Sphygmomanometric and ambulatory blood pressures as forerunners of carotid and femoral intima-media thickness

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Objective Studies directly comparing the associations of intima-media thickness with blood pressure (BP) on manual sphygmomanometric blood pressure measurement (SBPM) and 24-h ambulatory blood pressure measurement (ABPM) are scarce and have a cross-sectional design.

Methods At baseline, we measured systolic and diastolic blood pressures, pulse pressure, and mean arterial pressure in 532 randomly recruited patients (women, 48.3%; mean age, 38.9 years) by SBPM and ABPM. SBPM was the average of five consecutive readings obtained by trained observers at the patients' homes. We measured carotid intima-media thickness (CMT) and femoral intima-media thickness (FMT) by a wall-tracking ultrasound system, 26 months (median) after BP measurement (interquartile range, 21–29 months). We adjusted all analyses for observer, sex, age, BMI, smoking, and total/high-density lipoprotein-cholesterol ratio.

Results The multivariable-adjusted associations of CMT and FMT with all BP components on SBPM were not significant ($P \geq 0.12$). In multivariable-adjusted models, CMT increased with 24-h systolic blood pressure (effect size per SD increase, +0.131 mm; $P = 0.003$) and 24-h pulse pressure (+0.139 mm; $P = 0.001$), whereas FMT increased with 24-h diastolic blood pressure (+0.091 mm; $P = 0.03$) and 24-h mean arterial pressure (+0.090 mm; $P = 0.04$). Models including the ambulatory blood pressure components additionally adjusted for SBPM and more covariables than those listed above were confirmatory.

Conclusion In a general population, BP on ABPM predicts CMT and FMT over and beyond highly standardized SBPM. At the elastic carotid artery, CMT increased predominantly with the pulsatile component of BP, whereas at the muscular femoral artery, FMT increased with the steady component of BP. *J Hypertens* 27:813–821 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Abbreviations: ABPM, ambulatory blood pressure measurement; CMT, carotid intima-media thickness; FMT, femoral intima-media thickness; HDL, high-density lipoprotein; IMT, intima-media thickness; SBPM, manual sphygmomanometric blood pressure measurement

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Introduction

The joint guidelines of the European Societies of Hypertension and Cardiology currently propose carotid intima-media thickness (CMT) as an intermediate marker of target organ damage [1]. CMT predicts stroke and myocardial infarction [2]. The relation between cardiovascular events and CMT is continuous, but an IMT of more than 0.9 mm at the common carotid artery is a marker of atherosclerosis [1,3].

Studies [4–7] directly comparing the association of IMT with the ambulatory as opposed to the conventional blood pressure (BP) are scarce and have a cross-sectional design. They all based their conclusions on cross-sectional

analyses, focused only on CMT [4–7], and produced inconsistent results. In the European Lacidipine Study on Atherosclerosis (ELSA [4]), and in a smaller Swedish study of hypertensive patients and normotensive controls [6], the correlation coefficients of IMT with systolic blood pressure (SBP) [4] and pulse pressure (PP) [4] were of the same order of magnitude on clinic and ambulatory measurement. In multivariable-adjusted analyses of ELSA patients, CMT [4] correlated with both 24-h PP and clinic SBP. At baseline, in the Plaque Hypertension Lipid Lowering Italian Study (PHYLLIS [5]), IMT correlated with SBP on ambulatory monitoring, but not on conventional measurement. In a cross-sectional analysis [7] of the Ohasama population, CMT correlated

more closely with the daytime and night-time ambulatory blood pressures (ABPs) than with casual BP.

To our knowledge, no previous population-based study compared the relations of CIMT and femoral intima-media thickness (FIMT) with BP as measured by conventional sphygmomanometry and 24-h ambulatory monitoring. In the FLEMish study on ENvironment, Genes and Health Outcomes (FLEMENGHO), we investigate whether 24-h ABPM at baseline predicted IMT over and beyond highly standardized BP measurements, as obtained by skilled observers at the patients' homes.

