Amelioration of arterial properties with a perindopril–indapamide very-low-dose combination

R.G. Asmar[a], G.M. London[b], M.E. O'Rourke[c], J.M. Mallion[d], R. Romero[e], K.H. Rahn[f], B. Trimarco[g], D. Fitzgerald[h], T. Hedner[i], D. Duprez[j], P.W. De Leeuw[k], P. Sever[l], E. Battegay[m], G. Hitzenberger[n], N. de Luca[g], P. Polónia[o], A. Bénétos[p], C. Chastang[q], J.P. Ollivier[r], M.E. Safar[s], on behalf of the REASON* Project investigators

Background Epidemiological studies have shown that increased arterial stiffness and wave reflections, major determinants of systolic and pulse pressure, are associated with morbidity and mortality. Therapeutic trials based on cardiovascular mortality have recently shown that reduction of systolic blood pressure (SBP) requires normalization of both large-artery stiffness and wave reflections.

Aims To compare the antihypertensive effects of the very-low-dose combination of perindopril (2 mg) and indapamide (0.625 mg) (one or two tablets per day) with the β-blocking agent atenolol (50 mg; one or two tablets per day) in order to determine whether the combination decreased SBP and pulse pressure more than did atenolol, and whether this decrease occurred in relation to a reduction in arterial stiffness [aortic pulse wave velocity (PWV)] or a decrease in the intensity of, or delay in, wave reflections (augmentation index, measured by applanation tonometry) or a combination of both.

Material and methods This was a double-blind randomized study in 471 individuals with essential hypertension followed for 12 months. Arterial pressure was measured in the brachial artery (mercury sphygmomanometer) and in the carotid artery (applanation tonometry).

Results For the same reduction in diastolic blood pressure (DBP), the combination of perindopril and indapamide decreased brachial SBP and pulse pressure significantly more than did atenolol (adjusted differences between groups -6.2 ± 1.5 and -5.5 ± 1.0 mmHg, respectively; $P < 0.001$). This difference was even more pronounced for the carotid than for the brachial artery. Whereas both antihypertensive agents similarly decreased PWV, only the combination significantly attenuated wave reflections.

Conclusion Normalization of SBP, pulse pressure and arterial function – a haemodynamic profile known to improve survival significantly in hypertensive populations at high cardiovascular risk – was achieved to a greater extent with a very-low-dose combination of perindopril and indapamide than with atenolol. *J Hypertens* 19 (suppl 4): S15–S20 © 2001 Lippincott Williams & Wilkins

Journal of Hypertension 2001, 19 (suppl 4):S15–S20

Keywords: antihypertensive drug treatment, fixed combination, arterial stiffness, pulse pressure

[a]L'Institut Cardiovasculaire, Paris, [b]Hôpital Manhès, Fleury-Mérogis, [c]St Vincent Hospital, Darlinghurst, Australia, [d]Hôpital Universitaire, Grenoble, France, [e]Hospital Germans Trias y Pujol, Badalona, Spain, [f]Medizinische Universität-Poliklinik, Münster, Germany, [g]Università degli Studi di Napoli, Naples, Italy, [h]The Royal College of Surgeons in Ireland, Dublin, Ireland, [i]Sahlgrenska Hospital, Gothenburg, Sweden, [j]Universitair Ziekenhuis, Gent, Belgium, [k]Academisch Ziekenhuis, Maastricht, The Netherlands, [l]Saint Mary's Hospital Medical School, London, UK, [m]Medizinische Universitäts Poliklinik, Basel, Switzerland, [n]Institut für Hypertoniker, Vienna, Austria, [o]Hospital S João-Farmacologia Clinica, Porto, Portugal, [p]Unité INSERM 337, [q]Hôpital Saint Louis, [r]Hôpital Val de Grace, [s]Hôpital Broussais, Paris. *See Appendix.

This study was performed with the help of INSERM, Association Claude Bernard, GPH-CV and Laboratoires Servier.

