Pulse wave velocity as endpoint in large-scale intervention trial. The Complior® study

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Objective To evaluate the ability of an antihypertensive therapy to improve arterial stiffness as assessed by aortic pulse wave velocity (PWV) in a large population of hypertensive patients.

Setting Sixty-nine healthcare centres, private and institutional (19 countries).

Patients Subjects aged 18–79 years, with essential hypertension. A total of 2187 patients were enrolled; 1703 (52% male) completed the study: mean age $= 50 \pm 12$ years; mean baseline systolic/diastolic blood pressure (S/D BP) $= 158 \pm 15/98 \pm 7$ mmHg; mean baseline carotid-femoral PWV $= 11.6 \pm 2.4$ m/s.

Interventions Patients were treated for 6 months, starting with perindopril (angiotensin converting enzyme (ACE) inhibitor) 4 mg once daily (OD), increased to 8 mg OD, and combined to diuretic (indapamide 2.5 mg OD) if BP was uncontrolled ($> 140/90$ mmHg).

Results It was feasible to measure carotid-femoral PWV using the automatic device Complior® at inclusion, 2 and 6 months, along with conventional BP assessments in a population of 1703 patients. Significant decreases ($P < 0.001$) in BP (systolic: -23.7 ± 16.8, diastolic: -14.6 ± 10 mmHg), and carotid-femoral PWV (-1.1 ± 1.4 m/s) were obtained at 2 and 6 months.

Conclusions The Complior Study is the first study to show the feasibility of a large-scale intervention trial using PWV as the endpoint in hypertensive patients. Adequate results may be obtained using an automatic device and rigorous criteria for assessment. A long-term controlled intervention study is needed to confirm the results of the present uncontrolled trial. *J Hypertens* 19:813–818 © 2001 Lippincott Williams & Wilkins.

Introduction

Morbidity and mortality in hypertension are primarily related to arterial damages that may affect one or several organs. Structural and functional properties of the arterial wall have been described to be altered, even at early stages of hypertension [1–4]. Considering the potential implications of arterial assessment in the preventive management of cardiovascular disease, the evaluation of the effect of antihypertensive drugs on the arterial stiffness is recommended by numerous authorities [5]. Several pharmacological double-blind trials have shown that antihypertensive treatments present unequal efficacy on the arterial wall, despite a similar effect on blood pressure (BP) [3,6,7]. However, these results were observed in small and specific populations of subjects. Among the antihypertensive drugs, angiotensin converting enzyme (ACE) inhibitors are likely to improve arterial compliance independently of mean BP level [8–10] but the ability of antihypertensive treatment to reverse the arterial abnormalities observed in hypertension has never been assessed in large-scale studies.

The Complior Study is the first international multicentre clinical trial aimed at analysing the feasibility of using the automatic measurement of pulse wave velocity (PWV) as an endpoint in a large-scale intervention trial.

Methods
Study objectives
The study primary objective was to evaluate the ability of a long-term antihypertensive treatment to reverse arterial stiffness as assessed by an automatic measurement of aortic PWV in a large population of hypertensive patients.

Patients

Male and female patients were included in the study provided they were aged 18–79 years, and presented either untreated essential mild or moderate hypertension, defined as a diastolic BP (DBP) ≥ 95 and ≤ 114 mmHg, and/or a systolic BP (SBP) ≥ 160 and ≤ 200 mmHg, or treated uncontrolled hypertension (SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg), or treated and controlled hypertension (BP $< 140/90$ mmHg) with adverse effects due to the current antihypertensive treatment. Main exclusion criteria were: secondary hypertension, complicated hypertension with recent organ damage (< 6 months), arterial stenosis $> 70\%$, overweight defined as a body mass index (BMI) > 34 kg/m^2, uncontrolled diabetes or fasting glycaemia > 10 mmol/l, and kaliemia $> 5,2$ mmol/l.

Study design

At the end of the run-in period, patients received a 6-month treatment regimen based on perindopril 4 mg once daily (OD), increased to 8 mg OD and combined with a diuretic (indapamide 2.5 mg OD) in case of uncontrolled BP ($> 140/90$ mmHg). The assessment of the drug efficacy was performed over 1-month therapeutic periods during the first 3 months of the study (M0, M1, M2, M3), and at discharge (M6). At each visit, a complete clinical examination was carried out, and PWV was measured at M0, M2, and M6.

