 Characteristics of participants at baseline by incidence of expanded major adverse Cardiovascular events during follow-up in people with and without type 2 diabetes

	Participants without type 2 diabetes			Participants with type 2 diabetes		
	Expanded MACE		*p*	Expanded MACE		*p*
	No	Yes		No	Yes	
N (%)	18,374 (85.7)	3071 (14.3)		17,325 (80.6)	4159 (19.4)	
Female	4961 (27.0)	713 (23.2)	< 0.0001	6445 (37.2)	1314 (31.6)	< 0.0001
Age (years)	66.1 ± 7.3	68.5 ± 7.9	< 0.0001	64.3 ± 7.3	66.9 ± 7.7	< 0.0001
White European	13,640 (74.2)	2267 (73.8)	0.62	10,402 (60.0)	2554 (61.4)	0.11
History of hypertension	11,827 (64.4)	2159 (70.3)	< 0.0001	13,807 (79.7)	3447 (82.9)	< 0.0001
Prior cardiovascular disease	12,735 (69.3)	2386 (77.7)	< 0.0001	8556 (49.4)	2606 (62.7)	< 0.0001
Prior peripheral artery disease	945 (5.1)	211 (6.9)	< 0.0001	758 (4.4)	267 (6.4)	< 0.0001
Current smoking	2276 (12.4)	475 (15.5)	< 0.0001	1862 (10.8)	558 (13.4)	< 0.0001
History of former smoking	9646 (52.5)	1628 (53.0)		7795 (45.0)	1943 (46.7)	
Body mass index (kg/m^2)	27.7 ± 4.3	27.6 ± 4.6	0.38	29.5 ± 5.1	29.3 ± 5.2	0.04
Arm SBP (mmHg)	140 ± 18	142 ± 19	< 0.0001	144 ± 19	146 ± 21	< 0.0001
Arm DBP (mmHg)	82 ± 10	81 ± 11	0.01	83 ± 11	82 ± 12	0.01
Pulse pressure (mmHg)	58 ± 14	60 ± 15	< 0.0001	61 ± 15	64 ± 16	< 0.0001
Ankle SBP (mmHg)	153 ± 25	149 ± 28	< 0.0001	157 ± 26	153 ± 31	< 0.0001
Ankle-brachial index	1.10 ± 0.17	1.06 ± 0.19	< 0.0001	1.10 ± 0.18	1.05 ± 0.21	< 0.0001
APPD (mmHg)	95 ± 25	89 ± 28	< 0.0001	96 ± 27	89 ± 31	< 0.0001
LDL cholesterol (mmol/l)	2.92 ± 0.97	3.02 ± 1.01	< 0.0001	2.91 ± 1.02	3.01 ± 1.06	< 0.0001
HDL cholesterol (mmol/l)	1.28 ± 0.41	1.26 ± 0.41	0.03	1.21 ± 0.36	1.18 ± 0.35	< 0.0001
eGFR (ml/min/1.73 m^2)	72 ± 16	68 ± 18	< 0.0001	74 ± 18	67 ± 19	< 0.0001
Use of antihypertensive drugs	18,121 (98.6)	3020 (98.3)	0.22	16,208 (93.6)	3968 (95.4)	< 0.0001
Number of antihypertensive drugs	2.8 ± 1.0	2.7 ± 1.0	< 0.0001	2.2 ± 1.1	2.3 ± 1.1	0.0003
Use of statins	12,089 (65.8)	1805 (58.8)	< 0.0001	9080 (52.4)	2111 (50.8)	0.06
Use of ASA or antiplatelet drugs	18,009 (98.0)	3001 (97.7)	0.29	14,526 (83.8)	3584 (86.2)	0.0002

Categorical and continuous variables are expressed as n (%) and as mean ± SD, respectively. Comparisons were performed using x^2 test and ANOVA tests. MACE, major adverse cardiovascular events; SBP, systolic blood pressure; DBP, diastolic blood pressure; PAD, peripheral artery disease; APPD, ankle-pulse pressure difference; eGFR, estimated glomerular filtration rate; ASA, acetylsalicylic acid

were similar in people with and without type 2 diabetes (all *p* for interaction > 0.05).