Correspondence and requests for reprints to Professor Michel Safar, Médecine Interne 1, Groupe Hospitalier Broussais-George Pompidou, 96 rue Didot, 75674, Paris Cedex 14, France. Tel: +33 (1) 43 95 91 22; fax: +33 (1) 45 43 38 94; e-mail: michel.safar@brs.ap-hop-paris.fr

Introduction

Epidemiological studies have emphasized the close relationship between increased blood pressure and the incidence of cardiovascular disease [1]. Patients with essential hypertension frequently have a parallel increase in systolic blood pressure (SBP) and diastolic blood pressure (DBP) but, in the past, individuals with hypertension were principally classified on the basis of the DBP value [2]. From a haemodynamic point of view, systolic–diastolic hypertension is characterized principally by increased vascular resist-

0952-1178

ance [3]. Blood pressure and its haemodynamic characteristics are influenced by ageing, with a different pattern for SBP and DBP: whereas SBP continues to increase until the eighth and ninth decades of life, DBP tends to remain constant or decline after the fifth or sixth decades. As a consequence, the pulse pressure increases progressively with age [4]. The haemodynamic characteristics of high blood pressure are thus modified during ageing, characterized principally by a progressive increase in arterial stiffness and an increase in arterial wave reflections [5]. Arterial stiffening has several consequences: increased SBP as a result of the ejection during systole of a normal stroke volume into stiff arteries; a decreased time constant of the arterial system leading to a sharp decrease in blood pressure during diastole; and increased pulse wave velocity (PWV) and early return of wave reflections with increased SBP and decreased DBP in the aorta and central arteries. Moreover, the effect of arterial stiffening on SBP is potentiated by an increased intensity of wave reflections themselves (an increase in arterial reflectance), related to alterations in the small resistance arteries [5].

In middle-aged and elderly individuals, the increased pulse pressure has been found to be associated with an increased risk of cardiovascular disease, especially coronary heart disease [6,7]. Recent epidemiological studies in populations at high risk for cardiovascular morbidity and mortality showed that the risk associated with high pulse pressure was directly associated with determinants of pulse pressure [8]. It has been shown that increased aortic stiffness and an increased effect of wave reflections in central arteries are two independent factors associated with mortality in patients with end-stage renal disease, and in the general population [8,9]. A recently published interventional study has also documented that improvement in aortic stiffness in response to antihypertensive treatment has a favourable prognostic impact on a patient's survival [10].

Recent recommendations of hypertension guidelines have directed attention to SBP as a better guide than DBP for evaluating the cardiovascular risk. It has been shown that drug treatment of hypertension frequently results in adequate control of DBP (≤90 mmHg), whereas the ability to control SBP (≤140 mmHg) is achieved to a much lesser extent [11–13]. Such results have focused attention on large artery stiffness and wave reflections as determinants of SBP and pulse pressure, and on the role of drug treatments or regimens that may selectively reduce arterial stiffness and wave reflections.

Fixed combinations of an angiotensin-converting enzyme (ACE) inhibitor and a diuretic could, theoretically, selectively reduce SBP and pulse pressure [14]. Indeed, retrospective studies have shown that, given separately, these compounds may decrease SBP more selectively than DBP when compared with other antihypertensive agents such as β-blockers [15]. Moreover, in genetic models of hypertension in rats, the combination of a diuretic and an ACE inhibitor was shown to cause a significantly more pronounced pressure-independent decrease in arterial stiffness and reduction in aortic collagen accumulation than was produced by each component given alone [16]. Finally, in middle-aged persons with hypertension, whereas diuretics induced only minor changes in large artery stiffness, ACE inhibitors alone or in combination with a diuretic were able to normalize arterial stiffness [16]. These findings suggest that it is relevant to evaluate whether a fixed combination of an ACE inhibitor and a diuretic compound may be a suitable therapeutic procedure with which to selectively reduce SBP and pulse pressure.