Methods

Study population

The FLEMENGHO is part of the European Project on Genes in Hypertension (EPOGH). Starting from August 1985, we recruited a random sample of families from a geographically defined area in Northern Belgium [8,9]. The Ethics Committee of the University of Leuven approved the study. All participants gave informed written consent. The initial participation rate averaged 64.3%.

Of 1322 participants who after enrolment underwent a vascular ultrasound examination, 678 (51.3%) had high-quality IMT measurements at both the elastic common carotid and muscular femoral arteries. For the present analysis, we excluded 70 teenagers younger than 18 years and all 76 patients on antihypertensive drug treatment. Thus, the number of participants statistically analyzed totalled 532.

Blood pressure measurements at baseline (1991–2001)

As described elsewhere, the nurses involved in BP measurement participated in a standardized quality assurance and quality control programme of their BP readings [10,11]. Every 3 months, the accuracy of their BP readings was checked, using a video movie showing a falling mercury column with Korotkoff sounds, and by simultaneous BP measurements by the nurses and physicians on human volunteers. To pass the test, the film readings and the measurements on patients had to be within 5 mmHg of the standard for the video and the physician's readings. Nurses, who failed the test were given additional training, until they met the quality standards.

The trained nurses visited the participants at home [10,11]. The manual BP was the mean of five consecutive BP readings to the nearest 2 mmHg (phase V diastolic) obtained by auscultation of the Korotkoff sounds, using a standard mercury sphygmomanometer. The readings were taken after the patients had rested in the sitting position for 5 min. During the measurements, the patient's arm was supported at the heart level. In most

patients, standard cuffs with a 22 × 12 cm bladder were used. If arm circumference exceeded 31 cm, larger cuffs with a 35 × 15 cm bladder were applied. For analysis, we averaged the five BP readings obtained at home. Hypertension was a manual BP of at least 140 mmHg SBP or 90 mmHg DBP.

On a separate day, validated oscillometric SpaceLabs 90202 [12] or 90207 [13] monitors (Redmond, Washington, USA), for each patient fitted with the same cuff size as for the manual BP measurements, were programmed to record readings with an interval of 20 min from 8:00 a.m. until 10:00 p.m., and every 45 min from 10:00 p.m. to 8:00 a.m. The calibration of these devices was checked on a monthly basis against a mercury column. If the ambulatory recordings were longer than 1 day, only the first 24 h were analyzed. Intraindividual means of the ambulatory measurements were weighted by the time interval between successive readings. PP was SBP minus DBP. Mean arterial pressure (MAP) was directly measured by the oscillometric SpaceLabs recorders, and calculated as DBP and one-third of PP for the manual measurements.

Intima-media thickness measurement at follow-up (1992–2003)

For at least 3 h before the vascular examination, the participants refrained from smoking, heavy exercise, alcohol, or caffeine-containing beverages. By means of a pulsed ultrasound wall-tracking system (Wall Track System, Pie Medical, Maastricht, The Netherlands), trained researchers ($n=3$) obtained vascular measurements at the common carotid artery 2 cm proximal of the carotid bulb and at the femoral artery 1 cm proximal of the bifurcation into the profound and superficial branches [14].

The ultrasonographers measured off-line the distances from the adventitia-media boundary of the near wall to the lumen-intima and media-adventitia interfaces of the far wall. IMT was the mean difference between these distances measured over three separate intervals of 5.2 s, which on average included 15 heart cycles. An atherosclerotic plaque was defined as a distinct area, where the intima-media encroached into the vessel lumen and where its thickness was at least 50% greater than that of the adjacent sites [15]. When present, atheromatous plaques were included in the IMT measurements. Repeatability was determined in 10 patients, as previously described [16]. For CIMT, the repeatability coefficients were 29 μ m below age 40 years and 40 μ m in older patients [14]. For the femoral artery, these coefficients were 41 and 46 μ m, respectively [14]. For all ages combined, the intraobserver intrasession coefficients of variability [17] amounted to ($\pm$ SD) $5.2 \pm 1.7\%$ for the common carotid artery and to $5.6 \pm 4.6\%$ for the femoral artery.