Ankle blood pressure indices and the incidence of secondary outcomes

During the study period, cardiovascular mortality, total myocardial infarction, hospitalization for heart failure, and total stroke occurred in 3210 (7.5%), 2133 (5.0%), 1895 (4.4%), and 1966 (4.6%) participants, corresponding to the incidence rates of 1.51 (95% CI 1.46–1.56), 1.03 (95% CI 0.98–1.07), 0.91 (95% CI 0.87–0.95), and 0.94 (95% CI 0.90–0.98) per 100 person-years, respectively. The incidence rates of secondary outcomes were statistically higher in people with type 2 diabetes compared with those without diabetes, except for myocardial infarction, which was similar between groups (Additional file Table S2). Overall, inverse and nonlinear relationships were observed between each ankle BP indice and cardiovascular mortality, fatal and non-fatal myocardial infarction, and hospitalization for heart failure (all *p* for nonlinearity < 0.05), with lower levels associated with higher HRs (Additional file Fig. S5). The largest effect size was noted for hospitalization for heart failure. Hence, compared to people whose ankle BP indices were in the highest fourth, multivariable adjusted HRs of hospitalization for heart failure for each lower fourth were 1.05 (95% CI 0.90–1.21), HR 1.21 (95% CI 1.05–1.40), and HR 1.93 (95% CI 1.68–2.22) for ankle SBP; HR 0.90 (95% CI 0.77–1.05), HR 1.23 (95% CI 1.07–1.41), and HR 1.64 (95% CI 1.44–1.87) for ABI; and HR 1.08 (95% CI 0.93–1.26), HR 1.30 (95% CI 1.12–1.50), and HR 1.97 (95% CI 1.72–2.25) for APPD (Additional file Fig. S6, Panel C). Whereas, the smallest associations were observed for fatal and non-fatal stroke. Compared to people whose ankle BP indices were in the highest fourth, multivariable adjusted HRs of total stroke for each lower fourth were 1.04 (95% CI 0.92–1.18), HR 1.11 (95% CI 0.97–1.27), and HR 1.21 (95% CI 1.06–1.40) for ankle SBP; HR 1.29 (95% CI 1.12–1.48), HR 1.40 (95% CI 1.22–1.60), and HR 1.50 (95% CI 1.31–1.72) for ABI; and HR 1.07 (95% CI 0.94–1.22), HR 0.99 (95% CI 0.87–1.13), and HR 1.16 (95% CI 1.02–1.32) for APPD (Additional file Fig. S6, Panel D). The relationships between ankle BP indices and secondary outcomes for people with and without diabetes are shown in Fig. 3. The magnitude of these relationships was

