
**International Task Force for Prevention
Of Coronary Heart Disease**



*Clinical management of risk factors
of coronary heart disease and stroke*

Major recent drug trials

**Losartan Intervention For Endpoint
reduction in hypertension study**

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Slide 1:

Objective and design



Losartan Intervention for Endpoint (LIFE) Objective and Design



- **Objective**
Evaluation of the long-term effects (≥ 4 years) of losartan (angiotensin II receptor blocker) compared to atenolol (β -blocker) in hypertensive patients with electrocardiographically documented left ventricular hypertrophy (LVH) on the combined incidence of cardiovascular mortality and morbidity
- **Design**
multicenter, double-blind, randomised, prospective, active-controlled parallel group trial

Source: Dahlöf B et al., Am J Hypertension 1997;10:705-713

Objective and design

The treatment of hypertension mainly with diuretics and β -blockers reduces cardiovascular mortality and morbidity, largely due to a decreased incidence of stroke, but in a smaller degree of coronary events. Losartan is the first of a new class of hypertensive agents blocking angiotensin II at the type 1-receptor. Angiotensin II (A-II) is associated with development of left ventricular hypertrophy (LVH), a strong independent indicator of risk of cardiovascular morbidity and death. Thus, blocking A-II could be especially effective in reversing LVH.

The major hypothesis of the LIFE study is that in patients with essential hypertension and LVH, losartan will reduce the incidence of cardiovascular morbidity and mortality to a greater extent than the β -blocker atenolol, possibly through a greater effect on the regression of LVH.

Slide 2:

Eligibility



Eligibility



- **Men and women between 55 and 80 years of age with previously untreated or treated essential hypertension and electrocardiographically documented left ventricular hypertension (LVH).**
- **Mean through sitting**
 - **diastolic blood pressure readings of 95 to 110 mm Hg and/or**
 - **systolic blood pressure readings of 160 to 200 mm Hg**

Source: Dahlöf B et al., Am J Hypertension 1998;32:989-997
Dahlöf B et al., Lancet 2002;359:995-1003

Eligibility

This slide shows eligibility criteria of the LIFE study, the largest study ever to be undertaken in patients with left ventricular hypertrophy (LVH) and one of the largest intervention studies in essential hypertension. This study involved 9194 hypertensives with LVH.

Slide 3:

Patients characteristics at randomisation (n=9194)

Patients Characteristics at Randomisation (n=9194)		
	Losartan (n=4605)	Atenolol (n=4588)
Age (years)*	66.9	66.9
Women (%)	54	54
Body mass index (kg x m²)*	28.0	28.0
Systolic blood pressure (mm Hg)*	174.3	174.5
Diastolic blood pressure (mm Hg)*	97.9	97.7
Isolated systolic hypertension**(%)	14	15
Heart rate (bpm)*	73.9	73.7
Left ventricular mass		
Cornell voltage-duration product (mmxms)*	2834.4	2824.1
Sokolow-Lyon (mm)*	30.0	30.1
5 year risk for a coronary event estimated by Framingham Risk Score (%)*	22.3	22.5
Any vascular disease (%)	26	24
Diabetes (%)	16	17

