Beyond Blood Pressure Reduction in the Treatment of Arterial Hypertension. Clinical Implications of the LIFE Study

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To date, blood-pressure lowering has been the main therapeutic objective in patients with arterial hypertension, regardless of the drug used, except for drugs selected for accompanying conditions. The LIFE study, carried out in 9,193 high-risk hypertensive patients (with ECG criteria of left ventricular hypertrophy), has shown that a therapeutic regimen based on losartan combined with a thiazide was accompanied by a significant reduction in the risk of cardiovascular complications in more than 90% of patients compared with atenolol and a thiazide over a mean follow-up period of 4.8 years. The incidence of the primary endpoints (cardiovascular death, stroke, and myocardial infarction) was 11% in the losartan group and 13% in the atenolol group (13% relative risk reduction, p = 0.021). Losartan therapy was associated with more benefits in stroke risk reduction and in the development of new cases of diabetes. In the analysis of the subgroup of 1,195 patients with hypertension and diabetes included in the LIFE study, losartan had a special prognostic benefit. One of the cardiovascular events included as a primary endpoint was observed in 18% of the losartan-treated patients and in 23% of the atenolol-treated patients (24% relative risk reduction, p = 0.031).

The LIFE trial showed that losartan produced better cardiovascular protection than atenolol, a similar blood pressure reduction, and was better tolerated. This drug seems to confer extra cardiovascular protection in addition to reducing blood pressure.

Key words: *Arterial hypertension. Left ventricular hypertrophy. Losartan.*

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Más allá de la reducción de las cifras de presión en el tratamiento de la hipertensión arterial. Implicaciones del estudio LIFE

Hasta la actualidad, con independencia del fármaco empleado, la reducción de las cifras de presión arterial era el principal objetivo del tratamiento de la hipertensión arterial, salvo indicaciones farmacológicas específicas en función de la patología acompañante. Los resultados del estudio LIFE realizado en 9.193 hipertensos de alto riesgo (con criterios electrocardiográficos de hipertrofia ventricular izquierda) demuestran que una estrategia terapéutica basada en losartán combinada con tiazida en más del 90% de los pacientes se acompaña de una significativa reducción del riesgo de complicaciones cardiovasculares en relación al tratamiento con atenolol combinado con tiazida durante un seguimiento de al menos 4 años. La incidencia del objetivo primario (muerte cardiovascular, ictus e infarto de miocardio) fue del 11% en el grupo losartán frente al 13% en el atenolol (reducción del riesgo relativo del 13%, p = 0,021). Merece destacarse la especial protección del tratamiento con losartán frente al riesgo de ictus y sobre la aparición de casos nuevos de diabetes durante el seguimiento. En los 1.195 hipertensos diabéticos incluidos en el estudio LIFE, el tratamiento con losartán se acompañó de un particular beneficio pronóstico, el 18% de los pacientes tratados con este compuesto presentó durante el seguimiento un episodio incluido en el objetivo primario frente al 23% de los tratados con atenolol (reducción del riesgo relativo del 24%, p = 0,031).

Los resultados del estudio LIFE indican que losartán ejerce una protección cardiovascular mayor que atenolol para el mismo grado de reducción de la presión arterial y tiene mejor tolerabilidad. La protección cardiovascular ejercida por losartán parece mayor de la esperada por la reducción de presión.

Palabras clave: *Hipertensión arterial. Hipertrofia ventricular izquierda. Losartán.*

Essential arterial hypertension (AHT) is the most prevalent determinant of cardiovascular disease (CVD) in Spain,[1-3] although in clinical practice its contribution to the risk of CVD should be analyzed in the light of the overall risk induced by the interaction of different risk determinants (age, sex, plasma lipids, smoking,

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diabetes, and blood pressure).[4] The presence of clinical findings of organic CVD and renal involvement (microalbuminuria, retinopathy, and left ventricular hypertrophy) or clinical diseases associated with AHT identifies groups of patients at particularly high risk in which a stricter control of blood pressure is recommended (in most guidelines <130/85 mm Hg or even less).[4-6]