Material and methods

The very-low-dose combination of perindopril and indapamide combines the ACE inhibitor and diuretic at subtherapeutic dosages (2 mg/day perindopril and 0.625 mg/day indapamide) [17,18]. In order to verify that this very-low-dose combination decreased SBP and pulse pressure more than the β-blocking agent atenolol for the same reduction in DBP, and that this effect was mediated by a perindopril–indapamide-induced decrease in large-artery stiffness and attenuation of wave reflections, a multicentre, controlled, randomized, double-blind, two-parallel-group study was performed.

After the washout placebo period, 471 patients with essential hypertension entered a 12-month double-blind active treatment period, and were randomly allocated to groups to receive either perindopril–indapamide (2–0.625 mg/day, respectively, given in the same tablet; $n = 236$) or atenolol (given in the classic dosage of 50 mg/day; $n = 235$). The posology was then adjusted to the blood pressure: the dose could be doubled (two tablets once daily) every 3 months if the SBP remained greater than 160 mmHg or the DBP remained greater than 90 mmHg.

Haemodynamic investigations were performed 24 h after the last intake, at the end of the pre-inclusion placebo period (M0), at month 6, and at the end of the follow-up (M12). Carotid–femoral pulse wave velocity (aortic PWV) was determined using an automatic device, the Complior (Colson, Paris) as previously detailed [19]. For local determinations of pulse pressure, the brachial and radial artery SBP, DBP and mean blood pressures (MBP) were considered equivalent. The carotid pressure wave was measured by applanation tonometry and calibrated from the brachial pressure wave, assuming that the mean pressure (determined by mercury sphygmomanometer) was the same at both sites and that brachial and carotid DBP were nearly equal [20]. Carotid pressure amplitude was then computed from the DBP and the position of MBP on the carotid pressure wave [20]. On the carotid blood pressure curve, the augmentation index – a parameter evaluating the effect

of wave reflections on SBP and pulse pressure in the aorta and central arteries – was determined according to previously validated methods [5,20–22].

The results were analysed for the intent-to-treat population. For comparison of serial changes in blood pressure and arterial parameters, repeated-measures analysis of variance (period and group) was performed to examine treatment differences and interactions (period × group). Blood pressure and arterial parameters were constantly adjusted for age, sex and baseline value. For aortic PWV, adjustments for baseline mean arterial pressure and its changes were also performed.

Results

The baseline values of SBP (perindopril–indapamide 163.1 ± 13.4 mmHg; atenolol 161.4 ± 14.8 mmHg), PWV (perindopril–indapamide 12.19 ± 2.91 m/s; atenolol 12.32 ± 2.86 m/s), carotid augmentation index (perindopril–indapamide 29.1 ± 18.5%, atenolol 28.7 ± 21.4%) did not differ between the two groups. At the last evaluation, for the same decrease in DBP (perindopril–indapamide –12.6 ± 8.9 mmHg; atenolol –12.0 ± 9.8 mmHg), brachial SBP and pulse pressure were significantly lower with perindopril–indapamide (141.1 ± 15.3, 55.1 ± 12.9 and 104.4 ± 9.9 mmHg, respectively) than with atenolol (146.4 ± 20.7, 59.8 ± 16.9 and 106.5 ± 12.3 mmHg, respectively). Heart rate was lower with atenolol (65.3 ± 9.3 beats/min) than with perindopril–indapamide (71.1 ± 10.0 beats/min) (Table 1). Carotid SBP (perindopril–indapamide 154.1 ± 17.1 mmHg; atenolol 152.7 ± 17.1 mmHg) and carotid pulse pressure (perindopril–indapamide 58.1 ± 18.0 mmHg; atenolol 55.1 ± 16.4 mmHg) were similar at baseline, decreased significantly ($P < 0.001$ for SBP and $P < 0.01$ for pulse pressure) and were significantly lower with perindopril–indapamide (133.3 ± 14.5 mmHg and 46.9 ± 13.1 mmHg, respectively) than with atenolol (147.8 ± 23.0 mmHg and 59.1 ± 19.9 mmHg, respectively). The adjusted between-group differences were highly significant ($P < 0.001$) (Table 2).