* Data are mean (SD)
 ** Definition $\geq 160 / < 90$ mm HG

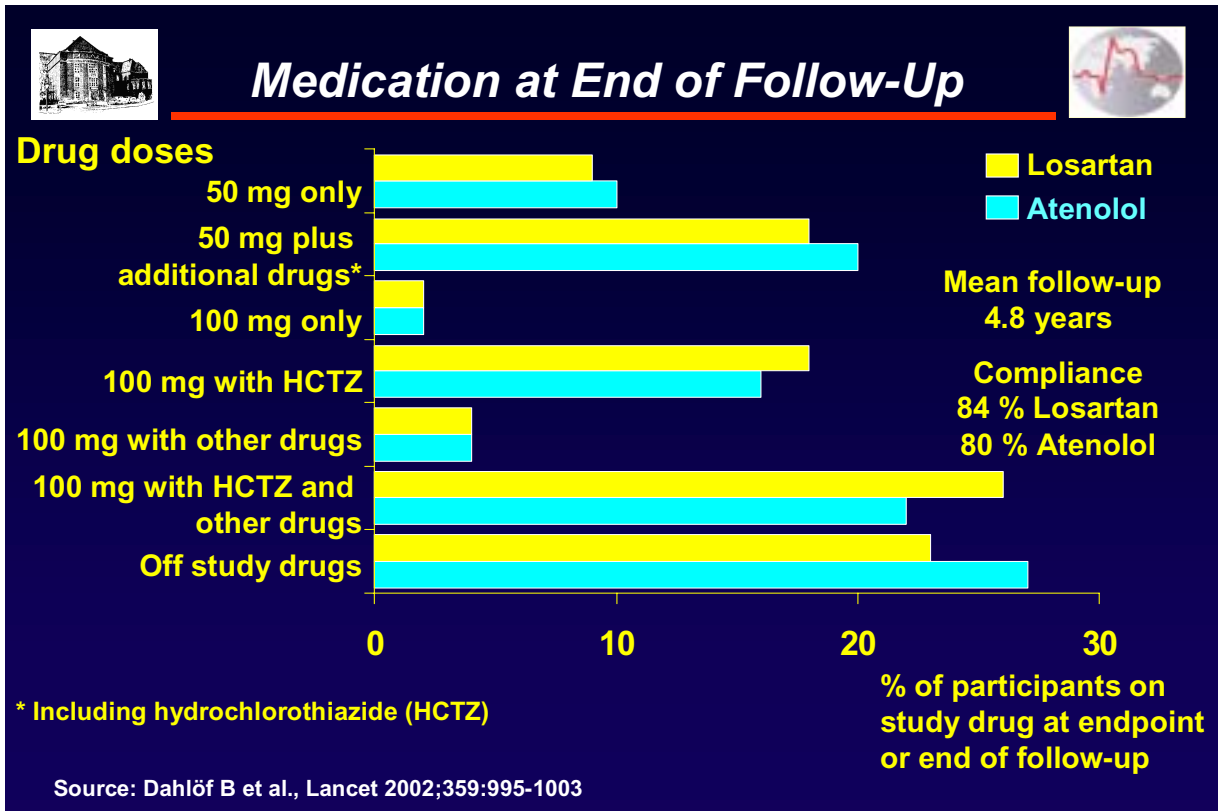
Source: Dahlöf B et al., Lancet 2002;359:995-1003

Patients characteristics at randomisation (n=9194)

This slide shows the characteristics of the LIFE-participants (9194). 9193 were available for final analyses, since one patient had wrongly been identified as randomised despite not receiving study drugs. The patients were enrolled from June, 1995, to May 2, 1997, in 945 centres in Denmark (n=1391), Finland (n=1485), Iceland (n=133), Norway (n=1415), Sweden (n=2245), UK (n=817), and the USA (n=1707). Almost 30 % of participants were untreated for their high blood pressure for at least 6 months when screened for the study. This population was to be treated (goal, <140/90 mm Hg) for at least 4 years after final enrolment and until at least 1040 patients suffer myocardial infarction, stroke, or cardiovascular death.

Slide 4:

Medication at end of follow-up

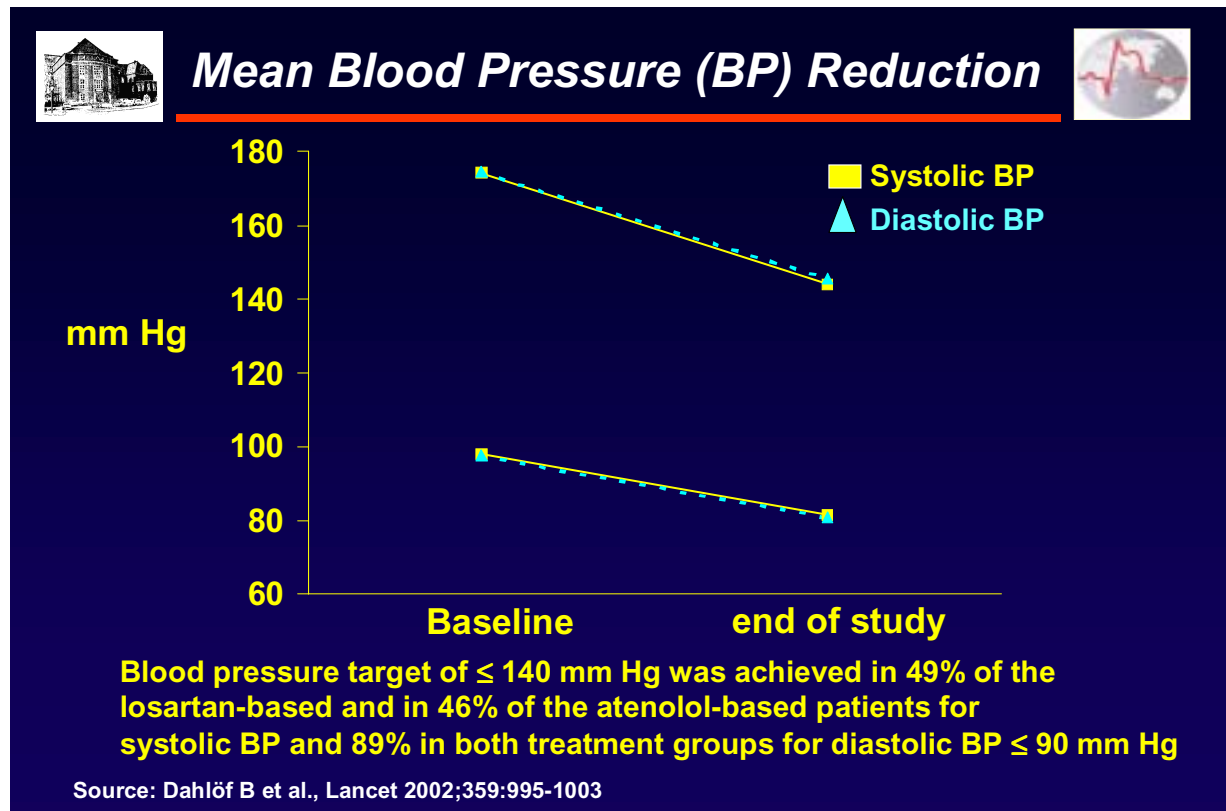


Medication at end of follow-up

This slide shows the distribution of study drugs at the end of follow-up or at occurrence of the first primary endpoint, if earlier. The distribution of additional drugs on top of masked study drug and hydrochlorothiazide did not differ between groups. Mean doses of losartan and atenolol in patients who stayed on study drugs until the end of study were 82 and 79 mg, respectively.

Slide 5:

Mean blood pressure reduction

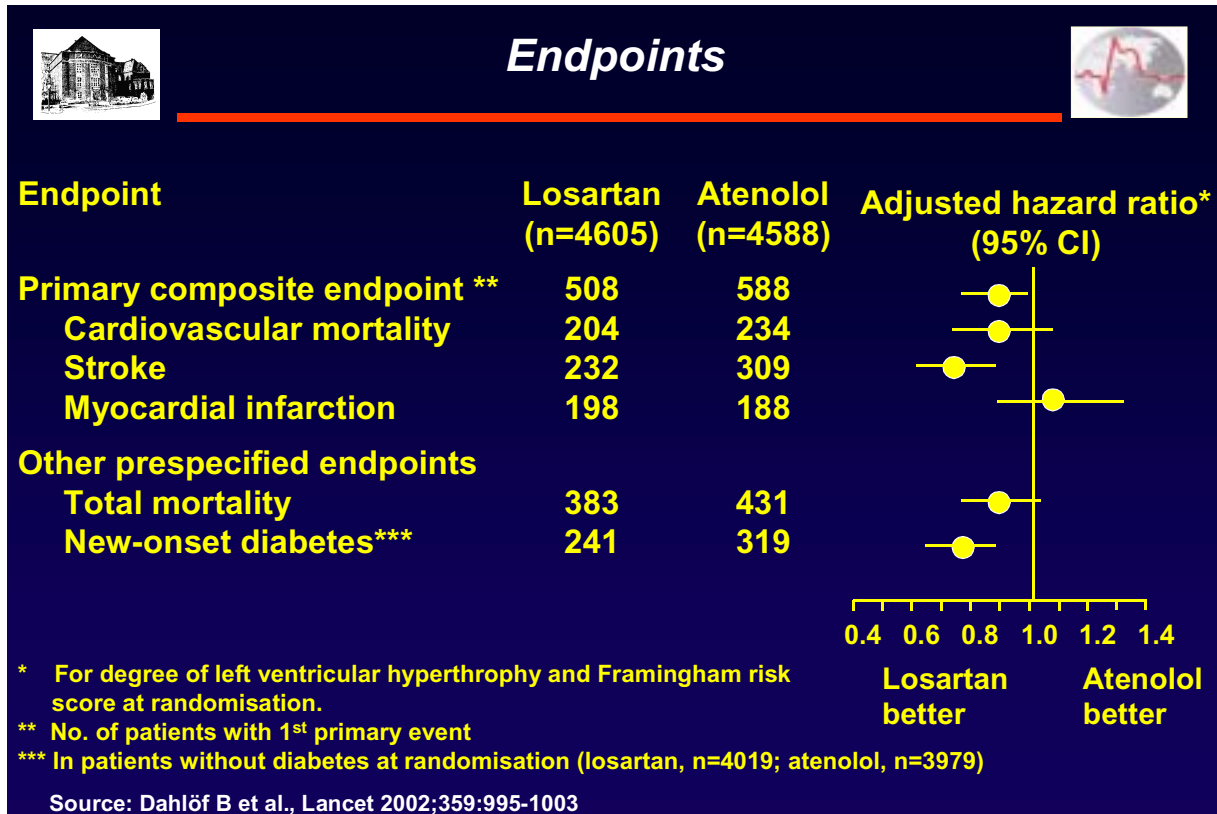


Mean blood pressure reduction

This slide shows, that similar reductions in systolic and diastolic blood pressure were achieved with both drugs.

Slide 6:

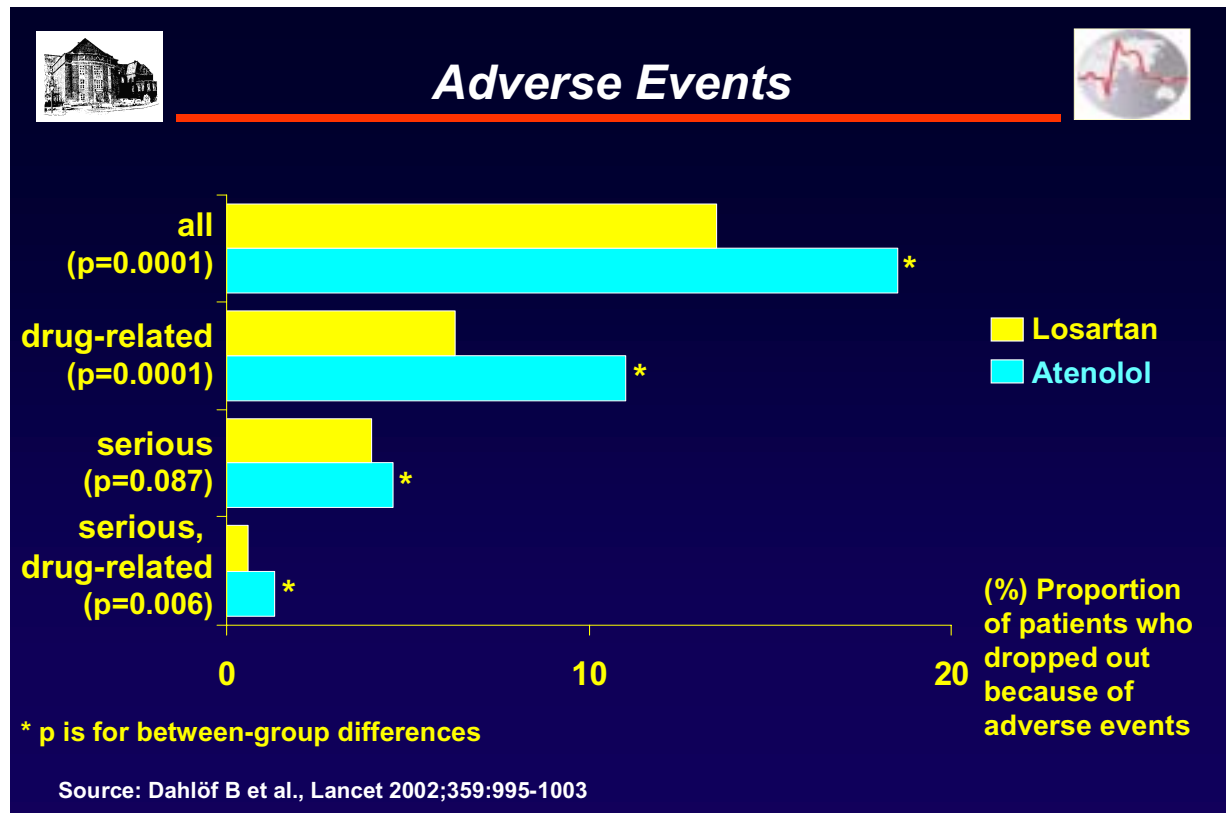
Endpoints



Endpoints

This slide shows that losartan reduced cardiovascular morbidity and mortality more than atenolol. Losartan treatment resulted in a remarkable significant 25% relative risk reduction for stroke compared with atenolol. Despite the central importance of blood pressure in the complications of hypertension, additional adjustment of the main outcome for small differences in systolic and diastolic pressure (see slide 5) had little effect on the estimate of the benefit associated with losartan. The greater effect of losartan compared with atenolol on primary composite endpoints may have been due to the greater reduction of left ventricular mass (LVH) with losartan (see slide 8) as well as due to benefits beyond blood-pressure reduction and LVH regression. This benefit could result from increased protection against the detrimental effects of angiotensin II or from specific effects of losartan. Among other prespecified endpoints, there was a significant 25% lower incidence of new-onset diabetes in the losartan than the atenolol group. This lower rate of new-onset diabetes with losartan may be due to a differential effect on insulin resistance. There was also a trend for lower total mortality with losartan.