The choice of antihypertensive treatment must be individualized based on patient characteristics, especially in higher-risk groups.[4-6] Until now, the extraordinary amount of scientific evidence available in the three last decades has suggested that «in hypertension, the most important thing is to lower blood pressure,» regardless of the antihypertensive selected. In this sense, clinical trials comparing different drugs have not documented differences in the prognosis of CVD, particularly the most recent clinical trials in which the effectiveness of classic antihypertensives (diuretics and beta-blockers) was compared to the latest groups (calcium antagonists and angiotensin-converting enzyme inhibitor [ACEIs]).[7] Certain reasons may explain the similarities in prognostic behavior. In practice, all of these trials have included groups of hypertensives that are not very high risk and have had a limited duration of follow-up (generally less than 5 years). It is especially relevant that the groups of patients randomly distributed to different drug treatments maintained blood pressure levels within the range of hypertensive values during follow-up and only a scant proportion achieved normal blood pressure. Consequently, it can be speculated that when blood pressure is high, the most important priority is to lower it, to some extent regardless of the drug used. Various experimental and clinical studies, including the HOPE study in patients with high risk CVD (diabetics with another associated risk factor and patients with ischemic heart disease, stroke, or peripheral arteriopathy), MICRO-HOPE in the subgroup of diabetics,[8,9] and studies of angiotensin II receptor antagonists (ARA II) in diabetics with nephropathy,[10-12] although not AHT studies in the strict sense, suggest that pharmacological intervention on the renin-angiotensin system could enhance protection against CVD in a way that is better than would be expected from reducing blood pressure.

The development of left ventricular hypertrophy (LVH) in AHT is related with demographic factors (age, race, etc.) as well as increased mechanical load (blood pressure levels, particularly the mean of 24 h of systolic blood pressure) and the activity of different mediators and neurohormonal systems.[13] Its prevalence in the general population of hypertensive patients varies widely (from 3% to more than 60%) with the characteristics of the group of patients studied, particularly the severity and duration of AHT, diagnostic technique (ECG or ECHO), and criterion used as the cutoff point.[14-17] The diagnosis of LVH is a powerful independent predictor of morbidity and mortality due to CVD. In particular, left ventricular mass determined by ECHO in hypertensive patients is a better predictor than any another risk factor, except age, of cardiovascular complications.[18-20] The remission of LVH with antihypertensives, determined by ECHO or ECG, has been shown to be associated with a better prognosis in hypertensives and currently is one of the endpoints of AHT treatment.[21-23] In this sense, almost all available pharmacological groups for the treatment of AHT have demonstrated their ability to reduce left ventricular mass and, although ACEIs are the pharmacological group most effective in remitting LVH in different meta-analyses, comparative drug studies have not found significant differences.[24-26] Until the results of the LIFE study (Losartan Intervention For Endpoint reduction in hypertension study) were published, we did not have prognostic information that would provide us guidance in clinical practice for choosing an appropriate therapy for hypertensives with LVH.[27,28]

LIFE STUDY

Study characteristics

This randomized, double-blind clinical trial of parallel groups included 9193 patients with essential hypertension ranging in age from 55 to 80 years, with a systolic blood pressure (SBP) of 160 to 200 mm Hg and/or diastolic blood pressure (DBP) of 95 to 115 mm Hg after 1-2 weeks of administration of placebo and electrocardiographic findings of LVH.[27] The patients were randomly distributed to therapeutic strategies based on either atenolol or losartan with the aim of achieving blood pressure figures of 140/90 mm Hg. Treatment began with 50 mg/day of each of the compounds, associated with 12.5 mg of hydrochlorothiazide. In patients in whom the blood pressure endpoint was not achieved after a 2-month interval, the dose was increased to 100 mg/day of atenolol or losartan after increasing the diuretic dose (25 mg/day) or adding another antihypertensive (other than ACEIs, ARA II, or beta-blockers). The ECG diagnosis of LVH was made using the product of QRS duration by the Cornell voltage criterion (R in aVL plus S in V3) and the Sokolow-Lyon index, with cutoff points for LVH of >2440 mm×ms and >38 mm, respectively. The sum of episodes of death due to CVD, myocardial infarction, and stroke was considered the primary endpoint of the study.