These differences also affected the carotid augmentation index, for which a decrease of –4.0 ± 17.7 with perindopril–indapamide contrasted with an increase of 3.1 ± 15.1 with atenolol ($P = 0.006$ after adjustment). Aortic PWV decreased significantly ($P < 0.001$) and identically with the two drugs and values were similar for the two groups at the end of the study (11.5 ± 2.8 compared with 11.4 ± 2.7), even after adjustment for changes in MBP.

Comments

The findings of the study showed that the very-low-dose combination perindopril–indapamide reduced SBP and pulse pressure more than did atenolol, for the same decrease in DBP. This differential effect was more pronounced in the central (carotid) artery than in the peripheral (brachial) artery. The perindopril–indapamide-induced decreases in SBP and pulse pressure were associated with changes in arterial haemodynamics, including a decrease in aortic stiffness and an attenuation of the effects of wave reflection on the blood pressure in central arteries. The effect on arterial stiffness was pressure-dependent and was observed with both therapeutic regimens, whereas attenuation of wave reflections was obtained with perindopril–indapamide but not with atenolol.

In the past, most therapeutic trials were unable to show that a given antihypertensive drug or regimen could selectively reduce SBP and pulse pressure more than was achieved with a standard comparator. In the present study, substantial differential effects occurred between perindopril–indapamide and atenolol in terms of changes in SBP and pulse pressure. In a previous double-blind study that compared atenolol with the ACE inhibitor fosinopril given alone (i.e. without a diuretic), Chen *et al.* [21] did not find any between-group difference in terms of changes in SBP, DBP or pulse pressure. Thus, in the present study, it is likely that it was the combination of the ACE inhibitor perindopril with low doses of diuretic that was responsible for the greater decrease in SBP and pulse pressure obtained with perindopril–indapamide, compared with that produced by atenolol alone. This effect was even more pronounced when the comparison was made for carotid SBP and pulse pressure, which were decreased more substantially than brachial SBP and pulse pressure.

DBP and mean arterial pressure remain relatively stable along the arterial tree, but SBP and pulse pressure increase physiologically from central (carotid) to peripheral (brachial) arteries [5]. This natural amplification is related to arterial wave reflections that occur at the peripheral reflecting sites. The reflected waves travel from peripheral arteries back towards the aorta. In stiffer arteries, the travelling velocity of reflected waves (PWV) is increased, allowing the reflected waves to return to the aorta in a shorter time – that is, before the closure of the aortic valves. This early return of reflected waves is responsible for abnormal increases in aortic (and carotid) systolic pressures, augmenting the systolic stress [5]. This is responsible for disappearance of the amplification of the pulse pressure with age, as a consequence of a more rapid increase in arterial stiffness with age in the aorta and central arteries [5]. Nowadays, the age-mediated disappearance of pulse pressure amplification is considered to be, *per se* [22], a significant independent cardiovascular risk factor; therefore, in this context, the combination perindopril–indapamide contributed to maintaining the amplification of pulse pressure to a greater extent than did atenolol. Moreover, with perindopril–indapamide, it was possible to achieve nearly normal values of brachial SBP and pulse pressure in the presence of even lower values of carotid SBP and pulse pressure. The same haemodynamic pattern has been observed previously with

Table 1 Changes in brachial blood pressure (intent-to-treat analysis)

	Per–Ind ($n = 235$)†	Atenolol ($n = 234$)†	Adjusted between-group difference‡ (95% CI)	P§
Brachial SBP (mmHg)				
Baseline (M0)	163.1 ± 13.4	161.4 ± 14.8		
M6†	141.5 ± 15.0	143.7 ± 19.1		
End (M12)	141.1 ± 15.3	146.4 ± 20.7		
Δ(End–M0)	−22.0 ± 15.6	−15.0 ± 16.3	−6.2 (−9.0 to −3.5)	<0.001
P	<0.001	<0.001		
Brachial DBP (mmHg)				
Baseline (M0)	98.6 ± 6.8	98.6 ± 7.0		
M6†	85.7 ± 9.0	85.3 ± 10.3		
End (M12)	86.0 ± 9.2	86.6 ± 10.5		
Δ(End–M0)	−12.6 ± 8.9	−12.0 ± 9.8	−0.6 (−2.2 to 1.0)	0.478
P	<0.001	<0.001		
Brachial PP (mmHg)				
Baseline (M0)	64.5 ± 14.9	62.9 ± 16.0		
M6†	55.8 ± 12.9	58.4 ± 15.9		
End (M12)	55.1 ± 12.9	59.8 ± 16.9		
Δ(End–M0)	−9.4 ± 12.2	−3.1 ± 13.2	−5.5 (−7.5 to −3.5)	<0.001
P	<0.001	<0.001		

