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## **Effects of Eprosartan on Pulse Pressure**

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## Effects of Eprosartan on Pulse Pressure

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Elevated systolic blood pressure, together with normal or low diastolic blood pressure, characterises isolated systolic hypertension, the most frequent form of hypertension in subjects older than 60. Pulse pressure is defined as the difference between systolic and diastolic pressures and probably reflects the rigidity of large arteries, especially the aorta. Epidemiological studies and prospective analyses of patients included in large randomised trials against placebo have demonstrated a close relationship between pulse pressure and cardiovascular morbidity and mortality. The prognostic importance of pulse pressure has lead to an increased interest in this parameter as a therapeutic target and some authors recommend that, in addition to other therapeutic goals, a reduction in pulse pressure below 50 mmHg is advisable for all hypertensive patients. Moreover, analysis of the effect on pulse pressure is also recommended in comparative trials of antihypertensive agents.

Recent analyses of these comparative trials suggest that differences in pulse pressure reduction may have influenced the cardiovascular outcome. In an observational study including more than 3000 patients, eprosartan promoted a substantial reduction in pulse pressure (13.5 mmHg) that was partially independent of the mean blood pressure reduction. This effect was more pronounced in older patients and those who had isolated systolic hypertension or previous cardiovascular disease. This clinical profile of eprosartan may reflect its specific pharmacological properties and help to understand its importance in terms of cerebrovascular, cardiovascular and renal protection. *J Clin Basic Cardiol* 2005; 8: 11–4.

**Key words:** eprosartan, pulse pressure, angiotensin-receptor blockers, isolated systolic hypertension

The classic concept of hypertension is defined by an elevation of systolic and/or diastolic blood pressure (BP). The diagnosis and management of hypertension have been dominated during decades by pathophysiological considerations, assuming that diastolic BP represents the status of peripheral resistance, whereas systolic BP represents the strength of cardiac output trying to overcome this arterial resistance. This tendency to consider diastolic BP as deleterious and systolic BP as beneficial was strengthened by the publication, in 1990, of two meta-analyses of observational [1] and intervention studies [2] that correlated diastolic BP elevation with cardiovascular morbidity and mortality and the reduction of elevated diastolic BP with a decrease in cardiovascular and cerebrovascular events.

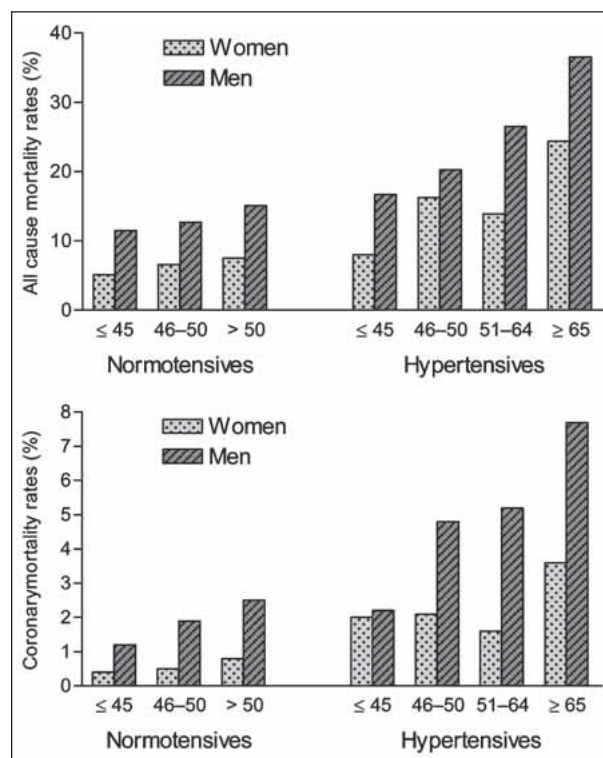
The priority given to diastolic BP over systolic BP has changed in recent years. Twenty years ago, the Framingham Heart study investigators suggested that systolic BP was a better predictor of cardiovascular disease than diastolic BP [3]. This epidemiological observation was strengthened by the excellent results of trials of antihypertensive treatment in patients with isolated systolic hypertension. Nowadays, most guidelines [4, 5] recognise that cardiovascular morbidity and mortality is more closely related to systolic than diastolic BP, especially in older subjects.

Recent data indicate that another BP component, pulse pressure (PP), is an independent predictor of cardiovascular risk. Pulse pressure is obtained by calculating the difference between systolic and diastolic BP and thus emphasises the importance of systolic rather than diastolic blood pressure.