The patients were followed-up for at least 4 years, with clinical examinations at minimum intervals of 6 months. Blood pressure was determined at the end of the dose interval (24 h after taking the drug, range, 22-26 h). The results were analyzed according to intention to treat and the differences in clinical episodes between the two groups of patients were analyzed using the Cox regression model with the degree of LVH (as a

TABLE 1. **Baseline characteristics**

	Losartan (n=4605)	Atenolol (n=4588)
Age, years	66.9	66.9
Women, %	54.0	54.1
BMI, kg/m^2	28.0 28.0	
BP, mm Hg	174.3/97.9	174.5/97.7
HR, bpm	73.9	73.9
Cornell product, mm×ms	2834.4	2824.1
Sokolow-Lyon, mm	30.0	30.1
Framingham risk index, %	22.3	22.5
Smokers, %	15.8	16.8
Without previous treatment, %	28.1	28.2
Diabetes mellitus, %	12.7	13.3
Isolated systolic hypertension, %	14.3	14.5
Coronary disease, %	16.7	15.2
Stroke (including TIA), %	8.0	7.8
Peripheral arteriopathy, %	6.0	5.0
Atrial fibrillation, %	3.0	4.0

BMI indicates body mass index; BP, blood pressure; HR, heart rate; TIA, transient ischemic attack.

continuous variable) and Framingham risk index (defined in relation to the baseline characteristics of patients) as covariables.

RESULTS

The baseline characteristics of both groups of patients are summarized in Table 1. Randomization resulted in two groups that had much in common in their baseline characteristics. The mean follow-up was 4.8 years, and only a small proportion of patients were treated with 50 mg/day of either compounds (9% in the losartan group and 10% in the atenolol group). Fifty percent of the patients received losartan 100 mg and 43% received atenolol 100 mg. The mean doses of losartan and atenolol in the patients who completed follow-up were 82 mg and 79 mg, respectively. SBP and DBP were reduced by 30.2 mm Hg and 16.6 mm Hg in the losartan group and 29.1 mm Hg and 16.8 mm Hg in the atenolol group. The mean blood pressure at the end of follow-up was 144.1/81.3 mm Hg and 145.4/80.9 mm Hg in the losartan and atenolol groups. Forty-nine percent of the patients treated with losartan and 46% of those treated with atenolol achieved SBP≤140 mm Hg. In 89% of the patients in both groups, DBP≤90 mm Hg was achieved. In 48% of patients treated with losartan and 45% of patients treated with atenolol, both components were adequately controlled. The reduction in heart rate was greater (P<.0001) in the group of patients treated with atenolol (–7.7 versus –1.8 beats/min).

The incidence of the primary endpoint, combined and broken down by components, is shown in Table 2. The Kaplan-Meier curves for the primary endpoint are shown in Figure 1. The losartan group showed a significant reduction in the relative risk for the primary endpoint (unadjusted [14.6%; P=.009] and in the risk adjusted for the baseline degree of LVH and Framingham risk index [13.0%; P=.021]), with progressive separation of the curves throughout follow-up. The reduction in the relative risk of stroke with losartan (24.5%; P=.001) and absence of differences in the relative risk of myocardial infarction between both therapeutic modalities were noteworthy. These results did not vary when the permanence on study treatment was analyzed, or when adjustments were made for the evolution of blood pressure in time. On the other hand, when an analysis was made considering the changes in ECG indices of LVH as a covariable, less than one-third of the benefit in the primary endpoint could be explained by these changes. It should be emphasized that in the group of patients at lower risk (without vascular disease or diabetes), the benefit of losartan on the primary endpoint persisted (relative risk 0.82; P=.029). During follow-up, the group treated with losartan presented a 25% reduction (6% of the patients treated with losartan and 8% in the atenolol group) in the incidence of newly diagnosed diabetes. Losartan was significantly better tolerated than atenolol, likewise, losartan treatment was accom-

TABLE 2. **Objectives of the LIFE study**

			Adjusted[a]		Unadjusted	
	Losartan (n=4605)	Atenolol (n=4588)	RR (%)	P	RR (%)	P
Principal combined endpoint[b]	508	588	–13	0.021	–15	.09
Mortality due to CVD	204	234	–11	0.206	–13	.136
Cerebrovascular accident	232	309	–25	0.001	–26	.0006
MI	198	188	+7	0.491	+5	.628
Overall mortality	383	431	–10	0.128	–12	.077
Newly diagnosed DM[c]	241	319	–25	0.001	–25	.001

[a]According to the degree of LVH and Framingham risk score at the time of randomization.
[b]Mortality due to CVD (cardiovascular disease), cerebrovascular accident, and MI (myocardial infarction); patients with a first primary event. RR indicates relative risk.
[c]In patients without diabetes mellitus (DM) at the time of randomization (losartan, n=4019; atenolol, n=3979).