Values are mean ± SD. Per–Ind, perindopril–indapamide combination; CI, confidence interval; SBP, DBP, systolic and diastolic blood pressures; PP, pulse pressure; M0, M6, M12, months 0, 6 and 12 (end) of study; Δ(End–M0), change from baseline.
†At M6, $n = 218$ for Per–Ind and 217 for atenolol. ‡Adjusted for age, sex and baseline. §Fisher test (ANCOVA).

Table 2 Changes in carotid blood pressures and augmentation index (intent-to-treat analysis)

	Per–Ind ($n = 70$)†	Atenolol ($n = 74$)†	Adjusted between-group difference‡ (95% CI)	P§
Carotid SBP (mmHg)				
Baseline (M0)	154.1 ± 17.1	152.7 ± 17.0		
M6†	135.1 ± 15.6	139.5 ± 18.9		
End	133.3 ± 14.5	147.8 ± 23.0		
Δ(End–M0)	−20.8 ± 17.6	−4.9 ± 16.2	−14.9 (−20.1 to −9.7)	<0.001
P	<0.001	0.011		
Carotid PP (mmHg)				
Baseline (M0)	58.1 ± 18.0	55.1 ± 16.4		
M6†	48.9 ± 14.9	54.2 ± 17.7		
End	46.9 ± 13.1	59.1 ± 19.9		
Δ(End–M0)	−11.2 ± 13.9	4.0 ± 12.8	−13.6 (−17.6 to −9.6)	<0.001
P	<0.001	0.009		
Carotid augmentation index (%)				
Baseline (M0)	29.1 ± 18.5	28.7 ± 21.4		
M6†	26.5 ± 21.2	27.2 ± 21.4		
End	25.1 ± 18.8	31.8 ± 22.2		
Δ(End–M0)	−4.0 ± 17.7	3.1 ± 15.1	−6.8 (−11.7 to −2.0)	0.006
P	0.06	0.08		

Values are mean ± SD. Per–Ind, perindopril–indapamide combination; CI, confidence interval; SBP, systolic blood pressure; PP, pulse pressure; M0, M6, M12, months 0, 6 and 12 (end) of study; Δ(End–M0), change from baseline.
†At M6, $n = 63$ for Per–Ind and 62 for atenolol. ‡Adjusted for age, sex and baseline. §Fisher test (ANCOVA).

other antihypertensive agents such as nitrates or the ACE inhibitor, perindopril, given alone – that is, without a diuretic [20,23].

In comparison with atenolol, perindopril–indapamide induced a more pronounced decrease in carotid SBP and pulse pressure. This was associated with a more pronounced effect of perindopril–indapamide on wave reflections. The effect of wave reflections on carotid systolic and pulse pressures depends on the timing of reflected and incident pressure waves and the intensity of the reflections. The timing of reflected and incident pressure waves in turn depends on three factors: the distance travelled by the pressure wave from the central arteries to the reflecting sites, the speed of travel of the pressure wave – that is, the PWV – and the duration of left ventricular ejection [5,24]. The distance travelled is closely related to the length of the arterial system and body height, which did not change during the study. The decrease in PWV as observed in the present study was responsible for a delayed return of reflected waves and could be responsible for the decrease in the observed effect of the reflected wave. Nevertheless, the decrease in PWV was similar with atenolol and perindopril–indapamide. Finally, the delayed return of the reflected wave associated with a decrease in PWV could be partly compensated by an increased left ventricular ejection time. Increase in the duration of left ventricular ejection increases the possibility of the reflected wave merging with the incident wave. Atenolol induced a small but significant increase in ventricular ejection time that could partly explain the difference observed. In addition to the changes in timing of the reflected waves, the difference in the effect