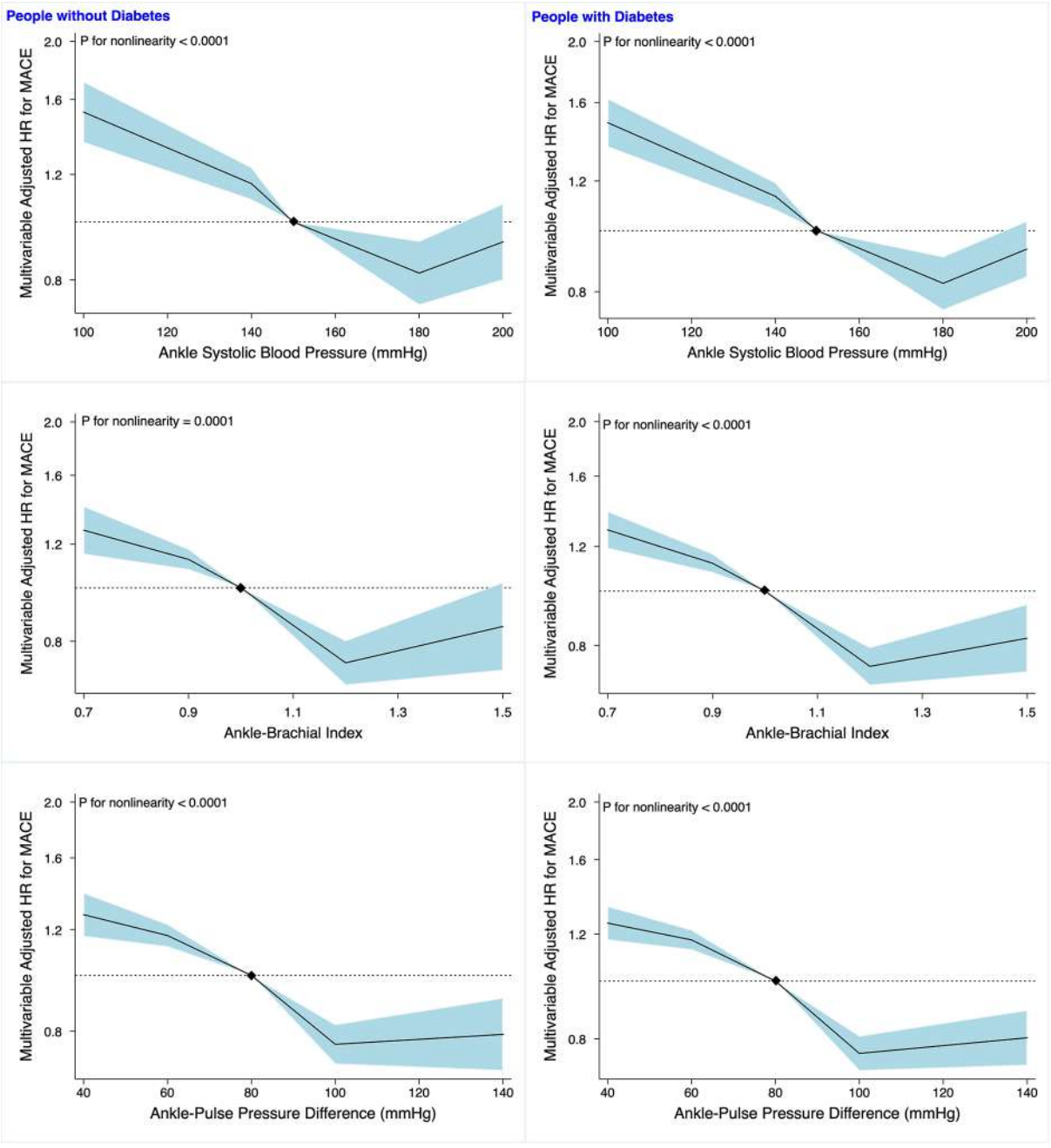


Fig. 1 Risk of primary outcome during follow-up by splines of ankle blood pressure indices at baseline in people with and without type 2 diabetes. Multivariable-adjusted hazard ratios (HR, solid line) and 95% confidence intervals (shaded region) for expanded major adverse cardiovascular events (MACE) during follow-up according to splines of ankle BP indices at baseline (as continuous variables) compared to a reference value (diamond) as described in Methods. Y axes are log scaled. Hazard ratios were adjusted for baseline age, sex, study membership, ethnic group, history of hypertension, CVD, and peripheral artery disease, current and former smoking, LDL cholesterol, HDL cholesterol, estimated glomerular filtration rate, the number of used antihypertensive drugs, the use of statin, acetylsalicylic acid or antiplatelet treatments, and arm SBP (for ankle SBP)

