Hypertension

Blood Pressure Response Under Chronic Antihypertensive Drug Therapy

The Role of Aortic Stiffness in the REASON (Preterax Regression of Arterial Stiffness in a Controlled Double-Blind) Study

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Objectives	We sought to evaluate the role of arterial stiffness on blood pressure (BP) response to drug treatment.
Background	Increased arterial stiffness (pulse wave velocity [PWV]) is associated with increased systolic blood pressure (SBP). Antihypertensive drug therapy achieves better control of diastolic blood pressure (DBP) than SBP does, implying that increased PWV might be a predictor of the SBP response to treatment.
Methods	The REASON (Preterax Regression of Arterial Stiffness in a Controlled Double-Blind) study is a randomized, double-blind trial comparing atenolol versus perindopril/indapamide; 375 patients with hypertension, with BP and PWV measurements at baseline and after 12 months of treatment, were divided into 3 tertiles according to baseline PWV and included in a post-hoc analysis.
Results	After 12 months of treatment, BP differed significantly between PWV tertiles (the third having the lowest response, $p < 0.05$). Factors related to smaller BP decline were low baseline BP, high baseline PWV, need for a double dose of treatment, use of atenolol (only for SBP response), and age (only for DBP). Although DBP control did not differ in the PWV tertiles, SBP control was significantly associated with PWV level ($p = 0.001$) as well as with the use of perindopril/indapamide ($p < 0.001$). The predictive value of PWV on BP response was independent of age, sex, mean BP, and cardiovascular risk factors.
Conclusions	Baseline PWV is a significant predictor of BP response to antihypertensive treatment, independent from age, the need for increasing drug dosage, and the presence of cardiovascular risk factors. Achievement of SBP control appears to be influenced by aortic stiffness as well as by angiotensin-converting enzyme inhibition. (J Am Coll Cardiol 2009;53:445–51) © 2009 by the American College of Cardiology Foundation

In management of hypertension, the degree of blood pressure (BP) reduction, independent of the class of antihypertensive agent, is the cornerstone of successful reduction of cardiovascular (CV) risk (1). Current international guidelines (2) give various recommendations for optimization of drug treatment, including: 1) the need for prompt initiation of drug treatment, or not; 2) selection of the most appropriate antihypertensive agents; and 3) use of monotherapy or combination therapy, based on the level of BP and the presence of other CV risk factors, target organ damage, or concomitant conditions. Based on the parameters above, all hypertension societies emphasize the need for treatment individualization. However, at present, there is no specific

marker able to predict BP response to chronic antihypertensive therapy.

Carotid-femoral (CF) pulse wave velocity (PWV) is a widely accepted marker of aortic (thoracic/abdominal) stiffness and a marker of arterial wall alterations, independent from mean arterial pressure (MAP). The gradual increase in PWV is a dominant trait of arterial wall aging, which is further accelerated by the effect of CV risk factors (3). Aortic stiffness is an independent and stronger predictor of new onset hypertension and also of total and CV mortality in hypertensive subjects than BP itself (3,4). Finally, increased aortic stiffness is closely associated with increased systolic blood pressure (SBP), so it is a major determinant of hypertension phenotypes (isolated systolic hypertension) (3). Antihypertensive drug therapy

**Abbreviations
and Acronyms**

ACEI = angiotensin-
converting enzyme inhibitor

BMI = body mass index

BP = blood pressure

CF = carotid-femoral

CV = cardiovascular

DBP = diastolic blood
pressure

MAP = mean arterial
pressure

Per/Ind = perindopril/
indapamide

PWV = pulse wave velocity

SBP = systolic blood
pressure

achieves effective control of dia-stolic blood pressure (DBP) (<90 mm Hg) more often than SBP (<140 mm Hg), implying that increased CF PWV might be a predictor of the SBP response to chronic antihypertensive drug treatment. A recent observational cross-sectional study in patients treated for hypertension showed that CF PWV is a significant pre-dictor of uncontrolled BP inde-pendently of MAP, the presence of atherosclerosis, drug treatment, and traditional CV risk factors (5).

