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Hotline Editorial

The LIFE study: the straw that should break the camel's back

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In the LIFE study, the most recent landmark trial in hypertension,^{1–3} more than 9000 hypertensive patients were randomized to either a losartan-based regimen or to an atenolol-based regimen. Although less than 10% of all patients remained on monotherapy of either drug at the end of the study, patients in the losartan arm experienced a significantly better reduction in morbidity and mortality than patients in the atenolol arm. This reduction in morbidity and mortality was mostly driven by a stroke reduction since in the whole study population no significant difference in myocardial infarction (MI) was demonstrated between the two treatment arms. To be included into the study all patients had to have left ventricular hypertrophy (LVH) by electrocardiographic (ECG) criteria. More than three decades ago, based on ECG findings, Kannel et al.⁴ documented LVH to be a powerful blood pressure independent risk factor for cardiac events, such as acute MI, sudden death, congestive heart failure and strokes. Since these findings were at odds with prevalent textbook opinion, they were greeted with a great deal of skepticism. However, over the years, evidence started accumulating, not only from ECG studies, but also from echocardiographic studies, from Framingham and from other sources, showing clearly that the occurrence of LVH in hypertension had to be considered a strong and independent herald for cardiovascular morbidity and mortality.^{5–8} Conversely, a reduction in LVH with antihypertensive therapy has been shown to be associated with an improvement in outcome and to reduce the risk of cardiovascular morbidity and mortality. Indeed, data from several sources convincingly demonstrated that LVH was a more

reliable and more powerful surrogate endpoint for cardiovascular fatal and non-fatal events than blood pressure per se.^{9,10} What has not clearly been shown, however, is that a reduction of LVH confers benefit to the patient over and above that conferred by the blood pressure alone. In other words, whereas it is clear that LVH is a blood pressure independent risk factor, hard data that an LVH reduction per se, independently of blood pressure, would improve outcome is lacking. Given this background, several points in the LIFE study deserve to be scrutinized.

1. LVH was significantly reduced in the losartan arm compared with the atenolol arm, and this was true for ECG LVH in the whole study population as well as for echocardiographic LVH in the sub-study of 960 patients with a total of 4677 echocardiograms. If LVH were indeed a powerful risk factor for hypertensive heart disease in general and for coronary artery disease in particular, as many studies lead us to believe, one would expect that such an LVH reduction would lead to a significant reduction in coronary events. Although this was true in the whole study population, surprisingly, there was no difference in MI between the two treatment arms. If anything, the rate of MI was slightly higher (7%) in the group with less LVH, i.e. patients on losartan, than in those on atenolol. Could it be that LVH is not necessarily always a detrimental process and that, therefore, a reduction is not *mutatis mutandis* beneficial to the patient? Along that line, a more than a century old thought from William Stokes¹¹ comes to mind: "Who can tell whether the process or reduction of the heart, once set up, can be made to stop exactly at the point when the organ is restored to its natural dimensions?" Conceivably, angiotensin receptor inhibition could also have some specific cerebroprotective effect that would

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allow us to explain the discrepancy between cerebral and cardiac events in the losartan arm.¹²

2. We should not forget that there were small, albeit distinct, differences between the two treatment arms. Although blood pressure seemed to have been reduced to a very similar level, close scrutiny of the blood pressure curves in the diabetic population² shows that systolic pressure was consistently higher and diastolic pressure consistently lower in patients on atenolol compared with those on losartan. This is not surprising since beta-blockers have a negative chronotropic effect and increase stroke volume to some extent, which in turn usually leads to an increase (or to a lesser fall) in pulse pressure than is seen with vasodilatory agents such as losartan which do not affect stroke volume. In the betablocker compared with the losartin group, more patients withdrew from double-blind medication (27.1 vs. 22.6%; $P < 0.001$), whereas fewer proceeded to combination therapy (61.7 vs. 65.9%; $P < 0.001$). Conceivably, some outcome differences between the two treatments observed in the study could be explained, at least to some extent, by these inherent inequalities.

3. Last, but not least, we should also scrutinize the efficacy of the comparator to losartan, i.e. atenolol. In the MRC study in the elderly,¹³ beta-blockers were no better than placebo, and whenever a beta-blocker was added to a diuretic,¹⁴ the risk of cardiovascular morbidity and mortality paradoxically increased. Even in the younger hypertensive population,¹⁵ beta-blockers only have been shown to reduce events in male non-smokers. The risk of strokes was between two and four times higher in the MRC study in middle-aged patients¹⁴ on atenolol compared with those on bendrofluzide.¹⁶ Data from this study allow us to calculate that for every heart attack or stroke prevented, three patients were made impotent and seven became depressed to the extent that they decided to withdraw from beta-blocker therapy. This is hardly an acceptable risk/benefit ratio for a completely asymptomatic disorder such as hypertension, and it is not surprising that losartan was much better tolerated than atenolol in the LIFE study. In a meta-analysis of all trials in a total of 16,164 patients over age 60 whose average age was similar as in the LIFE study, beta-blockers did not reduce fatal or non-fatal MIs, cardiovascular and all cause mortality compared with placebo.¹⁷ For practical purposes, the comparator of losartan in the LIFE study, i.e. atenolol, must therefore be considered a placebo. Not surprisingly, the superiority of losartan over atenolol was even more pronounced in the subgroup of 1326 patients with isolated systo-

lic hypertension.³ However, the statement in this manuscript, "Previous intervention studies in ISH with diuretics or beta-blockers or calcium antagonists or angiotension converting enzyme inhibitors have shown 36%, 42% and 38% reductions in stroke or placebo. A further 40% reduction in stroke with losartan-based therapy is an important finding", is disturbing. The authors seemingly want us to believe that had losartan been compared to placebo, a reduction in stroke in the order of magnitude of 80% would have been achieved. The references that they give for their statements are Syst-Eur, Syst-China, and SHEP. None of these studies documented a stroke reduction with beta-blockers (or ACE inhibitors). Given that in patients with isolated systolic hypertension there was a robust 40% difference in stroke reduction between losartan and atenolol, there seems to be little need to inflate these findings by a deceptive statement.

Although in the UK Prospective Diabetes Study trial in diabetic patients¹⁸ beta-blockers had some benefits that were similar to captopril, there was no significant reduction in coronary artery disease, sudden death or MI. On the contrary, beta-blocker therapy has been shown to cause systematic weight gain¹⁹ and to significantly increase the risk of developing diabetes.²⁰ Given the known spotty record of beta-blockers in the diabetic population, the superiority of an angiotensin receptor inhibitor in the LIFE study in these patients is hardly a surprise.

Thus, to put it somewhat pointedly, a losartan-based regimen did not reduce MI more than placebo (i.e. atenolol), but showed efficacy in reducing cerebrovascular events in the whole population, and cardiovascular events in the diabetic population. Of the two treatment strategies, the losartan-based one is clearly the better one, or as some might argue, since blood pressure was controlled only in about 10% of all patients with monotherapy, the lesser of the two evils. Underscoring the superiority of losartan over atenolol, Brunner and Gavras²¹ wrote an accompanying editorial with the title, "Angiotensin blockade in hypertension: a promise fulfilled". *Mutatis mutandis* one could change the title of this editorial to "Beta-blockers in hypertension—a promise broken". This semantic issue notwithstanding, the LIFE study should be considered as the final straw that will break the camel's back and hopefully motivate physicians to no longer expose their elderly hypertensive patients to the cost, inconvenience, adverse effects, and most importantly, to the inefficacy of beta-blockers.

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