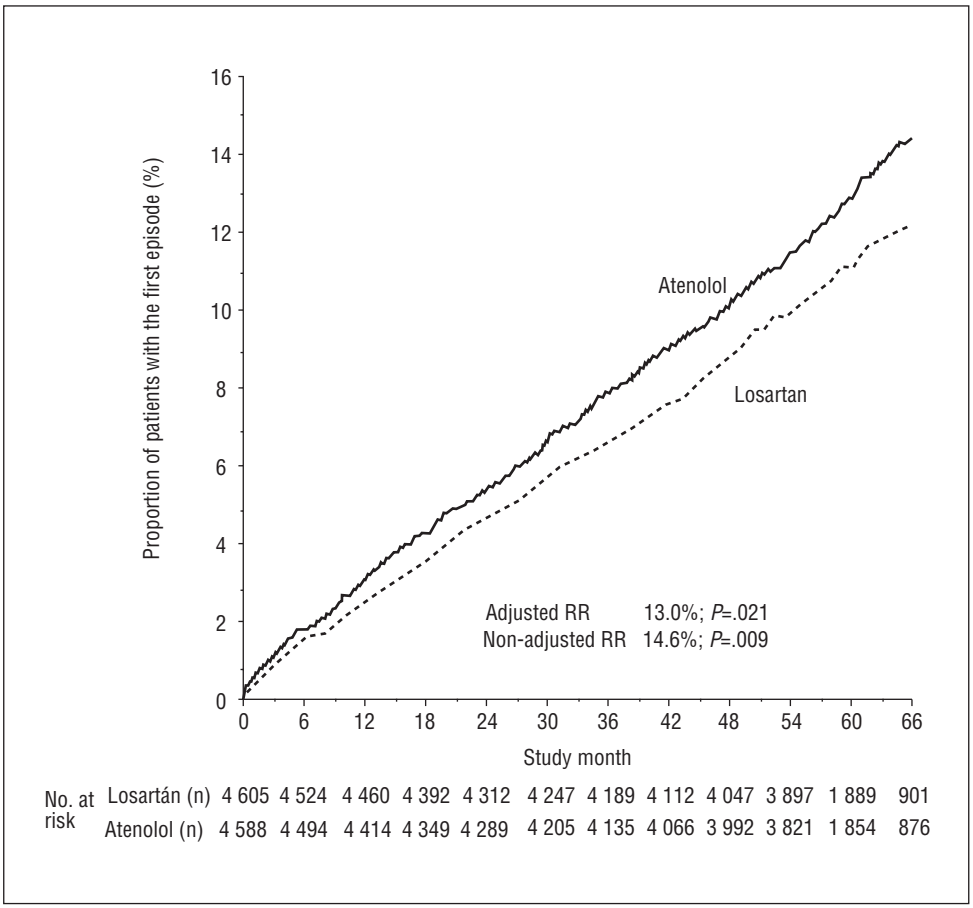

Fig. 1. Kaplan-Meier curves for the primary endpoint (cardiovascular death, stroke, and myocardial infarction).

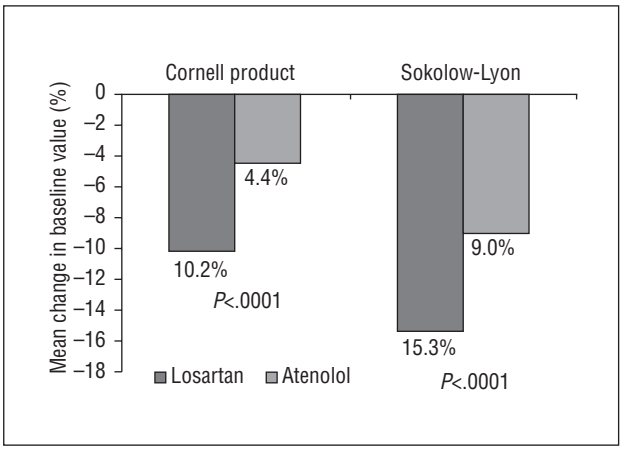

Fig. 2. Changes with respect to the baseline valor of the product duration of Cornell voltage and Sokolow-Lyon index. P value for differences between groups.

panied by a greater reduction in the ECG criteria of LVH, both the product of Cornell voltage and QRS duration (290 and 124 mm#xms for losartan and atenolol; *P*<.001) and the Sokolow-Lyon index (4.6 mm and 2.7 mm for losartan and atenolol; *P*<.001) (Figure 2).