The REASON (Preterax Re-gression of Arterial Stiffness in a Controlled Double-Blind) study (6–8) is a multicenter (13 coun-tries), randomized, double-blind, controlled, parallel group, 12-month trial, comparing the beta-blocker atenolol with the fixed-dose combination of the angiotensin-converting enzyme inhibitor (ACEI) perindopril with the diuretic indapamide. The primary objective of the REASON study was to investigate potential differences between treatment arms regarding their effects on BP and CF PWV. In the present post-hoc analysis, we specifically investigated whether CF PWV, measured in hypertensive subjects be-fore initiation of antihypertensive drug treatment (baseline, $[_0]$): 1) was associated with the degree of treatment-induced BP reduction; and 2) was an independent predictor of effective BP control after 12 months of treatment.

Methods

Study design. The design of the REASON study has been described in detail elsewhere (7,8). In brief, 562 subjects with uncomplicated hypertension and supine SBP ≥160 and <210 mm Hg and DBP ≥95 and <110 mm Hg were recruited. Patients on antidiabetic, hypo-cholesterolemic, or other CV agents were excluded. Written consent was obtained from each patient, and the protocol was approved by the ethics committees of the individual institutions of the study investigators.

After a 4-week placebo wash-out period, 469 subjects were randomly allocated to receive double-blind atenolol (50 mg once daily) or perindopril/indapamide (Per/Ind) (2/0.625 mg once daily) for 12 months. After 3 months of treatment, if SBP remained ≥160 mm Hg and/or DBP ≥90 mm Hg, the drug dosage was doubled (dosage effect). When needed, drug dosage was progressively decreased over 8 to 15 days in order to avoid complications due to beta-blockade.

The following hemodynamic investigations were in-cluded in the present study. Office BP was measured after 10 min rest in the supine position using a mercury sphyg-momanometer, just before study entry (M_0) and after 12 months (M_{12}). We previously showed that M_0 and M_{12} BP measurements were similar to office or ambulatory BP measurements (6). CF PWV was determined at M_0 and M_{12} by the automated device Complior (Colson, Paris, France), which allows online pulse wave recording and calculation, as previously described (7,8). The reproducibil-ity of Complior measurements has been previously reported (7,8).

From a total of 469 subjects, complete follow-up, includ-ing valid BP and CF PWV measurements at both M_0 and M_{12}, was achieved in 375 subjects: 182 in the atenolol group and 193 in the Per/Ind group. Previous use of antihyper-tensive drugs (before study entry) was reported in 269 subjects. Treatment dosage was doubled in 63 subjects in the atenolol group and 91 in the Per/Ind group.

Statistical analysis. In order to investigate the treatment-induced BP changes (BP_{12} to BP_0) according to the level of baseline aortic stiffness, the study population was divided into tertiles according to CF PWV_0 (3 subgroups with 125 subjects each were generated). Comparison of CV risk factors and hemodynamic parameters at M_0 and at M_{12} between CF PWV_0 tertiles was performed by using analysis of variance (for quantitative parameters) and chi-square test (for categorical parameters). Because the main goal of the present study was to investigate the independent role of increased CF PWV_0 on the BP response, all factors con-sidered to be potential confounders of the BP response to treatment (including CV risk factors, prior antihypertensive drug treatment, group effect, dosage effect, and baseline BP) were subsequently introduced as covariates in the analysis of covariance to adjust for their effects.

Group effect was classified as 1 = Per/Ind and 2 = atenolol. Dosage effect was classified as "dosage increase" = 1 and "no dosage increase" = 0. Previous use of antihypertensive drugs (yes, no), treatment arm (atenolol or Per/Ind), the need for treatment titration during the study, as well as the achievement of effective BP control (SBP <140 mm Hg and DBP <90 mm Hg) at M_{12} were compared among CF PWV_0 subgroups (tertiles) using chi-square tests. Linear regression analysis was applied in order to investigate the independent effect of CF PWV_0 on the treatment-induced BP decline and the BP control after 12 months. All previously mentioned confounders of BP response were entered into the regression models. In order to identify multicollinearity, we assessed the variance inflation factor. Receiver-operator curve analysis was applied to determine the ability of CF PWV_0 to predict adequate BP control after 12 months of treat-ment. Unpaired t tests were used to assess differences between subjects with and without treatment titration. A p < 0.05 was considered statistically significant. Analysis was performed with SPSS version 13.0 statistical soft-ware (SPSS Inc., Chicago, Illinois).