Other measurements

At baseline, the nurses administered a questionnaire to collect information about the patients' medical history, smoking and drinking habits, and intake of medications. In addition, they measured the patients' anthropometric characteristics. BMI was weight in kilograms divided by height in meters squared. At baseline, the participants gave a venous blood sample for the measurement of total and high-density lipoprotein (HDL)-cholesterol and blood glucose. Diabetes mellitus was a self-reported diagnosis, a fasting or random blood glucose level of at least 7.0 mmol/l (126 mg/dl) or 11.1 mmol/l (200 mg/dl), respectively, or the use of antidiabetic drugs [18]. Hypercholesterolemia was a total cholesterol level of at least 5.16 mmol/l (200 mg/dl) or the use of lipid-lowering drugs [19].

Statistical analysis

For database management and statistical analysis, we used SAS software, version 9.1.3 (SAS Institute, Cary, North Carolina, USA) and the Statistical Package for Social Science (version 13.0 for Windows, SPSS Inc., Chicago, Illinois, USA). Departure from normality was evaluated by Shapiro-Wilk's statistic [20] and the computation of skewness and kurtosis [21]. Throughout this article, statistical significance was a two-sided α level of 0.05 or less.

We compared means and proportions, using Student's *t* test and the χ^2 statistic, respectively. Our statistical methods also included single and multiple linear regression. To identify covariables of IMT, in addition to BP, we applied a stepwise selection procedure with the

P value for independent variables to enter and stay in the model set at 0.15. The baseline covariables considered for entry into the model were sex, age, BMI, 24-h pulse rate, smoking (0/1), use of alcohol (0/1), the ratio of total to HDL-cholesterol, and a history of cardiovascular disease (0/1). In fully adjusted models, we adjusted the ABP for the conventional BP. We ran regression diagnostics to exclude that possible collinearity inappropriately influenced our multivariable models. We computed the variance inflation factor, the condition index, Mallows' *C_p* statistic, and the adjusted *R*².

In sensitivity analyses, we forced additional covariables into the models, including 24-h pulse rate, use of alcohol (0/1), and a history of cardiovascular disease (0/1). Furthermore, because the time period between the BP readings at baseline and the subsequent IMT measurements ranged from 0.58 to 13.1 years, we additionally reanalyzed our cohort, stepwise including patients with a longer interval between the BP measurements at baseline and the ultrasound examinations. In these analyses, we used 6-month steps [22].

Results

Characteristics of the participants

The 532 participants included 257 women (48.3%), 49 hypertensive patients (9.2%) who were all untreated, and 263 (49.5%) hypercholesterolemic patients, of whom seven (2.7%) were on lipid-lowering drugs. As shown in Table 1, CIMT and FIMT were similar in both sexes (*P* ≥ 0.62). Women compared with men (Table 1) had lower manually measured and ABPs, lower BMI, less