of the two therapeutic regimens could be a result of alterations in the arterial reflectance, with decreased intensity of reflection [5,24]. Reflection sites are physiologically located at the origin of resistance arterioles – that is, very close to the distal muscular conduit arteries. Because, in these particular territories, the wall-to-lumen ratio of muscular arteries and arterioles is markedly reduced by ACE inhibitors but not by atenolol after long-term treatment [25], the weight of evidence suggests that the contrasting changes in vascular structure produced by perindopril–indapamide and atenolol might mediate differential patterns of wave reflections, with a more substantial reduction in SBP and pulse pressure in response to perindopril–indapamide than occurs in response to atenolol.

Conclusion

The very-low-dose combination perindopril–indapamide normalizes SBP, pulse pressure and arterial function to a larger extent than does atenolol. The principal difference consists in a significant attenuation of wave reflections with perindopril–indapamide, which is responsible for a more marked improvement in central blood pressure (aortic, carotid) than in brachial blood pressure.

Acknowledgements

The authors would like to acknowledge the following for their contributions to the analysis and data management of the study: Drs Bruno Pannier and Jirar Topouchian (coordination and quality control of PWV data), and Dr Olivio Crisan (data management). We thank Mrs Christiane Kaikati and Anne Safar for their skilful technical help.

References

1. Kannel WB. Blood pressure as a cardiovascular risk factor: prevention and treatment. *JAMA* 1996; **24**:1571–1576.
2. Collins R, Peto R, MacMahon S, Hebert P, Fiebach NH, Everlein KA, *et al.* Blood pressure, stroke, and coronary heart disease: part 2. Short-term reductions in blood pressure: overview of randomized drug trials in their epidemiological context. *Lancet* 1990; **335**:827–838.
3. Lund-Johansen P. Haemodynamics of essential hypertension. In: Swales JD (editor): *Textbook of Hypertension*. Oxford: Blackwell Scientific Publications; 1994. pp. 61–76.
4. Franklin SS, Gustin W IV, Wong ND. Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. *Circulation* 1997; **96**:308–315.
5. Nichols WW, O'Rourke M. *McDonald's Blood Flow in Arteries. Theoretical, Experimental and Clinical Principles*, 4th edn. London, Sydney, Auckland: E Arnold; 1998. pp. 54–113, 201–222, 284–292, 347–401.
6. Millar JA, Lever AF, Burke V. Pulse pressure as a risk factor for cardiovascular events in the MRC mild hypertension trial. *J Hypertens* 1999; **17**: 1065–1072.
7. Safar ME. Systolic blood pressure, pulse pressure, and arterial stiffness as cardiovascular risk factors. *Curr Opin Nephrol Hypertens* 2001; **10**:257–261.
8. London GM, Blacher J, Pannier B, Guerin AP, Marchais SJ, Safar ME. Arterial wave reflections and survival in end-stage renal failure. *Hypertension* 2001; **38**:434–438.
9. Blacher J, Guerin AP, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness on survival in end-stage renal disease. *Circulation* 1999; **99**:2434–2439.
10. Guerin AP, Blacher J, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness attenuation on survival of patients in end-stage renal failure. *Circulation* 2001; **103**:987–992.
11. Black HR. The paradigm has shifted to systolic blood pressure. *Hypertension* 1999; **34**:386–387.
12. Black HR, Elliot WJ, Neaton JD, Grandits G, Grambsch P, Grimm RH Jr, *et al.* Baseline characteristics and early blood pressure control in the CONVINCE trial. *Hypertension* 2001; **37**:12–18.