Table 1	Subject Characteristics at Baseline According to Tertiles of CF PWV$_0$			
	Tertiles of CF PWV$_0$ (m/s)			
Characteristic	First (5.5–10.65) (n = 125)	Second (10.66–13.0) (n = 125)	Third (13.1–24.1) (n = 125)	p Value
Age, yrs	46.0 (0.9)	53.1 (0.9)	60.9 (0.9)	**<0.001**
Males, %	41 (32.8)	44 (35.8)	49 (39.5)	0.542
Weight, kg	77.9 (1.1)	77.1 (1.1)	74.6 (1.1)	0.074
Height, cm	169.3 (0.8)	169.1 (0.8)	167.6 (0.8)	0.267
Body mass index, kg/m^2	27.1 (0.2)	26.8 (0.2)	26.4 (0.2)	0.210
Total cholesterol, mmol/l	5.60 (0.97)	5.56 (0.88)	5.58 (0.96)	0.259
Plasma glucose, mmol/l	5.31 (0.07)	5.54 (0.07)	5.53 (0.07)	0.055
Plasma creatinine, mmol/l	85.4 (1.2)	89.0 (1.2)	90.5 (1.2)	**0.012**
Smoking, n (%)	49 (39.2)	59 (47.2)	64 (51.2)	0.153
CF PWV$_0$, m/s	9.3 (0.1)	11.7 (0.1)	15.1 (0.1)	**<0.001**

Values are expressed as mean (standard error). Values in **bold** indicate significance. Analysis of variance was used to compare quantitative variables and chi-square test to compare categorical variables. CF PWV$_0$= baseline carotid-femoral pulse wave velocity.

Results

Table 1 summarizes the differences in CV risk factors at baseline among the tertiles of CF PWV$_0$. Only age and plasma creatinine increased significantly from the first to third tertiles. No significant differences were found regarding sex, weight, height, body mass index (BMI), total cholesterol, plasma glucose, and smoking.

Table 2 describes the BP at M$_0$ and M$_{12}$ according to the tertiles of CF PWV$_0$. The MBP$_0$ and SBP$_0$ increased significantly from the first to the third tertile. Similarly, after 12 months of treatment, BP (DBP$_{12}$, SBP$_{12}$, and MBP$_{12}$) increased significantly from the first to the third tertile.

Table 3 shows the achieved absolute (mm Hg) decline (BP$_{12}$ to BP$_0$) of SBP, DBP, and MBP after 12 months of treatment according to the tertiles of CF PWV$_0$ and after adjustment for age, sex, and the corresponding BP value at M$_0$. Significantly larger declines in SBP, DBP, and MBP were observed in subjects with the lowest CF PWV$_0$. Further step-by-step adjustments for previous antihypertensive drug treatment and CV risk factors (BMI, plasma creatinine, glucose, and cholesterol) did not change these findings (data not shown). Identical results were found when the BP changes were expressed as relative (rather than absolute) changes from baseline ([BP$_{12}$ − BP$_0$]/BP$_0$) (data not shown).