An analysis of the subgroup of 1195 patients with diabetes, hypertension, and ECG signs of LVH[28] showed that, after a mean follow-up of 4.7 years, losartan treatment compared with atenolol was accompanied by an adjusted reduction in the relative risk for the primary endpoint of the study was 24% (*P*=.031) (Figure 3). It should be emphasized that mortality due to all causes was documented in 63 patients treated with losartan and in 104 patients treated with atenolol, which was equivalent to a reduction in relative risk of 39% in the losartan group (*P*=.002). The mortality due to CVD decreased by 37% and admissions for heart failure by 40% in the losartan group. The mean reduction in SBP during follow-up in the group treated with losartan was 3 mm Hg greater than the reduction observed with atenolol (31 mm Hg versus 28 mm Hg, respectively), with no differences in the DBP reduction. The benefit observed with losartan persisted after adjusting for changes in blood pressure during follow-up. Plasma glucose concentrations remained high during the study, with no differences between the two therapeutic modalities. Albuminuria was reported less frequently as an adverse effect (*P*=.002) in the losartan group.

CLINICAL IMPLICATIONS OF THE LIFE STUDY

As the authors themselves indicate, the results of the

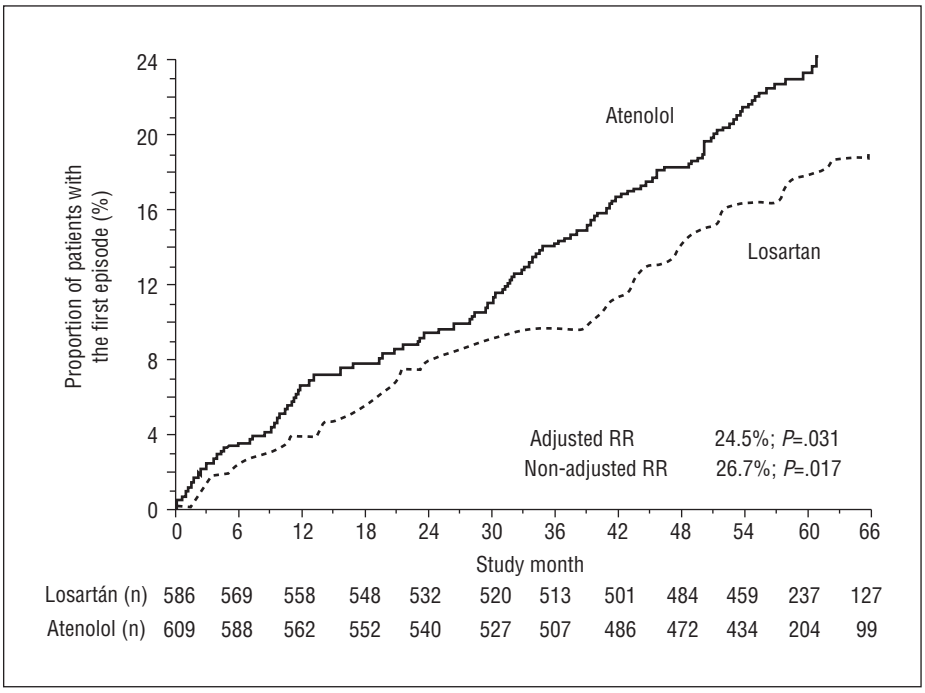

Fig. 3. Kaplan-Meier curves for the primary endpoint (cardiovascular death, stroke, and myocardial infarction) in the subgroup of hypertensive diabetics.