Table 1 Baseline characteristics of participants

Characteristic	Women (<i>n</i> = 257)	Men (<i>n</i> = 275)	<i>P</i>
Anthropometrics			
Age (years)	38.9 ± 12.9	38.8 ± 12.3	0.91
BMI (kg/m ²)	24.2 ± 4.6	25.6 ± 3.5	<0.0001
IMT (mm)			
Carotid	0.60 ± 0.18	0.59 ± 0.17	0.81
Femoral	0.71 ± 0.23	0.70 ± 0.28	0.62
BP (mmHg)			
Manually measured SBP	116.7 ± 11.0	124.1 ± 10.8	<0.0001
Manually measured DBP	73.2 ± 8.7	78.2 ± 10.0	<0.0001
Manually measured MAP	87.7 ± 8.6	93.5 ± 9.2	<0.0001
Manually measured PP	45.0 ± 10.2	45.9 ± 9.5	0.002
24-h SBP	119.0 ± 9.7	126.0 ± 10.0	<0.0001
24-h DBP	74.7 ± 8.3	77.6 ± 8.7	<0.0001
24-h MAP	89.6 ± 8.2	92.8 ± 8.1	<0.0001
24-h PP	44.3 ± 7.3	48.3 ± 8.5	<0.0001
Serum cholesterol (mmol/l)			
Total	5.27 ± 0.98	5.29 ± 1.13	0.87
HDL	1.67 ± 0.42	1.23 ± 0.30	<0.0001
Cardiovascular risk factors			
Current smoking, <i>n</i> (%)	74 (28.8)	88 (32.0)	0.42
Current alcohol intake, <i>n</i> (%)	55 (21.4)	135 (49.1)	<0.0001
History of cardiovascular disease, <i>n</i> (%)	12 (4.7)	8 (2.9)	0.26
Diabetes mellitus, <i>n</i> (%)	3 (1.2)	1 (0.4)	0.28
Untreated hypertensive patients, <i>n</i> (%)	10 (3.8)	39 (14.2)	<0.0001

Data are mean ± SD or number of patients (%). The conventional BP was the average of five readings obtained by an observer at the patients' homes. Hypertension was a conventional BP of at least 140 mmHg SBP or 90 mmHg DBP. All hypertensive patients were untreated. Diabetes mellitus was a self-reported diagnosis, a fasting or random blood glucose level of at least 7.0 mmol/l (126 mg/dl) or 11.1 mmol/l (200 mg/dl), respectively, or the use of antidiabetic drugs [18]. BP, blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; IMT, intima-media thickness; MAP, mean arterial pressure; PP, pulse pressure; SBP, systolic blood pressure.

Table 2 Unadjusted and mutually adjusted standardized partial regression coefficients (β) of carotid and femoral intima-media thickness with selected covariables

Variable	CIMT				FIMT			
	Unadjusted β	P	Adjusted β	P	Unadjusted β	P	Adjusted β	P
Sex	0.010	0.81	0.125	0.07	0.021	0.63	0.019	0.78
Age	0.363	<0.0001	0.367	<0.0001	0.373	<0.0001	0.343	<0.0001
BMI	0.128	0.03	-0.030	0.52	0.208	<0.0001	0.112	0.02
24-pulse rate	-0.022	0.62	0.007	0.88	0.004	0.91	-0.031	0.52
Current smoking	0.053	0.23	0.063	0.14	0.075	0.08	0.096	0.02
Current alcohol use	0.010	0.82	-0.018	0.68	0.085	0.05	0.046	0.29
Total/HDL-cholesterol	0.163	<0.0001	0.113	0.03	0.083	0.05	-0.055	0.28
Previous cardiovascular disease	0.094	0.030	0.059	0.16	0.084	0.05	0.039	0.34

The SDs of continuous variables appear in Table 1. CIMT, carotid intima-media thickness; FIMT, femoral intima-media thickness; HDL, high-density lipoprotein.

frequently reported intake of alcohol, but had higher serum HDL-cholesterol. In drinkers, the median daily alcohol consumption was 21 g. The prevalence of smoking was similar in both sexes (Table 1). In smokers, the median tobacco use was 12 cigarettes per day (fifth to 95th percentile interval, 2–23). Among 217 premenopausal and 40 postmenopausal women, 84 (38.7%) and five (12.5%) used oral contraceptives and hormonal replacement therapy, respectively.

Quality control of blood pressure measurements

The seven observers involved in the study obtained 2660 readings at home for SBP in 532 patients. Six observers did not show any number preference, that is repetition of the same BP value within each series of five consecutive measurements in 422 patients. One observer showed number preference in six of 110 patients (4.6%). For DBP, four observers did not show any number preference in 298 patients. The other three observers repeated the same values within a series of five measurements, in four of 35 patients (11.4%), in two of 89 patients (2.3%), and in seven of 110 patients (6.4%), respectively. In terms of digit preference, among the seven observers, there was an over-representation (expected 20%) of a terminal zero, amounting to 5.9% ($P < 0.0001$) for SBP and to 9.1% ($P < 0.0001$) for DBP. There were no significant differences in the frequencies of SBP values ending on 2, 4, 6, or 8 ($P = 0.88$). For DBP, there was an under-representation of values ending on four (approximately 3.8%, $P < 0.001$). None of the 2660 readings ended on an uneven number.