Table 4 shows independent predictors of the achieved BP reduction (BP$_{12}$ − BP$_0$, mm Hg) of SBP and DBP after 12 months of treatment. Variables entered in the model were age, history of antihypertensive therapy, drug and dosage effects, sex, smoking, and M$_0$ values of BMI, plasma glucose, plasma creatinine, total cholesterol, and CF PWV$_0$. Independent predictors for a small reduction of SBP (mm Hg) ([BP$_{12}$ top BP$_0$] takes negative values) were low SBP$_0$, the need for increased drug dosage (dosage effect), treatment with atenolol (group effect), and high CF PWV$_0$. Independent predictors of a small reduction in DBP (mm Hg) were the need for increased drug dosage, low DBP$_0$, young age, and high CF PWV$_0$. Independent predictors of low MBP (mm Hg) reduction were the need for increased

drug dosage, low MBP$_0$, and high CF PWV$_0$. It should be noted that in all 4 models, a high CF PWV$_0$ was consistently associated with a smaller BP response (SBP$_0$, DBP$_0$, or MBP$_0$).

No significant interaction was observed between CF PWV$_0$ tertiles and drug group or drug dosage, regarding their effects on BP reduction. No significant change in Table 4 findings was observed after further adjustment for baseline pulse rate or its change after 12 months. In addition, no collinearity was found between the independent variables entered in any of the multivariate models.

Table 5 presents a comparison of the 3 subgroups of participants (tertiles of divided CF PWV$_0$) regarding the antihypertensive drug treatment (previous use, group effect, and dosage effect) and the treatment-induced CF PWV decline during the study. The proportions of subjects with prior use of antihypertensive drugs and treatment with atenolol or Per/Ind were similar across the CF PWV$_0$ tertiles. The proportion of subjects who received dosage titration was significantly increased from the first to the third CF PWV$_0$ tertile (p < 0.001). The CF PWV

Table 2	SBP, DBP, and MBP at Baseline and After 12 Months of Treatment, According to CF PWV$_0$			
	Tertiles of CF PWV$_0$ (m/s)			
	First (5.5–10.65) (n = 125)	Second (10.66–13.0) (n = 125)	Third (13.1–24.1) (n = 125)	p Value
DBP$_0$	97.3 (0.6)	99.8 (0.6)	98.1 (6.3)	**0.012**
SBP$_0$	155.8 (1.1)	160.1 (1.1)	165.7 (1.1)	**<0.001**
MBP$_0$	116.8 (0.6)	119.9 (0.5)	120.6 (0.6)	**<0.001**
HR$_0$	72.4 (0.9)	72.6 (0.8)	72.7 (0.9)	0.970
DBP$_{12}$	83.0 (0.7)	84.2 (0.7)	86.7 (0.8)	**0.007**
SBP$_{12}$	137.0 (1.3)	140.0 (1.2)	143.5 (1.4)	**0.007**
MBP$_{12}$	101.7 (0.8)	102.9 (0.8)	105.4 (0.9)	**0.006**
HR$_{12}$	66.9 (0.9)	68.4 (0.8)	69.3 (0.9)	0.235

Values are expressed as mean (standard error). Values in **bold** indicate significance. Analysis of covariance was used to compare quantitative mean values. All parameters values are adjusted for age and sex.

CF PWV$_0$ = baseline carotid-femoral pulse wave velocity; DBP = diastolic blood pressure; HR = heart rate; MBP = mean blood pressure; SBP = systolic blood pressure.

Table 3	Blood Pressure Changes After 12 Months of Treatment Presented According to CF PWV$_0$			
	Tertiles of CF PWV$_0$ (m/s)			
	First (5.5–10.65) (n = 125)	Second (10.66–13.0) (n = 125)	Third (13.1–24.1) (n = 125)	p Value
DBP	−15.6 (0.8)	−14.2 (0.7)	−12.1 (0.7)	**0.011**
SBP	−24.5 (1.3)	−20.8 (1.2)	−17.6 (1.3)	**0.008**
MBP	−18.4 (0.9)	−16.3 (0.8)	−14.1 (0.9)	**0.007**

Values are expressed as mean (standard error) in mm Hg. Values in **bold** indicate significance. Results are adjusted for age, sex, and the corresponding baseline blood pressure by analysis of covariance.
Abbreviations as in Table 2.