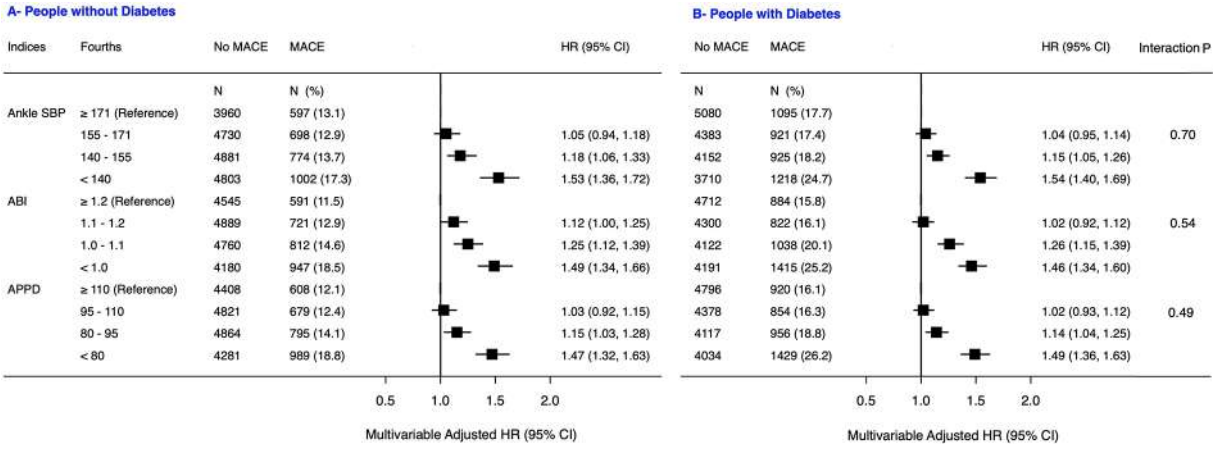


Fig. 2 Risk of primary outcome during follow-up by categories of ankle blood pressure indices at baseline in people with and without type 2 diabetes. Data presented as number of participants without and with (%) expanded major adverse cardiovascular events (MACE). Hazard ratio (HR, 95% CI) for expanded MACE during follow-up according to fourths of ankle BP indices (expressed as mmHg, except for ankle-brachial index). HRs were adjusted for baseline age, sex, study membership, ethnic group, history of hypertension, CVD, and peripheral artery disease, current and former smoking, LDL cholesterol, HDL cholesterol, estimated glomerular filtration rate, the number of used antihypertensive drugs, the use of statin, acetylsalicylic acid or antiplatelet treatments, and arm SBP (for ankle SBP). Interaction tested between history of type 2 diabetes and ankle BP indices in their associations with the primary outcome. SBP, systolic blood pressure; ABI, ankle-brachial index; APPD, ankle-pulse pressure difference

similar in people with and without type 2 diabetes (all p for interaction > 0.05).

Discussion

In this analysis of data from 42,929 people with and without diabetes, low ankle BP indices were progressively associated with a high risk of expanded MACE, a composite of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure. The incidence of expanded MACE rose with lower ankle BPs. These relationships were similar in people with and without type 2 diabetes, and were independent of prior CVD, history of PAD, and traditional risk factors, including arm SBP. The shape of the relationship between all three ankle BP indices and outcomes was similar. The associations were more pronounced for cardiovascular death, total myocardial infarction, and hospitalization for heart failure. Notably, the largest associations were observed for ankle SBP and APPD with the incidence of hospitalization for heart failure. However, only modest associations were observed between ankle BP indices and the incidence of total stroke. Arm BP indices, especially SBP and pulse pressure, were mainly associated with the incidence of total stroke.

Our findings confirm and extend previous reports focusing on the relationship between ABI and CVD [15]. In addition, we report here original data on the relationship between both ankle SBP and APPD, a new indice, and the incidence of expanded MACE and its individual components in people with and without type 2 diabetes. A previous small cross-sectional study has reported an inverse association between ankle SBP and the prevalence of CVD in 1087 participants [24]. We have also recently reported strong, and independent associations between low ankle BP indices and an excess risk of clinical PAD (a composite of lower-limb amputation for arterial causes or requirement for endovascular or surgical revascularization), total mortality, and the composite of either PAD or death, in ONTAGREGT, TRANSCEND and ORIGIN participants without a baseline history of PAD [17]. These associations were also comparable in people with and without diabetes. In a similar vein, we have previously reported independent associations between the absence of ankle pulses and major vascular outcomes in patients with type 2 diabetes [25].

Ankle and arm BP indices were weakly correlated, suggesting that they may provide different prognostic information. In particular, different relationships were observed for hospitalization for heart failure and stroke. The lowest ankle SBP and APPD provided the highest HRs (1.97 and 1.93, respectively) for heart failure hospitalization, whereas the highest arm SBP and pulse pressure provided only low hazard of this outcome (1.14 and 1.26, respectively). In contrast, the HRs for stroke were weaker for the lowest ankle SBP and APPD (1.21 and 1.16, respectively) than for the highest arm SBP and pulse pressure (1.94 and 1.44, respectively). While high arm BP is an established risk factor for stroke and lowering arm BP reduces the risk of stroke [26], it remains unclear whether low ankle BP is a risk factor or only a surrogate for CVD and heart failure. Low ankle SBP and APPD (a gradient between ankle systolic BP and pulse pressure) may reflect arterial stiffness and peripheral vascular resistance, common features observed in people with CVD [10]. Further studies are needed to understand the