Procedures for measuring blood pressure and pulse wave velocity

Clinic BP was measured at each visit, in compliance with World Health Organization guidelines, using a mercury sphygmomanometer with a cuff appropriate to the arm circumference, in patients at rest for 10 min (Korotkoff phase I for SBP and V for DBP). Three measurements were carried out and averaged for analysis.

Arterial distensibility was assessed by automatic carotid-femoral PWV measurement using the Complior® device; the technical characteristics of this device have been described [11], and indicate inter- and intra-observer repeatability coefficient values ≥ 0.9. The basic principle of PWV assessment is that the pressure pulse generated by ventricular ejection is propagated along the arterial tree at a speed determined by the geometric and elastic properties of the arterial wall [1]. PWV is calculated from measurements of pulse transit time and the distance travelled by the pulse between two recording sites, according to the following formula: PWV (m/s) = distance (m)/transit time (s). Carotid-femoral PWV is calculated from the time delay between the recorded proximal (carotid) and distal (femoral) feet of the wave, and the superficially measured distance separating the respective transducers.

Logistics and organization

Eighty centres (22 countries) were selected by the Scientific and Organization Committee of the study; all were provided with Complior® devices adapted to the national regulatory and custom requirements of each participating country.

Investigators, numbering 129, participated in specific training sessions on PWV assessment organized for small groups (four–six persons) of investigators by the Training and Certification Committee of the study. These sessions were aimed at making the investigators familiar with the Complior® device and technical aspects related to its handling, and to practice PWV measurements on healthy volunteers.

In order to limit inter-centre variability on PWV measurements, and to ensure data homogeneity, a pre-study was carried out for the investigators' certification. Each investigator was eligible for participation in the Complior Study provided he or she obtained this certification, on the basis of 20 validated series of PWV measurements. The validation of PWV recordings was performed as follows: in addition to a blind evaluation by two experts from the coordination centre (L'Institut CardioVasculaire, Paris), an objective analysis of PWV recordings was realized for quality control using specific software.

Online assistance (fax or e-mail) was set-up to answer investigators' queries. The criteria established for this quality control were the baseline stability of the recorded PWV, the variations of the baseline according to pulse wave amplitude, the wave shape and the abrupt systolic upstroke of the initial parts of the recorded proximal and distal pressure waves.

Recordings were electronically forwarded to the coordination centre and immediately reviewed for validation by the Quality Control Committee of the study, allowing rapid feed-back to the investigators and the progressive constitution of the study database, as well as questions related to the study protocol, methodology, scientific or technical problems. Two independent services were organized either to manage scientific and medical aspects of the study, or to provide technical assistance on Complior® handling. The most frequently asked questions forwarded through this 'Complior-Line' were summarized in the study newsletter *Complior News*, published periodically (3 months) in order to inform the participating teams on the study progress.

Statistical analysis

Statistical analyses were performed using the NCSS software (Number Cruncher Statistical Systems, NCSS 6.0 for Windows, Kaysville, Utah, USA). The quantita-

tive variables are presented as mean values ± standard deviation; the qualitative variables as absolute values and percentages. Comparisons of quantitative variables between untreated and previously treated patients, or according to gender were carried out, using an analysis of variance adjusted for age and BP level. Analysis of variance for repeated measurements (M0, M2, M6) for both absolute and relative changes and adjustment for BP values were performed. $P < 0.05$ was considered significant.