Table 5	Comparison of Subgroups of Participants (Tertiles) Divided by CF PWV$_0$			
	Tertiles of CF PWV$_0$ (m/s)			
	First (5.5–10.65) (n = 125)	Second (10.66–13.0) (n = 125)	Third (13.1–24.1) (n = 125)	p Value
Previous use of antihypertensive drugs	70.4	70.4	74.4	NS
Group effect, %	50.4	46.4	48.8	NS
Dosage effect, %	25.6	40.8	52.8	**<0.001**
CF PWV$_{12}$ to PWV$_0$, m/s*	0.2	−0.5	−2.2	**<0.001**

Antihypertensive drug treatment refers to previous use of drugs; group effect refers to atenolol versus perindopril/indapamide; and dosage effect refers to dosage increase (chi-square test). CF PWV$_{12}$ to PWV$_0$ is the treatment-induced pulse wave velocity decline (as measured by analysis of covariance) during the study. Results did not change when pulse wave velocity (PWV) changes were expressed as relative change from baseline ([PWV$_{12}$ to PWV$_0$]/PWV$_0$; data not shown). Values in **bold** indicate significance. Adjusted for age, sex, baseline MBP, and its change after 12 months of treatment.
Abbreviations as in Table 2.

decline after 12 months of treatment was larger in the third tertile (Table 5).

The proportion of subjects with effective BP control (SBP <140 mm Hg and DBP <90 mm Hg) significantly decreased from the first to the third CF PWV$_0$ tertile (p < 0.001) (Fig. 1). This difference among CF PWV$_0$ tertiles was observed exclusively regarding SBP control (p < 0.001), but not DBP, and was found even in subjects with doubled drug dosage (n = 154) during follow-up (Fig. 1). Similar results were found in the total study population (n = 375) at 3-month (before treatment titration) or 12-month follow-up.

Figure 2 shows the ability of CF PWV$_0$ to predict control of SBP with treatment (SBP ≤140 mm Hg after 3 or 12 months of treatment). CF PWV$_0$ did not predict the DBP control (DBP ≤90 mm Hg) (data not shown).

Discussion

This article presents 3 major findings regarding the role of aortic stiffness, assessed by CF PWV before initiation of antihypertensive drug treatment, on the long-term BP

Table 4	Predictors of SBP and DBP Decline After 12 Months of Treatment			
BP Reduction (BP$_{12}$ − BP$_0$), mm Hg	Predictors	p Value	B	95% Confidence Interval
SBP	SBP$_0$	**<0.001**	−0.666	−0.779 to −0.553
	Dosage effect	**<0.001**	6.218	3.409 to 9.152
	Group effect	**0.001**	4.647	1.799 to 7.134
	CF PWV$_0$	**0.001**	1.059	0.454 to 1.664
DBP	Dosage effect	**<0.001**	3.899	2.128 to 5.669
	DBP$_0$	**<0.001**	−0.490	−0.616 to 0.384
	CF PWV$_0$	**0.019**	0.441	0.074 to 0.807
	Age	**0.036**	−0.091	−0.176 to −0.006
MBP	Dosage effect	**<0.001**	4.789	2.837 to 6.741
	MBP$_0$	**<0.001**	−0.593	−0.738 to −0.448
	CF PWV$_0$	**0.003**	0.596	0.201 to 0.990

Variables entered in the linear regression models: age, sex (male), body mass index, smoking, and baseline (0) values of plasma glucose, plasma creatinine, total cholesterol, pulse wave velocity, group effect (1 = perindopril/indapamide, 2 = atenolol), dosage effect (1 = dosage increase, 2 = no dosage increase), previous use of antihypertensive drugs, and corresponding blood pressure (BP) (systolic, diastolic, or mean). Values in **bold** indicate significance.
Abbreviations as in Table 2.

response to antihypertensive drug treatment. First, the highest CF PWV$_0$ tertile was associated with the smallest BP response to drug treatment and a greater need for drug dosage increase. Second, CF PWV$_0$ was a highly significant independent predictor of effective SBP control, but not of DBP, after 12 months of drug treatment. Third, these results were independent of age, baseline BP, previous antihypertensive drug therapy, drug class, and dosage effects as well as traditional CV risk factors. Taken together, these findings suggest that PWV, which is an established marker of the stiffness of central arteries, gives supplementary information to those obtained from brachial BP measurements, regarding the BP response to drug treatment.