13. Safar ME. Therapeutic trials and large arteries in hypertension. *Am Heart J* 1988; **115**:702–710.
14. Carretero OA, Oparil S. Essential hypertension. Part II: treatment. *Circulation* 2000; **101**:446–453.
15. Pannier B, Garabedian VG, Madonna O, Fouchard M, Darne B, Safar ME. Lisinopril versus atenolol: decrease in systolic versus diastolic blood pressure with converting enzyme inhibition. *Cardiovasc Drugs Ther* 1991; **5**:775–782.
16. Safar M, van Bortel L, Struijker-Boudier H. Resistance and conduit arteries following converting enzyme inhibition in hypertension. *J Vasc Res* 1997; **81**:34–67.
17. Myers MG, Asmar R, Leenen FH, Safar M. Fixed low-dose combination therapy in hypertension – a dose response study of perindopril and indapamide. *J Hypertens* 2000; **18**:1–9.
18. Chalmers J, Castaigne A, Morgan T, Chastang C. Long-term efficacy of a new, fixed, very-low-dose angiotensin-converting enzyme-inhibitor/diuretic combination as first-line therapy in elderly hypertensive patients. *J Hypertens* 2000; **18**:327–337.
19. Asmar R, Benetos A, Topouchian J, Laurent P, Pannier B, Brisac A-M, *et al.* Assessment of arterial distensibility by automatic pulse wave velocity measurement: validation and clinical application studies. *Hypertension* 1995; **26**:485–490.
20. London GM, Pannier B, Guerin AP, Marchais SJ, Safar ME, Cuche JJ. Cardiac hypertrophy, aortic compliance, peripheral resistance, and wave reflection in end-stage renal disease. Comparative effects of ACE inhibition and calcium channel blockade. *Circulation* 1994; **90**:2786–2796.
21. Chen CH, Ting CT, Lin SJ, Hsu FCP, Siu CO, Chou P, *et al.* Different effects of fosinopril and atenolol on wave reflections in hypertensive. *Hypertension* 1995; **25**:1034–1041.
22. Safar ME, Blacher J, Pannier B, Guerin AP, Marchais SJ, Guyonvarc'h PM, *et al.* Central pulse pressure and mortality in end-stage renal disease. *Hypertension* 2001 (in press).
23. Yaginuma T, Avolio AP, O'Rourke MF, Nichols WW, Morgan J, Roy P, *et al.* Effect of glyceryl trinitrate on peripheral arteries alters left ventricular hydraulic load in man. *Cardiovasc Res* 1986; **20**:153–160.
24. Kelly R, Daley J, Avolio A, O'Rourke M. Arterial dilatation and reduced wave reflection: benefit of dilevalol in hypertension. *Hypertension* 1989; **14**:14–21.
25. Schiffrin EL, Deng LY, Larochelle P. Effects of a beta-blocker or a converting enzyme inhibitor on resistance arteries in essential hypertension. *Hypertension* 1994; **23**:83–91.

Appendix

Investigators (by alphabetical order of country) of the pREterax in regression of Arterial Stiffness in a contrOlled double-bliNd study (REASON) project*

Australia: M.F. O'Rourke (Darlinghurst); R. Gordon (Greenslopes); B.M. Grath (Clayton); T. Morgan (West Heidelberg); R. Zacest (North Adelaide).

Austria: G. Hitzenberger, D. Magometschnigg (Vienna); F. Skrabal (Graz).

Belgium: D. Duprez, I. Vanhoudt, P. Debackere, D. Feys, L. Delvaux (Gent); P. Cleen (Zwijnaarde); M. Fiers (Mariakerke); E. Schatteman (Dronger); P.G. Silance, P. Vandenbossche (Brussels).

France: M.E. Safar, R. Asmar, B. Levy (Paris); J.M. Mallion, P.H. Baguet, J.M. Senechal (Grenoble); M. Andrejak, J.P. Bondois (Amiens); B. Chamontin, J. Amar, T. Brillac, P. Monsegur (Toulouse); P. Fressinaud, G. Berrut, J. Daugy, M. Lambert, A. Mario, J. Tondut, R. Gaudichon (Angers); P. Gosse, V. Jullien, P. Dejean, F. Devenyns, J. Gayet, P. Guerin, F. Paccalin, P. Uge (Bordeaux); D. Herpin, S. Ragot

* See Proceedings of the 4th Workshop on Structure and Function of Large Arteries. *Hypertension* 2001, **38**:922–926.