The 532 ABP recordings spanned a median of 22 h [fifth to 95th percentile interval, 20–24; interquartile range (IQR), 21–23]. The median number of readings per recording was 43 (fifth to 95th percentile interval, 34–60; IQR, 39–56).

Carotid and femoral intima-media thickness and its covariables

The distributions of CIMT ($W = 0.961$, $P < 0.001$) and FIMT ($W = 0.937$, $P < 0.001$) departed from normality; the coefficients of skewness were 0.915 ± 0.106 (SE)

and 1.168 ± 0.106 , respectively, and kurtosis was 1.998 ± 0.211 and 2.587 ± 0.211 . Table 2 displays the unadjusted and mutually adjusted standardized regression coefficients of CIMT and FIMT with several covariables of interest. Age was the only explanatory variable independently related to CIMT and FIMT in all models. Figure 1 depicts the association of CIMT and FIMT across sixths of the age distribution by sex. The ratio of total to HDL-cholesterol was a significant correlate of CIMT, whereas BMI and smoking were independently associated with FIMT (Table 2). We adjusted all models for sex, age, BMI, smoking, the ratio of total to HDL-cholesterol, and in addition for observer.

Intima-media thickness in relation to the manually measured blood pressure

In unadjusted analysis (Table 3), CIMT and FIMT correlated positively with the manual measurements of SBP and PP ($P \leq 0.02$). With the exception of a borderline significant correlation between FIMT and MAP ($P = 0.05$), CIMT and FIMT were not correlated with DBP or MAP on manual measurement ($P \geq 0.17$). With adjustments applied for observer, sex, age, BMI, smoking, and the ratio of total to HDL-cholesterol, the partial correlations of CIMT and FIMT with all manually measured BP components lost statistical significance ($P \geq 0.12$; Table 3).

Intima-media thickness in relation to 24-h ambulatory blood pressure

In unadjusted models (Table 4), CIMT and FIMT showed significant ($P \leq 0.01$) or borderline significant ($P = 0.08$) correlations with the 24-h SBP and 24-h MAP. Figure 2 shows the associations of CIMT and FIMT across sex-specific eighths of the distribution of 24-h SBP and 24-h MAP. Furthermore, in single regression, there was a positive correlation between FIMT and 24-h DBP ($P = 0.002$). The correlations of CIMT and FIMT with 24-h PP were not significant ($P \geq 0.13$, Table 4).

With adjustments applied for observer, sex, age, BMI, smoking, and the ratio of total to HDL-cholesterol

Fig. 1

Sex-specific associations of femoral (closed squares) and carotid (open circles) intima-media thickness across sixths of the age distribution. Values are means $\pm$ SE. IMT, intima-media thickness.

(Table 4), CIMT increased with 24-h SBP ($P=0.003$), 24-h PP ($P=0.001$), and to a lesser extent, with 24-h MAP ($P=0.06$). In adjusted models (Table 4), FIMT increased with 24-h DBP ($P=0.03$) and 24-h MAP ($P=0.04$). In fully adjusted models, which also included the manually measured BP components, the findings were almost identical.