In the REASON study, antihypertensive drug treatment reduced SBP, DBP, MBP, CF PWV, and presumably, peripheral resistance, in both treatment arms (atenolol and Per/Ind) (6–8). The present analysis showed that in the high CF PWV$_0$ tertile, there was a smaller decrease in peripheral resistance, concluded from the MBP response, even after doubling the drug dosage (Tables 3 and 4). This observation suggests that large artery structural changes reflect less reversible structural alterations at the level of the arterioles, even after long-term antihypertensive drug treatment. Thus, the present findings support the hypothesis of a common pathophysiologic pathway in hypertensive subjects affecting both the macro- and the microcirculation.

The design of the REASON study, as well as the wide range of CF PWV$_0$ (5.5 to 24.1 m/s) that was observed in this population, has provided advantages and also difficulties in interpreting the previously mentioned findings. First, the double-blind design enabled comparison of a monotherapy (atenolol) versus a combination therapy (Per/Ind) as first-line drug treatment. This study feature was not jeopardized by separating the population into tertiles of arterial stiffness. Thus, the present findings suggest that, in the presence of increased aortic stiffness, inadequate BP response to antihypertensive drug treatment (particularly regarding MBP)
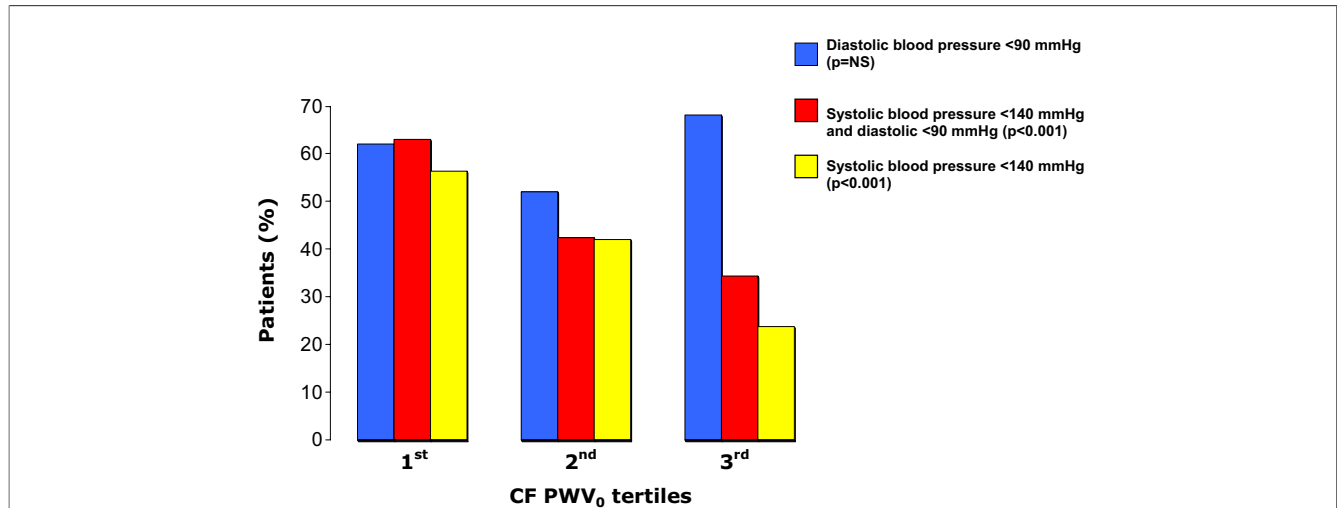
Figure 1 | Percentage of Patients* With Effective Blood Pressure Control After 12 Months of Treatment

*Population with increased dosage (n = 154), similar results were found in the whole population (n = 375) after 3 months (i.e., before dosage increase) and at 12 months. CF PWV$_0$ = baseline carotid-femoral pulse wave velocity.