### Pulse Pressure and Cardiovascular Disease

Epidemiological studies have linked PP and cardiovascular disease. In 1994, Madhavan et al. [6] suggested that hypertensive subjects in the upper tertile of PP (> 63 mmHg) had a significantly increased risk of coronary heart disease mortality. Benetos et al. [7], in a large epidemiological study of

almost 20,000 Parisians, demonstrated a relationship between PP and both coronary and cardiovascular mortality that was independent of the contribution of other cardiovascular risk factors (Fig. 1). In a posterior analysis, this relationship was present not only in hypertensives but also in normotensive individuals [8]. Similar results were obtained by



**Figure 1.** All-cause mortality (top) and coronary mortality (bottom) in normotensive and hypertensive men and women depending on pulse pressure categories; data obtained from [8]

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Alderman et al. [9], in 8690 hypertensives with 20 years of follow-up.

The Framingham Heart study [10] also examined the relationship between PP and cardiovascular disease. In a survey of 1924 men and women aged 50 to 79 free from cardiovascular disease and antihypertensive treatment at baseline, PP was the BP component that had the closest relationship with coronary heart disease. For each systolic BP value, the incidence of ischaemic heart disease directly correlated with PP elevation. However, in patients with PP higher than 50 mmHg, systolic or diastolic BP elevation had no added prognostic importance.

In addition to coronary and cerebrovascular morbidity and mortality, elevated PP has been related to the development of congestive heart failure in older subjects [11, 12] and those with end stage renal disease [13].

Finally, PP has also been related to target organ damage in the hypertensive population. In the European Lacidipine Study of Atherosclerosis (ELSA), the main determinants of vascular wall damage were age and PP [14]. Other studies have related PP to the degree of carotid stenosis [15] or left ventricular hypertrophy [16].

### Pathophysiology of Pulse Pressure Elevation

In developed countries, BP increases with age from childhood onwards. The Framingham Heart study has clearly demonstrated that not all the components of BP run in parallel with aging [17]. Diastolic BP increases until around 50 years of age and then begins to decrease. On the other hand, systolic BP continues to increase throughout life. As a consequence, PP increases more steeply during the last decades of life. Isolated diastolic hypertension is common in young subjects whereas isolated systolic hypertension is the most frequent form of hypertension in older subjects. The epidemiological importance of isolated systolic hypertension and, thus, elevated PP, is mirrored by its pathophysiological significance which is related to the rigidity of large arteries. In fact, it is clearly recognised that a wide PP is a marker of arterial stiffness. Large artery stiffness is affected by many factors including aging, disease states, and pharmacological interventions, although age and hypertension are the most important. When arterial distensibility is reduced due to elastin degeneration and subsequent remodelling resulting in increased collagen content and the deposition of extracellular matrix and calcium, the pulse wave velocity increases and then reflects when the impulse reaches the high resistance vessels at the periphery. This wave reflection travels backwards and increases pressure at the end of the systole, thus promoting an amplification of the pulse pressure wave and increasing systolic pressure, whereas diastolic pressure decreases. This pattern is typically seen in older patients with isolated systolic hypertension and aorta stiffness and may impair myocardial and cerebral perfusion, especially at the diastole [18–20].

### Antihypertensive Treatment and Pulse Pressure. Information from Studies on Isolated Systolic Hypertension

The effect of antihypertensive treatment on cardiovascular morbidity and mortality in older subjects with isolated systolic hypertension has been evaluated in three studies: the Systolic Hypertension in the Elderly Program (SHEP) [21], with a chlorthalidone-based treatment; the Systolic Hyper-

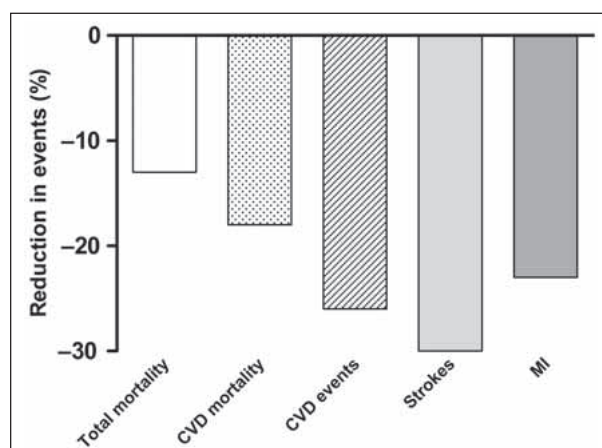


Figure 2. Reduction in morbidity and mortality by antihypertensive treatment in patients with isolated systolic hypertension. Metaanalysis from randomised trials; data from [24]

