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Efecto del losartán sobre la muerte cardíaca súbita en personas con diabetes: estudio LIFE

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Sudden cardiac death prevention in coronary heart disease is an important goal for treatment. In placebo controlled long-term studies, several beta-blockers including atenolol have shown consistent reductions in post-infarction mortality by up to 50% reduction in the risk of sudden cardiac death[1]. It has been suggested that in patients with diabetes mellitus, particularly if associated with autonomic neuropathy, increase in heart rate and decrease in heart rate variability may be critical risk factors for sudden cardiac death and increased all-cause mortality. In a pre-specified subgroup of diabetics (n = 1,195) with left ventricular hypertrophy, the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study reported a major reduction of all-cause mortality and especially cardiovascular mortality with a losartan-based *vs* an atenolol-based antihypertensive therapy[1]. Against this background, we hypothesised *post-hoc* that the losartan-based therapy may have affected sudden cardiac death better than atenolol-based therapy.

As part of the main LIFE study, and in a double-masked, randomised, parallel-group design, 1,195 men and women (53% women) with diabetes, hypertension (mean age 67 years, average pressure 177/96 mmHg after placebo run-in) and ECG-documented left ventricular hypertrophy, were assigned once-daily losartan- or atenolol-based antihypertensive therapy and followed for at least 4 years (mean 4.7 years)[1]. Baseline data as well as treatment profile are given in[1]. In both groups, around 85% received a diuretic as supplementary treatment. Cox regression analysis with baseline Framingham risk score and ECG-LVH as covariates was used to compare effects of the two regimens on cardiovascular morbidity and mortality (defined as cardiovascular death, stroke, or myocardial infarction). An independent end-point committee, masked to the type of treatment the patients had received, classified all endpoints including sudden cardiac death.

As previously reported[1], there were fewer (p = 0.028) cardiovascular deaths in the losartan group than in the atenolol group and there was a similar tendency (p = 0.052) for coronary deaths. When analysed separately, there was significantly less (p = 0.027) sudden cardiac deaths in the losartan-based group (14 patients) than in the atenolol-based group (30 patients), as shown in table I and figure 1. This tended to be so, regardless of whether deaths occurred within one hour or within 24 hours of symptom onset (table I). Our finding that the risk was lower in the losartan-treated diabetics than in those who received atenolol was independent of other risk factors for sudden cardiac death. A difference in regression of LVH between the two treatment groups of diabetics did not explain the difference in sudden cardiac death. The last serum potassium value before sudden death (mean and standard deviation) was similar, 4.26 (0.42) mmol/L in the losartan-based group and 4.23 (0.40) mmol/L in the atenolol-based group (NS); the change from baseline was 0.01 mmol/L in both groups. In the non-diabetics of the LIFE trial, there were equal numbers of sudden cardiac deaths (67 patients) in the two treatment groups.

The results from the diabetic subgroup in the LIFE-study, showing a much lower rate of cardiovascular death and total death in losartan-treated patients than in atenolol-treated patients[5], prompted us to carry out a *post-hoc* analysis of sudden cardiac death. To our surprise, the analysis showed a close to 50% risk reduction in sudden death in losartan treated diabetic patients as compared to atenolol-treated patients, whereas this was not so in the non-diabetics.

The results should be viewed against the background that beta-blockers are known to offer protection against cardiovascular death and sudden cardiovascular death, particularly in patients with active coronary heart disease. A possible explanation for the better outcome in the losartan group is a better anti-arrhythmic property of losartan as compared to atenolol. Our data showed that among patients with diabetes, 19 (9.9%) of those *with* atrial fibrillation (n = 191) at baseline or during the trial, died of sudden cardiac death. In the diabetics *without* atrial fibrillation (n = 1,004), 25 (2.5%) died of sudden cardiac death. The corresponding figures for the losartan

group were 5 of 86 (6%) *vs* 9 of 500 (2%) and in the atenolol group 14 of 105 (13%) *vs* 16 of 504 (3%). Study drug discontinuation, particularly discontinuation of atenolol, did not explain these differences. It should be underlined that the number of sudden cardiac deaths (n = 44) in the present analyses comprised 44% of all cardiovascular deaths and 26% of all deaths in the LIFE diabetics during follow-up.

It is known from experimental studies, as well as analyses of the LIFE study, that losartan as compared to atenolol reduced the risk of episodes of atrial fibrillation. It is likely that losartan, by leading to regression of left ventricular hypertrophy and possibly less atrial fibrosis, would favor an anti-arrhythmic effect. It is also known from the LIFE study that abnormalities in QT-dispersion and heart rate variability are related to left ventricular hypertrophy, possibly by left ventricular hypertrophy-induced repolarization abnormalities. A modulation of sympathetic nerve activity might be involved as well. It is known from clinical and experimental work that ACE-inhibition, and also angiotensin-II antagonism, might inhibit sympathetic nervous system by a blunting of the facilitating effect of angiotensin-II on sympathetic tone. Finally, and importantly, our analyses were exploratory and require confirmation.

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