Slide 7:
Adverse Events

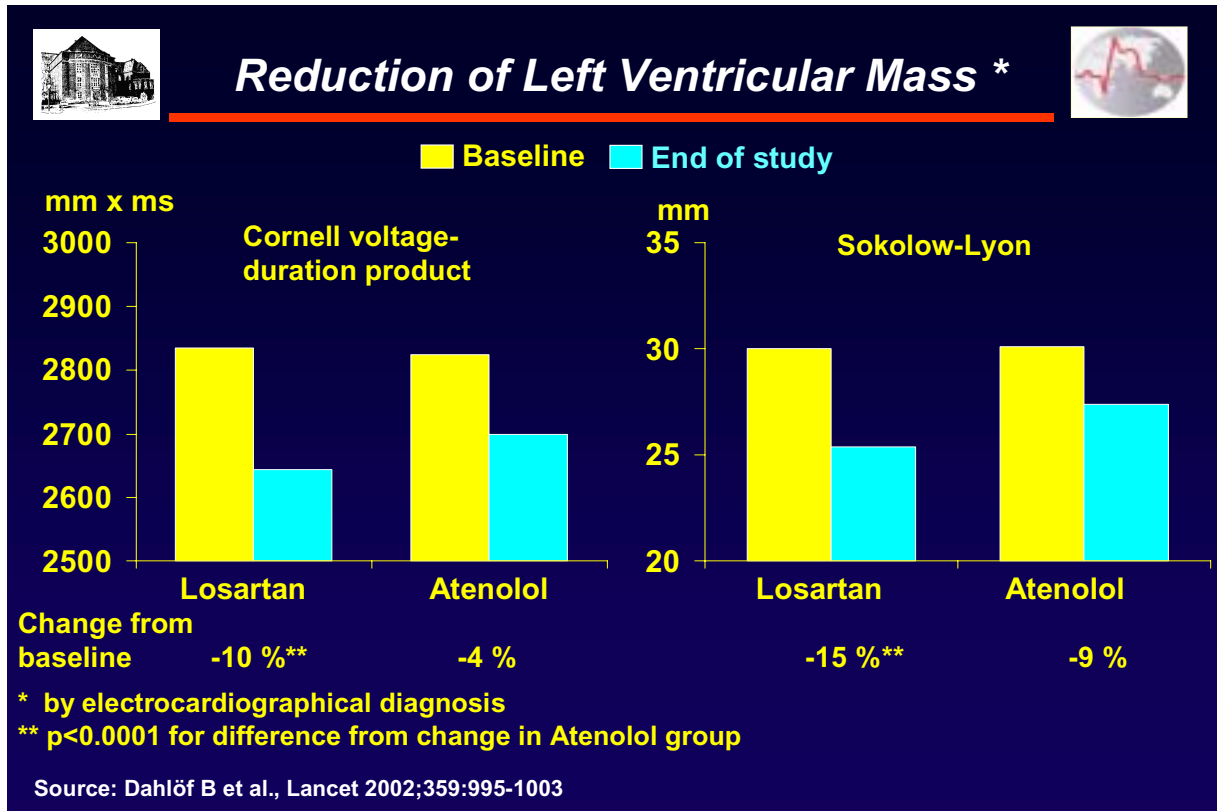


Adverse Events

This slide shows that discontinuation as a result of adverse events was significantly less common in losartan than atenolol patients.

Slide 8:

Reduction of left ventricular mass



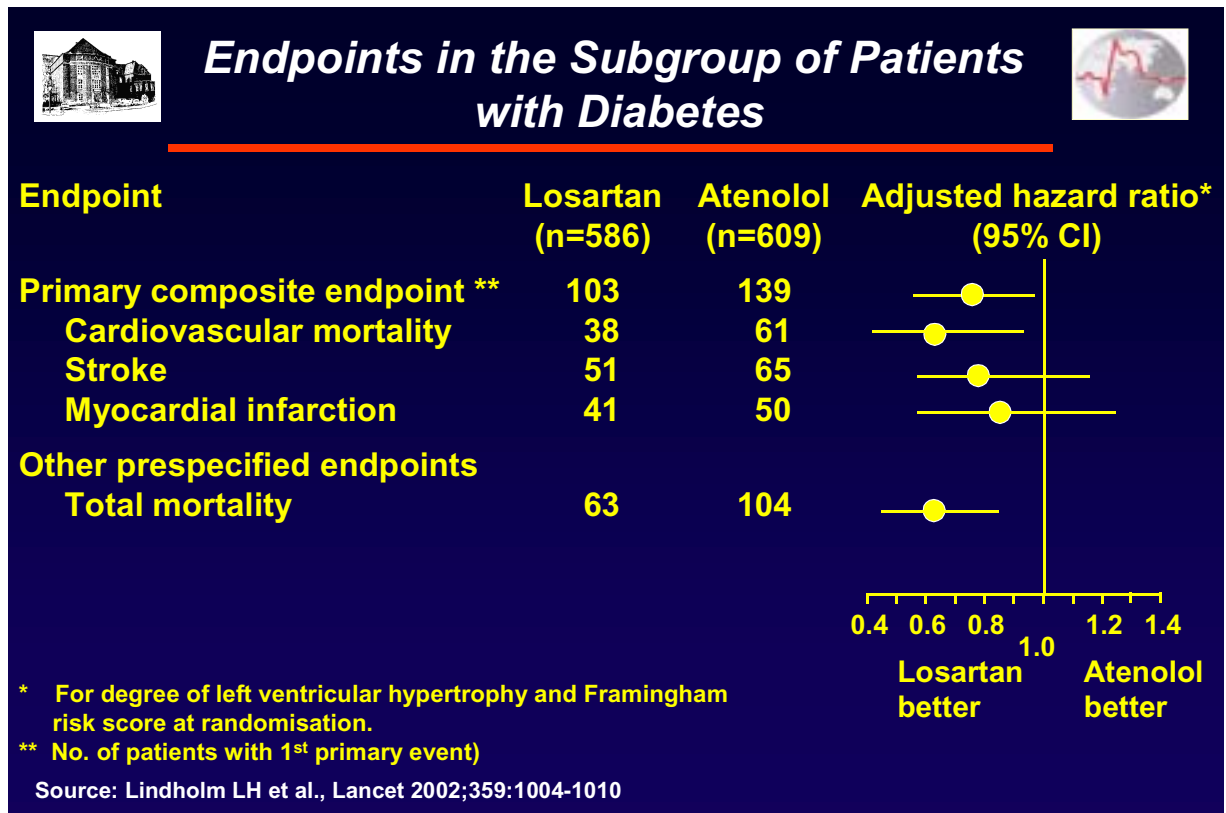
Reduction of left ventricular mass

This slide illustrates left ventricular mass at baseline and at the end of study measured with two different criterions, the Cornell voltage-duration product and the Sokolow-Lyon voltage. Because combined electrocardiography (ECG) assessment of QRS duration and Cornell voltage and duration enhances sensitivity for detection of left ventricular hypertrophy (LVH) at acceptable levels of specificity, the product of QRS duration and Cornell voltage was used to recognise LVH. Sokolow-Lyon voltage was chosen as an alternative LVH criterion.