LIFE study demonstrate that losartan prevents cardiovascular morbidity and mortality better than atenolol in relation to similar reductions in blood pressure in a group of high-risk hypertensives. This suggests that losartan produces greater benefits than those derived from its hypotensive effect. Although the results should be interpreted in the context of the study population (hypertensives with LVH in the ECG), it undoubtedly has important clinical implications. The findings in the subgroup of hypertensive diabetics reinforce the observations of the RENAAL study in which losartan significantly delayed the progression of renal disease in diabetics with nephropathy, and indicate that this compound should be included in first-line therapy, at least in high-risk diabetics (with LVH or nephropathy).[10,27] Although the two groups of patients in the LIFE study were very similar, it is noteworthy that the group of patients treated with losartan probably had a higher risk of CVD since, compared with the atenolol group, there was a larger number of patients with ischemic heart disease (84) and peripheral arteriopathy (32). This observation reinforces the results of the LIFE study.

It should be underlined that for the first time in an AHT study, a drug showed a greater prognostic benefit than its comparator, thus modifying the present paradigm of AHT treatment. Although the priority in this pathology is to normalize blood pressure levels, now that the results of the LIFE study are known, in some subgroups of hypertensives drug selection will also be important. This observation is in key with previous studies that have demonstrated that pharmacological blockade of the renin-angiotensin system should be a primary concern, in the absence of formal contraindications, in the therapeutic strategy of almost all forms of clinical presentation of CVD (heart failure, ischemic heart disease, stroke, and diabetic nephropathy).[29]

Comments on the study design

The design of the LIFE study shows similar characteristics as recent studies of pharmacological intervention in CVD pathology, using the same combined primary endpoint as in the HOPE study.[8] The drug chosen as the comparator with losartan deserves some comment. International guidelines on AHT indicate that diuretics and beta-blockers should be the first therapeutic alternative, except when other compounds are specifically indicated.[4-6] In addition, various studies of AHT have compared beta-blockers with ACEIs and calcium antagonists (BCC), but have not demonstrate that the more modern antihypertensives (BCC and ACEI) produced more protection against CVD in hypertensives than the classic drugs (beta-blockers and diuretics).[7,30] On the other hand, the inclusion of a thiazide as an obligatory alternative to be associated approximates the design of the LIFE study to routine clinical practice. The association of a beta-blocker with thiazide (less than 10% of patients received single-drug therapy in either study branch) has conclusively demonstrated its prognostic effectiveness, especially in the prevention of stroke.[7,31,32] The VALUE study, currently under way in high-risk hypertensives, compares a strategy based on valsartan to another one

with amlodipine,[33] and the SCOPE study compares candesartan with placebo in patients over 70 years with mild hypertension.[34] These studies should help to define the role of ARA II in the treatment of AHT and will aid us in determining if the protection against CVD associated with losartan treatment in the LIFE study is a «drug class effect.»

The losartan dose used (mean dose 82 mg, with almost 50% of patients treated with 100 mg) could have influenced results. In a recent study with irbesartan in patients with diabetic nephropathy, a 300-mg dose was accompanied by more renal protection than 150 mg, suggesting a possible relation between dose and effectiveness.[12] The dose of the beta-blocker comparator (mean dose 79 mg) was greater than the dose usually used in the treatment of the AHT. Its effectiveness in combination with a thiazide underlines the clinical implications of the results of the LIFE study. Consequently, the findings of this study should be interpreted as the result of the comparison in high-risk hypertensives of a losartan/thiazide therapeutic strategy versus atenolol/thiazide rather than as a comparison of an ARA II and beta-blocker.

Comments on results

The superior protection against CVD associated with losartan/thiazide treatment versus atenolol/thiazide was observed for similar reductions in blood pressure (difference of 1 mm Hg in SBP). This finding allows us to speculate on the effects of losartan independently of the pressure changes that could be responsible for this finding. The reduction in pressure observed in the LIFE study was greater than the reduction found in most prognostic studies in AHT,[7] with the exception of the INSIGHT study, which compared a therapeutic strategy based on nifedipine GITS to a combination of diuretics (thiazide/amiloride) in hypertensives with an additional risk factor (in most cases, dyslipidemia). However, the INSIGHT study did not disclose any differences in prognosis between the two therapeutic modalities.[35] These results and, to a certain extent, those of the HOPE study, suggest that in the presence of high blood pressure the important thing is to lower it without concern for the drug selected. However, when blood pressure is close to normal, blockade of the renin-angiotensin system may confer greater benefits. At this point it is necessary to discuss whether the results of losartan in the LIFE study are also applicable to the ACEIs. As mentioned above, earlier studies that compared the prognostic effectiveness of ACEIs versus other antihypertensives found no differences.[7] Although the blood pressure levels reached during follow-up were significantly superior to those obtained in the LIFE study and in several studies of ACEI intervention in vascular pathology,[29] the evidence now available for losartan obliges us to consider this compound as a therapeutic strategy of choice in AHT. Although not specifically an AHT study, the results of the ONTARGET study currently under way (which compares a strategy based on telmisartan versus ramipril and another strategy combining both compounds in patients at high risk of CVD) should help to clarify if blockade of the renin-angiotensin system with ACEI or ARA, or a combination of the two, is accompanied by differences in prognosis.[36]