may be observed regardless of the use of monotherapy or combination therapy. However, the lack of an intensive add-on treatment strategy during the study (on top of the initial drug treatment) resulted in uncontrolled BP in almost one-half of the population, limiting the study conclusions regarding the ability of CF PWV to predict the response of BP to a scenario closer to clinical practice. Another issue is that in the REASON study, office BP was estimated in the

Figure 2 | Aortic Stiffness Predicts Systolic Blood Pressure Response After 12 Months of Treatment

Receiver-operator curve analysis evaluating the ability of pulse wave velocity at baseline to predict the adequate control of systolic blood pressure (<140 mm Hg) after 12 months of drug treatment (area under curve 0.67, p < 0.001, 95% confidence interval: 0.62 to 0.73).

supine position. Therefore, cautious interpretation of these results is needed since PWV and baroreflex sensitivity are inter-related and modulate postural changes of BP (9). However, in a subpopulation of the REASON study (n = 201), identical results have been reported using either ambulatory BP or supine office BP readings (6), suggesting that the present results might be extrapolated to clinical practice.
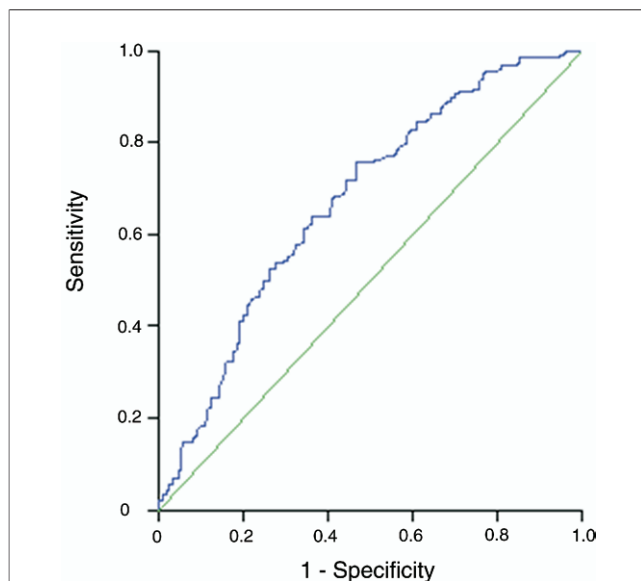
The second major finding of this study was that when participants were classified into CF PWV$_0$ tertiles, the response of SBP differed from that of DBP. The SBP was increased in parallel with increasing PWV, both at baseline and after 12 months of treatment. However, the situation was different regarding DBP. Before treatment initiation, DBP was poorly associated with PWV tertiles and presented an inverse "U-shaped" relationship, as usually observed in isolated systolic hypertension in the elderly (Table 2). However, after 12 months of treatment, DBP was significantly and positively correlated with baseline PWV, and the smaller treatment-induced DBP decline corresponded to the higher baseline PWV tertile (Tables 2 and 3). These findings are in line with the theory that in subjects older than 50 years, and for a given cardiac function, increased SBP is influenced mainly by increased arterial stiffness and/or altered amplitude or timing of wave reflections; low DBP is modulated mainly by low vascular resistance, but also by the increase of arterial stiffness. Since the main determinants of aortic SBP and DBP differ (10), it might be highly expected that in middle-aged subjects (as is the REASON study population), aortic stiffness is a better predictor of effective SBP rather than DBP control with treatment. Indeed, these data showed that: 1) aortic stiffness is a major predictor of effective SBP, but not of

DBP control; and 2) this predictive value is independent of both drug class and dosage.