Results
Study population
After certification, 2187 patients were pre-included in the study; 484 were subsequently excluded, either due to non-compliance with the protocol criteria, or after their PWV recording was eliminated for insufficient quality ($n = 211$). A total of 1703 patients (52% male) were included at M0, aged 50 ± 12 years and presenting the following anthropometric characteristics: mean weight $= 73 \pm 13$ kg, height $= 165 \pm 10$ cm, body mass index (BMI) $= 26.8 \pm 3.6$ kg/m^2, and waist-to-hip ratio $= 0.89 \pm 0.08$. According to the BP level, 63% were classified as having grade I hypertension, 32% as grade II, and 4% as grade III. Regarding cardiovascular parameters, the patients had a mean baseline SBP $= 158 \pm 15$ mmHg, DBP $= 98 \pm 7$ mmHg, heart rate $= 75 \pm 10$ bpm, and carotid-femoral PWV $= 11.6 \pm 2.4$ m/s. Among these patients, 83% had never received an antihypertensive treatment (85% for men, 80% for women), while 17% had been previously treated (15% for men, 20% for women), with β-blockers ($n = 102$), diuretics ($n = 28$), calcium channel blockers ($n = 143$), central agents ($n = 8$) and others ($n = 9$). 1371 patients presented available PWV data at each of the M0, M2, and M6 evaluations.

Effects on blood pressure and pulse wave velocity
Table 1 shows the mean values and changes (Δ) in BP and PWV after 2 and 6 months; significant reductions in SBP, DBP, mean, and pulse BP were observed ($P < 0.001$). The rate of normalized patients was 52% (the treatment resulted in a SBP < 140 mmHg in 60% of the patients and in a DBP < 90 mmHg in 70% of the patients). At M6, the protocol treatment regimen

was: perindopril 4 mg OD in 67%, perindopril 8 mg OD in 22%, and perindopril plus indapamide in 11% of the patients. Regarding PWV, a significant reduction in values was observed (0.9 ± 1.4 after 2 months, and 1.1 ± 1.4 after 6 months; $P < 0.001$).

Table 2 shows mean changes values in BP and PWV after 6 months of treatment, according to baseline BP level (Table 2a) and pre-study treatment status (Table 2b). BP and PWV improvements, were significantly ($P < 0.001$) related to baseline hypertension grade in both men and women. BP reduction was more pronounced ($P < 0.001$) in previously untreated patients than in those previously treated, whereas similar PWV changes were observed in both groups (Table 2b).

Discussion
The Complior Study is the first study aimed at assessing the feasibility of using PWV as endpoints in a large-scale intervention trial. The major finding of this study is that the assessment of arterial stiffness in hypertensive patients, and the evaluation of arterial effects of long-term antihypertensive therapy in a large-scale multicentre study are feasible using an automatic device for aortic PWV measurements, provided some methodological aspects are considered. Different methodological aspects related to these results need to be discussed.

Methodological aspects
Choice of automatic pulse wave velocity measurements
Several non-invasive methods are available and may be useful in assessing large artery hemodynamics (arterial geometry, function), or in analysing the shape of the BP curve [12]. Most are complex, expensive, time-consuming, need specifically qualified operators, and they remain reserved to very few clinical research labs. Since the objective of this study was to evaluate the arterial stiffness in a large multicentre clinical trial, the use of a simple and accurate method appears suitable. PWV is a well-established index of arterial distensibility and stiffness, related to the arterial geometry and wall function (see Methods) [13]. Aortic PWV assessment was therefore utilized in this study and an automatic device that has been shown to provide accurate and

Table 1 Treatment effects on blood pressure and pulse wave velocity; mean values and changes from baseline (M0) during (M2) and at the end of the study (M6)

Variables	M0	M2	M6	Δ(M2−M0)	P	Δ(M6−M0)	P
SBP (mmHg)	158 ± 15	139 ± 16	134 ± 13	-20 ± 17	< 0.001	-24 ± 17	< 0.001
DBP (mmHg)	98 ± 7	86 ± 9	84 ± 8	-12 ± 10.1	< 0.001	-14 ± 10	< 0.001
MAP (mmHg)	118 ± 8	103 ± 10	100 ± 9	-15 ± 11	< 0.001	-18 ± 11	< 0.001
PP (mmHg)	59 ± 15	52 ± 12	50 ± 10	-7 ± 14	< 0.001	-9 ± 15	< 0.001
HR (bpm)	75 ± 10	75 ± 9	75 ± 10	-0.4 ± 10	NS	-0.3 ± 10	NS
PWV (m/s)	11.6 ± 2.6	10.7 ± 2.2	10.5 ± 2.1	-0.9 ± 1.4	< 0.001	-1.1 ± 1.4	< 0.001

SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP: mean arterial pressure; PP, pulse pressure; HR, heart rate; PWV, pulse wave velocity.