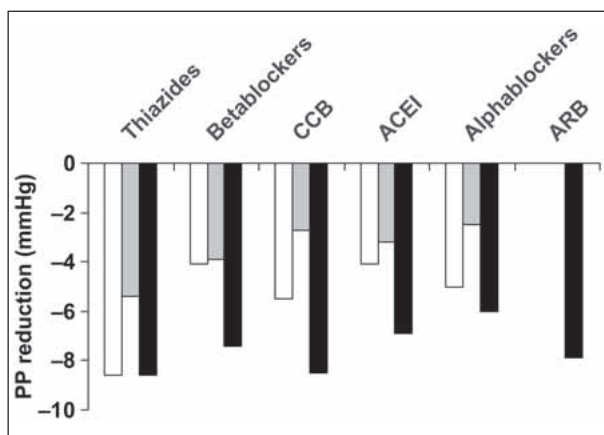
tension in Europe (Syst-EUR) [22] and the Systolic Hypertension in China (Syst-China) [23], both using treatment based on the calcium channel-blocker nitrendipine. Data from these trials and from other trials in the elderly with isolated systolic hypertension (a total of more than 15,000 patients) were included in a metaanalysis [24] concluding that a decrease in systolic BP of 10.4 mmHg (from baseline values of 174/83 mmHg) promoted significant reductions in total mortality (13 %), cardiovascular mortality (18 %), cardiovascular events (26 %), strokes (30 %), and myocardial infarctions (23 %) (Fig. 2). The benefit observed was directly correlated with the degree of PP elevation. The number needed to treat during 5 years to prevent a cardiovascular complication was 63 if baseline PP was higher than 90 mmHg or 119 if the baseline PP was lower than 90 mmHg.

The predefined subgroup analysis from the LIFE study (Losartan Intervention For Endpoint reduction) [25] was the first direct comparative trial between two antihypertensive drugs in patients with isolated systolic hypertension. In losartan-treated patients, the primary combined endpoint (cardiovascular death, stroke, and myocardial infarctions) was reduced in comparison with those receiving an atenolol-based treatment. Moreover, a decrease in total mortality was observed with losartan.

Another important lesson from trials on isolated systolic hypertension is the need for combination therapy to reduce BP below the therapeutic goal. Rates of combination therapy were 46 % in the SHEP (systolic goal 160 mmHg or a decrease of 20 mmHg), 41 % in the Syst-EUR (systolic goal 150 mmHg) and 90 % in the LIFE study (systolic goal 140 mmHg).

### Are there Differences in PP Reduction between Antihypertensive Drug Classes?

There are no clinical trials focusing on the reduction of PP by antihypertensive treatment and the data available come from a specific analysis of previous trials. The Veterans Affairs Single-Drug Therapy for Hypertension [26] study compared BP reduction between six antihypertensive drug classes. A posterior analysis of PP reduction showed that hydrochlorothiazide had a greater effect compared to the other classes [27]. These results favouring the effect of thiazide diuretics on PP reduction were also observed in the Treatment of Mild Hypertension Study (TOMHS) using chlorthalidone [28].



**Figure 3.** Reduction in pulse pressure by different antihypertensive drug classes in three different comparative trials. Open bars represent data from [27], light grey bars represent data from [28], solid bars represent data from [29]. CCB = calcium channel blockers; ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin-receptor blockers

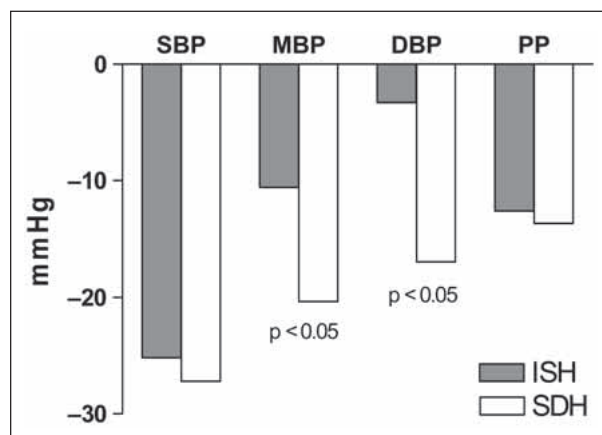
In a study including more than 800 Spanish hypertensive patients, we found no significant differences in PP reduction between antihypertensive drug classes. However, as in previous trials, thiazide diuretics tended to a somewhat greater reduction in PP (Fig. 3) [29].