(Poitiers); G. London, A. Guerin, S. Marchais, B. Pannier (Ste Geneviève des Bois); R. Luccioni, P. Ambrosi, B. Vaisse, J.L. Poggi, F. Silhol, D. Bousquet, G. Recorbet, M. Vauthier (Marseille); H. Michalski, O. Gourdon, C. Tardy, C. Delhomme, J.L. Englebert, C. Malzac, R. Said (Perpignan); A. Mimran, G. du Cailar, S. N'Guyen (Montpellier); D. Stephan, P. Desarnauts, A. Zech, J.L. Imbs, J.F. Badina, T. Geist, P. Marmor (Strasbourg); C. Thuillez, R. Joannides, M. Godin, B. Adam, J. Ennasr, P. Mazingue Desailly, G. Pelage (Rouen); Y. Weiss, F. Tertrain, J.M. de Kermadec (Meaux); C. Cavat (Domène); B. Chassery (Fontaine); P. Jallon (Meylan); C. Boulnois (Cagny); A. Delannoy (Moreuil); P. Desobry (Warloy Baillon); M. Bonnefoy, J.P. Boyes (Seysses); B. Dauptain (Pamiers); M. Hercyk (Gragnague); L. Rouperas (Launac); P. Igigabel (Tierce); M. Quenelle, J.P. Hubault (Avrille); B. Courtot (Carbon Blanc); X. Magnac (Beglas); M. Behar (Longpont sur Orge); R. Benady (Marcoussis); J. Cimignani (Athis Mons); J. Rebot (Epinay sur Orge); P. Beffara (Bages); D. Ching, G. Elgrishi (Leucate); D. Sar (Fourques); M. Tabary (Le Barcares).

Germany: K.H. Rahn, D. Barenbrock, R. Kisters (Münster); R.M. Lederle (Dortmund); N. Prokynitopoulos (Nienburg-Langendamm); A. Schreckenberg (Weyhe-Mitte); J. Zehner Lehmann (Passau); R. Krallinger (Fürstenzell).

Ireland: D. Fitzgerald, E. O'Brien (Dublin).

Italy: B. Trimarco, N. de Luca (Naples); G. Cerasola, G. Mule (Palermo); R. de Cesaris, A. Andriani, I. Ieva, P. Panettieri (Foggia); M. Giardinieri, F. Ceccarelli, G. Coliviveti, L. Nosorti (Rome); E. Uslenghi, G. Uliengo (Cuneo).

Portugal: J. Polonia, J. Maldonado, J. Alberto da Silva, G. Campelo (Porto); J. Gorjao Clara (Morais); G. Silva Nunes (Lisbon).

Spain: R. Romero, J. Bonet, B. Bayés (Badalona); C. Calvo, E. Lopez Paz (Santiago de Compostela); J. Olivan Martinez, E. Ramos Gonzalez, C. Fernandez Andrade, C. Navarro, V. Garcia (Sevilla); A. Roca Cusachs, T. Benet (Barcelona); J.L. Palma-Gamiz, A. Calderón Santos Casado Perez, T.A. Rico Zalba, B. Marron, J.L. Rodicio, L. Guerrero, M. Cruz Casal (Madrid), J. Herrera Pérez de Villar (Oviedo).

Sweden: T. Hedner (Göteborg); B. Polhem, G. Dahlen (Grästorp).

Switzerland: E. Battegay, K. Tschudin (Basel).

The Netherlands: P.W. De Leeuw, F. Kroon, B. Houben, W. Spiering (Maastricht).

UK: P. Sever, N. Chapman, C.J. Bullpitt, S. Bonapace, C. Rajkumar, S. Jackson, J. Close, D. Lyons (London); J.L. Reid, A. McKay (Glasgow).