Differential impact of blood pressure in elastic and muscular artery

At the elastic carotid artery, IMT increased predominantly with peak pressure, as reflected by SBP or PP (Table 4). For example, in fully adjusted models, per SD

Table 3 Unadjusted and adjusted standardized regression coefficients (β) of intima-media thickness with the manually measured blood pressure

Variable	CIMT		FIMT	
	$\beta \pm \text{SE}$	P	$\beta \pm \text{SE}$	P
SBP (mmHg) (SD = 11.5)				
Unadjusted	0.120 $\pm$ 0.078	0.006	0.132 $\pm$ 0.082	0.002
Adjusted	0.021 $\pm$ 0.069	0.66	0.049 $\pm$ 0.074	0.28
DBP (mmHg) (SD = 9.7)				
Unadjusted	0.026 $\pm$ 0.083	0.54	0.059 $\pm$ 0.070	0.17
Adjusted	-0.069 $\pm$ 0.075	0.13	0.002 $\pm$ 0.075	0.97
PP (mmHg) (SD = 9.1)				
Unadjusted	0.123 $\pm$ 0.079	0.004	0.103 $\pm$ 0.080	0.02
Adjusted	0.083 $\pm$ 0.088	0.12	0.048 $\pm$ 0.066	0.24
MAP (mmHg) (SD = 9.4)				
Unadjusted	0.057 $\pm$ 0.066	0.19	0.086 $\pm$ 0.085	0.05
Adjusted	-0.050 $\pm$ 0.068	0.28	0.017 $\pm$ 0.081	0.72

Adjusted models account for observer, sex, age, BMI, smoking, and the total-to-HDL-cholesterol ratio. CIMT, carotid intima-media thickness; DBP, diastolic blood pressure; FIMT, femoral intima-media thickness; HDL, high-density lipoprotein; MAP, mean arterial pressure; PP, pulse pressure; SBP, systolic blood pressure.

Table 4 Unadjusted and adjusted standardized regression coefficients (β) of intima-media thickness with the 24-h ambulatory blood pressure

Variable	CIMT		FIMT	
	$\beta \pm \text{SE}$	P	$\beta \pm \text{SE}$	P
24-h SBP (mmHg) (SD = 10.4)				
Unadjusted	0.106 $\pm$ 0.080	0.01	0.076 $\pm$ 0.085	0.08
Adjusted	0.131 $\pm$ 0.086	0.003	0.063 $\pm$ 0.087	0.15
Fully adjusted	0.158 $\pm$ 0.089	0.002	0.052 $\pm$ 0.088	0.30
24-h DBP (mmHg) (SD = 8.6)				
Unadjusted	0.065 $\pm$ 0.074	0.13	0.131 $\pm$ 0.079	0.002
Adjusted	0.013 $\pm$ 0.077	0.74	0.091 $\pm$ 0.080	0.03
Fully adjusted	0.049 $\pm$ 0.075	0.30	0.108 $\pm$ 0.088	0.02
24-h PP (mmHg) (SD = 8.2)				
Unadjusted	0.066 $\pm$ 0.079	0.13	-0.041 $\pm$ 0.083	0.33
Adjusted	0.139 $\pm$ 0.080	0.001	-0.022 $\pm$ 0.081	0.61
Fully adjusted	0.124 $\pm$ 0.082	0.005	0.040 $\pm$ 0.084	0.37
24-h MAP (mmHg) (SD = 8.3)				
Unadjusted	0.110 $\pm$ 0.084	0.01	0.120 $\pm$ 0.087	0.003
Adjusted	0.080 $\pm$ 0.082	0.06	0.090 $\pm$ 0.088	0.04
Fully adjusted	0.127 $\pm$ 0.085	0.008	0.104 $\pm$ 0.087	0.03

Adjusted models account for observer, sex, age, BMI, smoking, and the total-to-HDL-cholesterol ratio. Fully adjusted models additionally included the corresponding manual BP measurement. CIMT, carotid intima-media thickness; DBP, diastolic blood pressure; FIMT, femoral intima-media thickness; HDL, high-density lipoprotein; MAP, mean arterial pressure; PP, pulse pressure; SBP, systolic blood pressure.