Several aspects of the association between SBP and PWV should be considered. The principal finding of the REASON study was that, for the same decrease in DBP and MBP, the Per/Ind combination decreased SBP significantly more than atenolol did, although in both arms PWV was equally decreased (7,8). A previous analysis of a REASON subgroup (n = 181) with measurements of central BP and wave reflections (augmentation index) showed that the effect of the Per/Ind combination on SBP was even more pronounced at the level of the central (carotid artery, thoracic aorta) than the peripheral arteries and was associated with a significant attenuation of wave reflections (not observed with atenolol) (7,8). Due to the limited number of subjects with complete follow-up regarding central BP measurements (8,11), no subgroup analysis according to CF PWV_0 tertiles was performed in the present study. However, the results of the REASON study were verified by the results of a larger epidemiologic study (CAFÉ [Conduit Artery Function Evaluation]) (12), and both studies suggest that the difference in SBP response to drug treatment is mainly related to changes in wave reflections rather than in aortic stiffness. Moreover, since in both the REASON and CAFÉ studies, the beta-blocker atenolol was used in 1 treatment arm, the observed results support the view that this particular drug reduces aortic SBP less than the other treatments.

In the present study, although aortic stiffness was reduced more in the highest tertile of CF PWV_0 (Table 5), this reduction was not associated with better control or a larger SBP decline, compared with the other tertiles (Fig. 1). This finding might be explained by several observations that we have reported previously (8). First, in the entire REASON study, the MAP decline was identical in the 2 treatment arms, as confirmed by both office conventional and ambulatory BP measurements (11). In this respect, the change in the distending pressure does not seem to modulate the results of the present analysis. Second, as we have previously shown, within the first 6 months of treatment, the SBP decline was influenced mainly by the changes in wave reflections (primarily their timing) (8). Third, according to studies on human biopsies, regression of structural arteriolar changes is known to begin at the end of the first year of treatment (13), suggesting that this structural modification corresponds to changes in reflection sites and results in significant SBP decline (8,13,14).

Thus, the present findings suggest that, independently of MAP, time-dependent changes in wave reflections and vascular remodeling occur and may interfere with 2 other particularities. First, in some patients, irreversible structural damage might occur at the arteriolar and/or large artery level, due to advanced stage and long-duration hypertension. Although the natural history of vascular aging (microcirculation vs. macrocirculation) (15) and the reversibility of

damage have to be further elucidated, in the same line of argument, a smaller BP reduction is commonly observed in patients with more severe cardiac hypertrophy. This observation is important to consider because the same subjects are expected to have more severe arterial stiffness and higher central BP levels. Second, the regression of structural arteriolar changes observed with the ACEI is less pronounced (or even absent) under beta-blockade (7,12,14), even in subjects with high CF PWV_0, as suggested by the lack of interaction between PWV tertiles and drug group.

The fact that CF PWV_0 did not predict the effective DBP control, even in subjects with dose titration, might be attributed to the hypothesis that peripheral resistance is the predominant mediator of DBP response to drug treatment. Another plausible explanation is that the inverse U-shaped pattern of association between DBP and CF PWV_0 level is a strong confounder. Indeed, there is a U-shaped pattern of association between CF PWV_0 subgroups (tertiles) and effective DBP control rates (Fig. 1, blue bars).

Clinical implications. In the present study, we showed that vascular aging of the macrocirculation, as assessed by CF PWV, rather than age itself, is a major determinant of the BP response to chronic antihypertensive drug treatment and that in the presence of increased large artery stiffness, SBP is more difficult to control than DBP. This effect was independent from the BP level, antihypertensive agents, and CV risk factors. This result might be explained by the fact that aortic stiffness integrates most of the currently known CV risk factors as well as most of the described markers related to poor BP response to drug treatment (16). On the other hand, arterial stiffening per se is considered the cause of isolated systolic hypertension and at the same time, may be the cause of the poor response of SBP to drug treatment. The development of de-stiffening drugs may provide the basis for future research that will clarify this issue. In line with our previous cross-sectional study (6), these results imply that effective BP control requires the concomitant reduction of large artery stiffness, which is a major determinant of SBP reduction. CF PWV may represent a useful index to determine the need for more aggressive antihypertensive therapy. This conclusion has already been suggested, particularly in high-risk patients, such as those with end-stage renal disease (14). The REASON study addressed this question in subjects with relatively lower risk since a beneficial effect may be obtained from early and optimal BP control.

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