Table 2 **Changes in blood pressure and pulse wave velocity according to the initial hypertension grade (a) and pre-study treatment (b). Results are adjusted for age**

(a) Hypertension grade (SBP/DBP mmHg)	ΔSBP (mmHg)		ΔDBP (mmHg)		ΔPWV (m/s)	
	Men	Women	Men	Women	Men	Women
Grade I (140–159/90–99)	−19 ± 15	−21 ± 16	−12 ± 10	−12 ± 10	−1.00 ± 1.39	−1.12 ± 1.39
Grade II (160–179/100–109)	−28 ± 16	−33 ± 14	−18 ± 8	−18 ± 8	−1.03 ± 1.29	−1.22 ± 1.44
Grade III (180/110)	−44 ± 12	−50 ± 14	−22 ± 8	−27 ± 18	−2.03 ± 1.33	−1.48 ± 1.35

± SD; SBP, systolic blood pressure; DBP, diastolic blood pressure; PWV, pulse wave velocity; Δ, change from baseline.

(b) Pre-study treatment status	Δ SBP (mmHg)		ΔDBP (mmHg)		Δ PWV (m/s)	
	Men	Women	Men	Women	Men	Women
Previously treated	−20 ± 18	−23 ± 17	−12 ± 9	−11 ± 10	−1.00 ± 1.55	−0.98 ± 1.42
Previously untreated	−22 ± 16	−26 ± 17	−14 ± 9	−16 ± 9	−1.03 ± 1.33	−1.19 ± 1.40

± SD; SBP, systolic blood pressure; DBP, diastolic blood pressure; PWV, pulse wave velocity; Δ, change from baseline.

reproducible measurements was employed for these measurements [11]. On the other hand, two disadvantages related to PWV determination need to be mentioned. First, this method allows an *overall assessment* of the arterial wall which is related to the arterial geometry and wall function; it does not provide information about the exact underlying mechanisms or specific factors that may be involved in creation of arterial abnormalities or their changes. In fact, changes in PWV may be due to changes either in structural parameters such as the arterial wall thickness, the internal diameter or, to changes in functional parameters such as changes in blood pressure (see Methods). This methodological limitation is not a problematic point in this study, since its primary objective was not to analyse the precise mechanisms of the observed changes in arterial properties. Second, the superficial measurement of the distance travelled by the pulse wave between the carotid and femoral arteries constitutes the major error in PWV determination. In fact, the non-invasive superficial measurement of the arterial pathway allows only an estimate of the distance; accurate measurements of this distance are obtained only by invasive procedures. Some authors suggested a possible correction based on anatomic dimensions, whereas others recommended subtracting the distance between the suprasternal notch to the carotid location from the total distance because the pulse is travelling in the opposite direction [13]. Consequently, and in order to limit the observer errors in the distance measurement by adding up a supplementary measurement (from the carotid to the suprasternal notch), no subtraction has been performed in this study, the distance being determined using a direct linear measurement between the carotid and the femoral sites. Elsewhere, considering that direct superficial measurement of the distance between the carotid and the femoral arteries includes the chest and the abdominal area, men with abdominal obesity and women with large bust measurements, present an overestimation of the real arterial pathway and hence of the PWV. In order to limit such overestimation, it is recommended that one measures the superficial distance as directly as possible; moreover patients with a very high degree of obesity (body mass index > 40 kg/m^2) were not included in this study. Furthermore, it is to be noted that if the distance error is important for the determination of PWV absolute value, it represents only a relative limitation in this study where analysis were based on within patient comparison.