Fig. 2

Associations of femoral (closed squares) and carotid (open circles) intima-media thickness across sex-specific eighths of the distributions the 24-h systolic blood pressure (left panel) and 24-h mean arterial pressure (right panel). Values are means $\pm$ SE. *P* values are for linear trend. IMT, intima-media thickness.

increase in 24-h SBP (SD, 10.4 mmHg) and 24-h PP (SD, 8.2 mmHg), the increments in CIMT were 0.158 mm ($P=0.002$) and 0.124 mm ($P=0.005$), respectively (Table 4). At the muscular femoral artery, IMT increased predominantly with the steady component of BP, as reflected by 24-h DBP (SD=8.6 mmHg) or the 24-h MAP (SD=8.3 mmHg), with effect sizes in fully adjusted models of 0.108 mm ($P=0.02$) and 0.104 mm ($P=0.03$), respectively (Table 4).

Sensitivity analyses

When we forced additional covariables into the regression models, including the 24-h pulse rate, use of alcohol (0/1), and a history of cardiovascular disease (0/1), our results remained consistent as shown in Fig. 3 for the fully adjusted associations between CIMT and the 24-h SBP and between FIMT and 24-h MAP. We did not find any evidence for influential collinearity in any of our regression models.

The time period between the BP readings at baseline and the IMT measurements at follow-up was not normally distributed ($W=0.48$, $P<0.0001$). The coefficient of skewness was 4.34. The median interval was 26 months (fifth to 95th percentile interval, 18–58 months; IQR, 21–29 months). However, when we repeated the analyses, including progressively more recordings with the interval between the BP measurements and the ultrasound examinations lengthening in steps of 6 months, the point estimates of the standardized partial regression coefficients between CIMT and 24-h

SBP and between FIMT and 24-h MAP did not substantially change (Fig. 3).

Discussion

The key findings of our study of a general population were two-fold. First, highly standardized manual BP measurements, when adjusted for covariables, did not predict CIMT or FIMT. In contrast, the 24-h ABP was an independent predictor of IMT, over and beyond the manually measured BP. Second, at the elastic carotid artery, IMT increased predominantly with the pulsatile component of BP (24-h SBP and 24-h PP), whereas at the muscular femoral artery, IMT increased with the steady component of BP (24-h DBP and 24-h MAP).

The lack of an independent association between IMT and the conventional BP cannot be ascribed to the low quality of the manual BP readings. Our observers were highly trained. The quality of their readings was high in terms of digit and number preference. At screening in the Second Australian National Blood Pressure Study [23], observers obtained three consecutive conventional measurements of BP. For both SBP and DBP, observed digit preference fell within 7% of the expected frequency. In standardized audits of general practices in Merseyside (United Kingdom) [24], 86% of all SBPs and 77% of DBPs ended in zero. In the Systolic Hypertension in Europe Trial [25], the prevalence of use of terminal digit zero when measuring sitting SBP (first readings) reduced from an average of 42.4% in the year prior to the date when a centre first randomized a patient to 31.5,

Fig. 3

Associations between carotid intima-media thickness and 24-h systolic blood pressure (open circles) and between femoral intima-media thickness and the 24-h mean arterial pressure (closed diamonds). Values are standardized partial regression coefficients ($\pm$ SE). Numbers indicate patients contributing to each plotted point. Asterisks mark significant multivariable-adjusted associations ($P < 0.05$). IMT, intima-media thickness; MAP, mean arterial pressure; SBP, systolic blood pressure.

25.0, 22.3, 26.3, 23.2, and 22.0% in the subsequent 6 years.

Few studies [4–7] directly compared the associations of IMT with BP on sphygmomanometric measurement and 24-h ABPM. The analyses in all these studies [4–7] were cross-sectional and only involved CIMT. None of the studies gave an account of the quality of the conventional BP measurements [4–7]. At baseline in the ELSA trial, Zanchetti *et al.* [4] reported on the association in 1544 untreated hypertensive patients between CIMT and BP on clinic measurement (average of three readings) and 24-h ABPM. IMT was measured at up to 12 different sites in the carotid arterial tree and expressed as the mean of the maxima at these sites ($M_{\max}$), the mean of the maxima at four sites in the distal common carotid artery and bifurcation ($CBP_{\max}$) and the maximum IMT ($T_{\max}$). Because of the potential problem of collinearity, the ELSA researchers introduced in multivariable regression only the component of the clinic and ABP, which in single regression correlated most closely with IMT. In multivariable-adjusted analyses, $M_{\max}$, $CBP_{\max}$, and $T_{\max}$ correlated with 24-h PP and $M_{\max}$, and $CBP_{\max}$, but not $T_{\max}$, correlated with clinic SBP.