In the LIFE study the differences in the combined primary endpoint (death due to CVD, stroke, and myocardial infarction, with 80 fewer events in the group losartan versus the atenolol group) were strongly influenced by differences in the number of strokes (232 versus 309 stroke episodes in the losartan and atenolol groups, respectively, with a reduction in the relative risk of 25%). This finding is of special clinical relevance if we consider that most patients (more than 90%) in both branches of treatment received combined treatment with a thiazide, a drug that has been shown to be effective in the prevention of stroke in hypertensives,[7,31,32] and, more recently, associated with an ACEI in the prevention of stroke recurrence.[37] On the other hand, as observed in the HOPE study, losartan treatment was accompanied by a lower incidence of new cases of diabetes during follow-up (241 cases [6%] in the losartan group and 319 [8%] in the atenolol group), with a reduction in the relative risk of 25%. This behavior cannot be explained by differences in pressure control or in the degree of remission of LVH during follow-up, as observed by other authors.[38,39] The different degrees of insulin resistance present in many hypertensives could help to explain the greater incidence of type 2 diabetes in relation to the general population. On the one hand, pharmacological blockade of the renin-angiotensin system could improve glucose tolerance and, on the other hand, the reduction in peripheral sensitivity to insulin that accompanies beta-blocker treatment could explain the differences in the incidence of new cases of diabetes during follow-up reported in the LIFE study.[40]

The differences in the combined primary endpoint and, in particular, the special protection against the risk of stroke, could be due to losartan effects that are not pressure-dependent. This compound has demonstrated beneficial effects on various mechanisms implicated in the atherothrombotic process. It has been found to inhibit platelet aggregation in healthy and hypertensive persons,[41,42] and to limit atherogenesis in monkeys fed high-cholesterol diets,[43] as well as lipid peroxidation in mice with lipoprotein E eficiency.[44]

In my opinion, the absence of differences in the number of myocardial infarctions observed during the follow-up of both therapeutic modalities merits special attention. This finding acquires special relevance considering that the losartan comparator was atenolol, a drug pertaining to a family that has been shown to pro-

vide strong protection against the risk of infarction.[45]

As reported in previous publications, losartan treatment demonstrated an excellent tolerability and with an exceptionally low frequency of serious adverse effects related with the beta-blocker. What is more, no significant differences in the overall incidence of serious adverse effects were observed. This finding has special relevance in Spain, since the use of beta-blockers as drugs of choice in pathologies like ischemic heart disease and heart failure is far from what would be considered adequate.[3]

The good results observed in the group of diabetics included in the LIFE study reinforce the conclusions of the RENAAL and PRIME studies (IDNT and IRMA II) of diabetics with microalbuminuria or nephropathy and indicate that pharmacological blockade of the renin-angiotensin system must be an objective of the therapeutic strategy of type 2 diabetics.[10-12,46] In spite of the limited sample size, it should be emphasized that in the group treated with losartan, 103 (18%) events included in the primary endpoint were observed, versus 139 (23%) in the atenolol group. Sixty-three patients (11%) died during follow-up in the losartan group versus 104 (17%) in the atenolol group. There were fewer hospital admissions for heart failure in the group treated with losartan, but hospitalizations for angina were similar in both groups.

Although in a strict sense the results of the LIFE study are applicable to patients with AHT and LVH, in view of the high prevalence of LVH in the general population of hypertensives I feel that they have inaugurated a new era in AHT treatment and require that guidelines for clinical practice be reconsidered, since a more extensive use of losartan could be accompanied by a significant improvement in the prognosis of hypertension.

The author states that he has participated as principal investigator in various international clinical trials sponsored by Merck, Sharp & Dohme, on the effect of losartan on cardiovascular diseases.

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