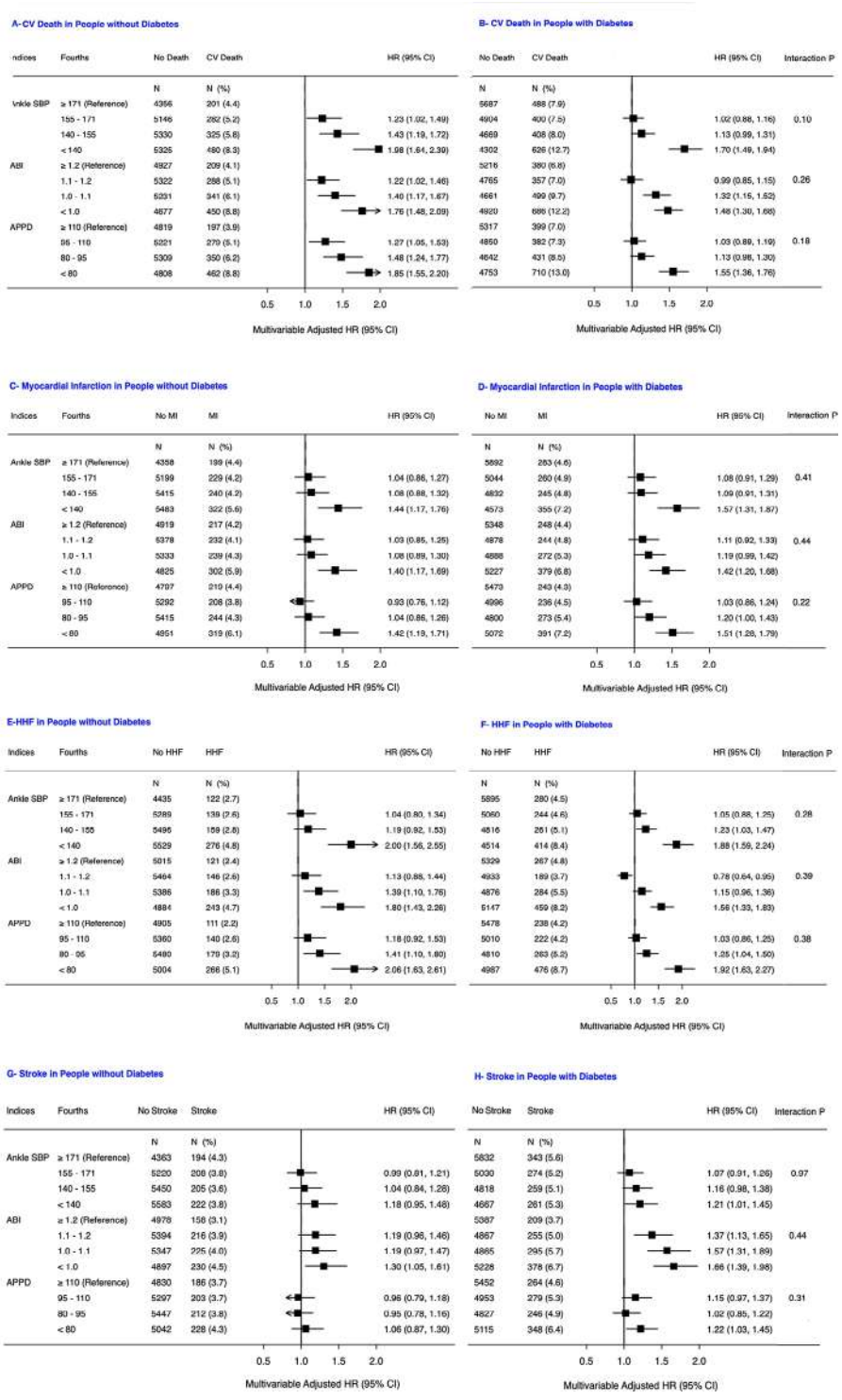


Fig. 3 Risk of secondary outcomes during follow-up by categories of ankle blood pressure indices at baseline in people with and without type 2 diabetes. Data presented as number of participants without and with (%) secondary outcomes. Hazard ratio (HR, 95% CI) for cardiovascular mortality (Panels **A** and **B**), total myocardial infarction (Panels **C** and **D**), hospitalisation for heart failure (Panels **E** and **F**), and total stroke (Panels **G** and **H**) during follow-up according to fourths of ankle BP indices (expressed as mmHg, except for ankle-brachial index). HRs were adjusted for baseline age, sex, study membership, ethnic group, history of hypertension, CVD, and peripheral artery disease, current and former smoking, LDL cholesterol, HDL cholesterol, estimated glomerular filtration rate, the number of used antihypertensive drugs, the use of statin, acetylsalicylic acid or antiplatelet treatments, and arm SBP (for ankle SBP). Interaction tested between history of diabetes and ankle BP indices in their associations with the secondary outcomes. SBP, systolic blood pressure; ABI, ankle-brachial index; APPD, ankle-pulse pressure difference; HHF, hospitalisation for heart failure

underlying mechanisms linking low ankle BP indices and CVD.