In a cross-sectional analysis [7] of the Ohasama population ($n = 775$, 68.8% women, mean age 66.2 years), in both unadjusted and adjusted analyses, CIMT correlated more closely with the daytime and night-time ABPs than

with the casual BP. There was no association between CIMT and the casual DBP. More recently, Swedish researchers reported that in a group of normotensive individuals ($n = 23$) and hypertensive patients ($n = 110$), the correlation coefficients of common CIMT with the mean of three clinic measurements of SBP ($r = 0.34$; $P < 0.001$) and with the ambulatory SBP ($r = 0.29$ and $r = 0.32$ for daytime and night-time BP, respectively; $P = 0.001$) were of similar magnitude. Pooling normotensive individuals with hypertensive patients, the relatively small sample size, and the use of correlation coefficients without adequate adjustment, however, limit the interpretation of this Swedish study.

IMT at the elastic carotid artery increased with the pulsatile component of 24-h BP, whereas at the muscular femoral artery, it increased with the steady component. The large elastic arteries, such as the carotid artery, represent the most distensible part of the arterial system and are vulnerable to systolic stress. In elastic arteries, cyclic stress with each heart beat leads to fracture of the elastin fibres and transfer of the stress to the less extensible collagen filaments in the wall, leading to dilatation and stiffening, respectively [26]. Elastin fibres also fulfil a structural role by containing vascular smooth muscle cells in concentric layers [27]. The integrity of the ring structure of the arterial wall depends on the interaction between fibrillin-1, a protein associated with elastin, and α V β 3 integrins expressed at the outer side of the

vascular smooth muscle cell membrane [27]. Fracture of elastin fibres therefore leads to vascular muscle cell proliferation and increased IMT. The observation that CIMT increases with the pulsatile component of BP is also in line with in-vitro evidence, showing that in elastic arteries cyclic stress rather than the static load stimulates the growth of vascular smooth muscle cells [28]. Systolic augmentation as a consequence of ageing or hypertension furthermore adds to the cyclic stress imposed on the central elastic arteries [29]. The peripheral muscular conduit arteries, such as the femoral artery, are less affected by cyclic stress, because smooth muscle cells support the elastin fibres.

The present study must be interpreted within the context of its potential limitations and strengths. First, the observer-made BP readings in the relaxed home environment are different from the conventional BP measured in a medical setting, as well as from the self-measured BP at home. Our current findings can therefore not be extrapolated to these other types of BP measurement. Second, we measured BP at the brachial artery, using standard mercury sphygmomanometers. Third, at variance with previous reports [4–7], our study had a longitudinal design in that the BP readings preceded the arterial ultrasound examination by a median of 26 months. Several studies [22,30,31] showed that arterial remodelling with adaptation of the arterial IMT/diameter ratio occurs in elastic [22] and muscular arteries [30,31] within a few weeks [31] to 6 months [22] after an alteration of the hemodynamic condition. However, the length of the interval between the BP measurements at baseline and the subsequent ultrasound examination did not materially alter the associations between CIMT and 24-h SBP or between FIMT and 24-h MAP.

In conclusion, in our longitudinal study of a general population, ABPM predicted CIMT and FIMT over and beyond highly standardized conventional BP measurements. In multivariable-adjusted models, the conventional BP was not predictive. At the elastic carotid artery, IMT increased predominantly with the pulsatile component of BP, whereas at the muscular femoral artery, IMT mainly increased with the steady component of BP.

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There are no conflicts of interest.

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