Another important source of data on the importance of PP reduction comes from recent comparative trials on antihypertensive agents showing superiority in cardiovascular protection. The Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack Trial (ALLHAT) [30, 31] demonstrated a better outcome (based on secondary endpoints) in patients treated with chlorthalidone with respect to those who received doxazosin, amlodipine or lisinopril, although the PP reduction was not homogeneous in all the treatment arms. The chlorthalidone arm reduced PP between 2 mmHg and 3 mmHg more than other drugs. Differences in PP reduction were also observed in the LIFE trial (1.4 mmHg in the whole trial [32] and more than 2 mmHg in the subgroups of diabetics [33] and patients with isolated systolic hypertension [25]), in the VALUE trial (more than 2 mmHg in the first six months of follow-up) [34] and in the recent ASCOT trial [35]. In all these cases, differences in PP reduction may have influenced the better outcome in one of the comparative groups.

### Effect of Eprosartan on Pulse Pressure

The ETAPA-2 trial [36] was an observational study designed to assess the effect of eprosartan on PP in real clinical practice. The study included 3133 hypertensive patients, 55 % women, with a mean age of 67 years. They received 600 mg/day of eprosartan (87 % in monotherapy) and were then followed-up during 12 weeks in primary care centres. Blood pressure was measured using a validated oscillometric device.

The main results showed that eprosartan effectively reduced PP (13.5 mmHg at 12 weeks) and also produced significant reductions in systolic, mean, and diastolic pressures (26.0 mmHg, 17.1 mmHg, and 12.6 mmHg, respectively). The PP reduction was homogeneous in all the subsets of patients, independently of age, sex, smoking status, diabetes, dyslipidaemia, left ventricular hypertrophy, or previous cardiovascular disease.



**Figure 4.** Effects of eprosartan on different blood pressure components in patients with isolated systolic hypertension (ISH) or systo-diastolic hypertension (SDH). In patients with ISH the effect on systolic (SBP) and pulse pressure (PP) is maintained, whereas the effect on diastolic (DBP) and mean (MBP) pressures is clearly less pronounced.

An analysis of the effect of treatment with eprosartan on the relative reductions of the static (represented by diastolic BP and mean BP) versus the pulsatile components (represented by systolic BP and PP) of blood pressure was performed. Pulse pressure/mean blood pressure ratio was calculated in an attempt to normalise PP based on the severity of hypertension. Treatment with eprosartan resulted in a significant reduction of the pulse pressure/mean blood pressure ratio from  $61.9 \pm 14.8$  % to  $58.5 \pm 12.7$  % ( $p < 0.05$ ). The PP reduction can be considered to be 3.4 % greater than the overall mean blood pressure reduction. Factors that significantly predicted a greater reduction in the pulse pressure/mean blood pressure ratio included age over 60 years, a higher baseline ratio and the presence of cardiovascular disease.

A special analysis of the ETAPA study was performed in patients with isolated systolic hypertension [37]. Compared with those having both systolic and diastolic BP elevation, those with isolated systolic hypertension (895 patients) maintained both systolic BP and PP reduction, whereas diastolic BP was not significantly reduced by eprosartan treatment (Fig. 4). This lack of effect on diastolic BP in patients with isolated systolic hypertension may be of importance in terms of the safety of eprosartan treatment, as it has been shown that reduction of diastolic BP to below 70 mmHg in patients with isolated systolic hypertension may be related to increases in cardiovascular events [38].

### Closing Remarks

Pulse pressure probably constitutes a new cardiovascular risk marker, especially in subjects older than 60 years. Elevated PP is associated with a poor cardiovascular prognosis and reflects the stiffness of large arteries. However, data on specific cardiovascular protection due to PP reduction are lacking, although it is suggested that the impact of this reduction may have influenced the cardiovascular outcome in comparative trials of antihypertensive treatment. Eprosartan, a fourth-generation angiotensin receptor blocker has been shown to have an important effect on PP reduction in observational studies. This effect, combined with other characteristics of eprosartan, such as its specific mechanism of action and the cardiovascular and cerebrovascular protection observed in clinical trials [39], suggests that eprosartan may play an im-



portant role in the current and future treatment of hypertension and cardiovascular disorders.

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