A limitation of the present study is the use of an automated oscillometric device rather than a more sensitive ultrasound-based Doppler device to measure ankle BPs [27]. In addition, we conducted a secondary analysis of earlier trials completed more than ten years ago involving people at moderate to very high risk of cardiovascular events, who may not be representative of unselected contemporary people at lower risk. Of the 44,083 participants in the pooled cohort, only 1154 (2.6%) were excluded due to missing data. Although there was a higher incidence of outcomes in the excluded participants with missing data than in those with available data, it seems unlikely that the exclusion of 2.6% of our pooled cohort could introduce a selection bias. Strengths of our study include the large sample size, the diverse patient population with and without type 2 diabetes from 53 countries, and the follow-up for more than 5 years. In addition, the methods used to measure arm and ankle BP in these studies were standardized worldwide, including the patient's position during measurement, the size of the arm and leg cuffs, the position of the cuff on the extremity, and the technique of pulse detection over the brachial artery and at the ankles.

Conclusions

In summary, inverse and independent associations were observed between low ankle BP indices and high 5-year incidence of cardiovascular adverse events. The associations were similar in people with and without type 2 diabetes. The largest effect size was noted for ankle SBP and APPD with respect to hospitalization for heart failure, but only a marginal association was observed for stroke. Arm SBP and pulse pressure seem to be more relevant for stroke. Our findings suggest that the use of ankle BP indices in routine clinical assessment may help identify individuals at highest risk of cardiovascular outcomes. Further studies are needed to understand the underlying mechanisms linking low ankle BP and CVD, and its potential use as a therapeutic target in clinical trials.

Abbreviations

ABI	Ankle-Brachial Index
ACE	Angiotensin-converting enzyme
APPD	Ankle-pulse pressure difference
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
eGFR	Estimated glomerular filtration rate
HR	Hazard Ratio
IC	Confidence interval
IQR	Interquartile range
MACE	Major adverse cardiovascular events
ONTARGET	ONgoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial
ORIGIN	Outcome reduction with an initial glargine intervention
PAD	Peripheral artery disease
SBP	Systolic blood pressure
SD	Standard deviation
TRANSCEND	Telmisartan Randomised AssessmeNt Study in ACE intolerant subjects with cardiovascular disease

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-024-02383-z.

Additional file 1.

Additional file 2.

Additional file 3.

Additional file 4.

Additional file 5.

Additional file 6.

Additional file 7.

Additional file 8.

Additional file 9.

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Author contributions

K.M. and H.G. designed the study, research data, and drafted the manuscript. M.P., J.B., and S.Y. contributed to the discussion and reviewed and edited the manuscript. K.M. and H.G. are 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. All authors approved the final version of the manuscript.

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Data availability

The data sharing policy is described in the Additional file 2.

Declarations

Ethics approval and consent to participate

The protocols of ORIGIN, ONTARGET and TRANSCEND trials were approved by the ethics committee at each study site, and all participants provided written informed consent.

Consent for publication

Not applicable.

Competing interests

K.M. reports consulting fees from Novo Nordisk; honoraria for lectures, presentations, or speaker bureaus from Novo Nordisk, Astra Zeneca, Boehringer-Ingelheim, Eli Lilly, Sanofi, Lifescan, Abbott, and Bayer; and participation to Advisory Board from Novo Nordisk, Sanofi and Amarin. M.P. declares no conflicts of interest. J.B. reports personal fees from Bayer AG for event adjudication. S.Y. declares no conflicts of interest. HCG holds the McMaster-Sanofi Population Health Institute Chair in Diabetes Research and Care. He reports research grants from Eli Lilly, Novo Nordisk, and Sanofi; honoraria for speaking from Astra Zeneca, Eli Lilly, Novo Nordisk, Sanofi, Zuellig, and Jiangsu-Hansen; and consulting fees from Abbott, Eli Lilly, Novo Nordisk, Sanofi, Pfizer, Boehringer Ingelheim, Kowa and Hanmi.

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