Logistics and organization
From the 129 investigators (80 centres, 20 countries) who entered the certification pre-study, 107 (69 centres, 19 countries) obtained certification and participated in the Complior Study *per se*. Most of them were clinicians and very few had previous experience in non-invasive arterial hemodynamics research. Our results show that evaluation of large arteries using an automatic device for PWV measurement is applicable to clinical trials performed in large populations, in healthcare centres. Moreover, this study took into account some important methodological aspects: (1) the certification procedures allowed the construction of an homogeneous database; (2) online assistance and quality control allowed to limit the loss of data as frequently observed in long-term treatment and large-scale studies; (3) the electronic management of data directly acquired from computerized recordings has the advantage to save time of data input and prevents typing errors. However, since even electronic data transfer may also be erroneous, rigorous evaluation and coherence analysis were performed by two independent

observers to ensure quality. These procedures, that may seem cumbersome and restrictive when setting-up multicentre studies may have benefit when one considers the low rate (under 10%) of PWV data eliminated due to insufficient quality. In fact, among the 211 PWV recordings eliminated for insufficient quality, 142 were at baseline (M0), 39 at M2 and 30 at M6 showing that more than 50% were excluded before the inclusion and that the recording quality was stable during the study period. Nevertheless, advantages related to such quality procedures can only be presumed and suggested since no comparison has ever been performed with another system lacking such procedures. Moreover, arguments for this cannot come from previous pharmacological studies with PWV measurements since most of them were either monocentric or performed in research centres familiar with this technique; thus, their results may not be extrapolated to those observed in the Complior Study where assessments were performed by clinicians with no previous experience of PWV measurement.

Comments on the observed results

The other results of the Complior Study are the decrease of BP and aortic PWV in subjects with essential hypertension after long-term antihypertensive treatment regimen based on ACE inhibitor. In previous phar-
macological controlled studies performed in limited numbers of patients, we and others showed that ACE inhibition improves the properties of large arteries [14–24]. Therefore, the results of the present study are in agreement with those obtained previously in controlled studies.

Although rigorous quality criteria were employed and different committees were involved in this trial, the present study was designed as an open uncontrolled treatment study, for feasibility reasons, and thus was not aimed at answering questions raised by pharmacological studies, or at analysing precisely the mechanisms that may be involved in the observed changes. The analysis of the relationship between PWV and BP showed a significant correlation ($P < 0.001$), but the scatter plots of individual changes in BP and PWV show a significant but weak correlation between changes ($r = 0.264$), with numerous divergent points indicating that change in PWV is not always concomitant with BP changes and vice-versa. It is possible that the observed decrease in BP and PWV could be exclusively related to a regression toward the mean or to a placebo effect. However, several points constitute arguments against this simplistic hypothesis. First, in this investigation, analysis of the results adjusted according to gender, the grade of hypertension and the existence of previous treatment clearly show that the regression to the mean could not be the exclusive factor involved in BP and PWV changes. Second, from previous separate double-blind studies [25–27], the proportion of the placebo effect and the regression to the mean were estimated -6 ± 11 mmHg for SBP, -5 ± 8 mmHg for DBP, and -0.18 ± 1.20 m/s for PWV. Third and mostly, the results of a control group of 369 normotensive subjects (67% male) aged 55 ± 11 years showed over a 6-year follow up period an increase of BP of 6 ± 2 mmHg for the SBP and 2 ± 1 mmHg for the DBP and of 1.50 ± 2.2 m/s for the carotid-femoral PWV (about 0.25 m/s per year) (personal data, A.B.). In this study, the observed changes from baseline (-24 ± 17 mmHg for SBP, -14 ± 10 mmHg for DBP, and -1.10 ± 1.40 m/s for PWV) were first higher than the estimated placebo and regression to the mean effects, and second higher than those observed in the control group.

In conclusion, the Complior Study has shown that changes in arterial stiffness during chronic treatment of hypertension may be assessed noninvasively in a clinical trial involving a large population. Adequate results may be obtained using an automatic device with rigorous criteria for assessment. A long-term double-blind randomized, controlled intervention study is needed to evaluate whether long-term arterial changes, such as the decrease of PWV observed in this study, are due to BP changes, to antihypertensive treatment itself, or to a combination of both factors. Whether this reversion of arterial stiffness may improve the cardiovascular prognostic of hypertensive-treated patients is to be confirmed by specific studies.

Acknowledgments

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Appendix

Participants in the Complior Study

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