A greater reduction of left ventricular mass was attained with losartan than with atenolol, which was independent of blood pressure reduction. This effect may result from a more complete protection against angiotensin II with losartan, whether generated by the circulating renin-angiotensin system or other mechanisms, especially since angiotensin II is a myocardial growth factor and an independent risk factor for cardiovascular disease.

Slide 9:

Endpoints in the subgroup of patients with diabetes

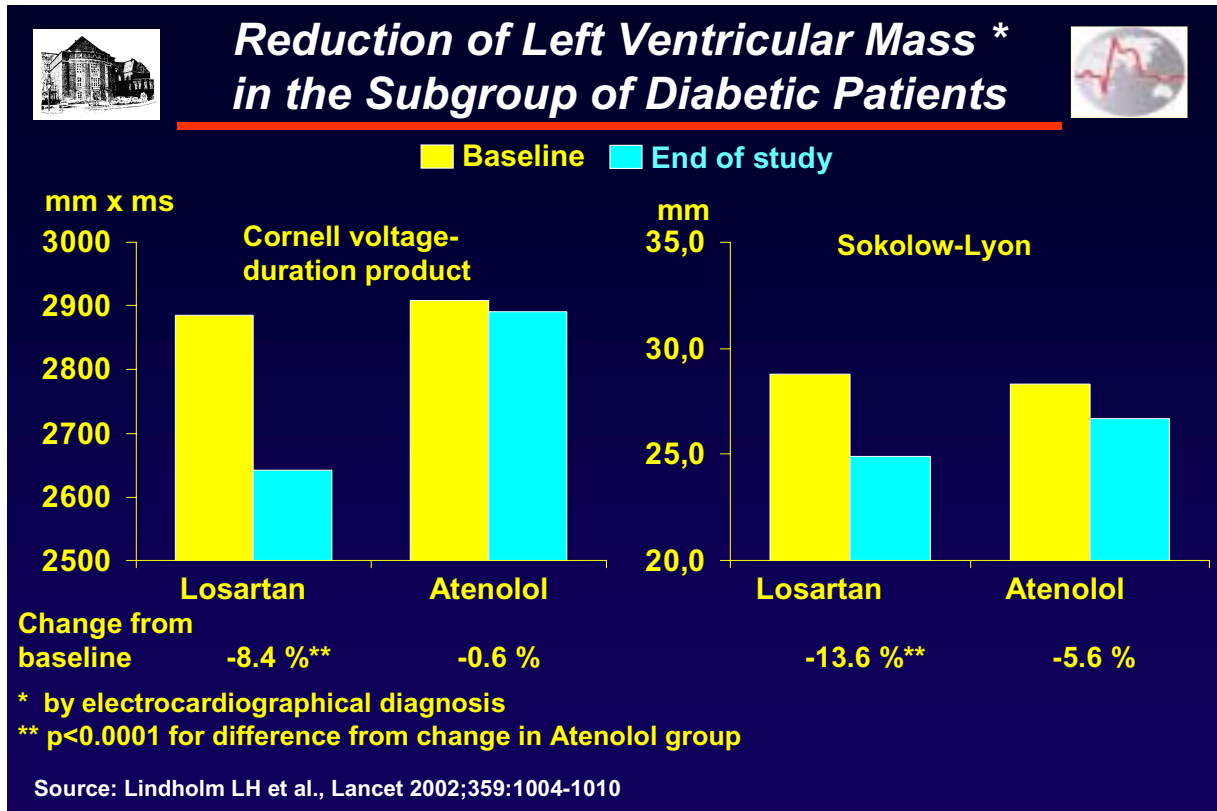


Endpoints in the subgroup of patients with diabetes

This slide shows the results of the prespecified subgroup of patients who had diabetes mellitus at the start of the LIFE study (n=1195). Losartan was more effective than atenolol in reducing cardiovascular morbidity and mortality as well as mortality from all causes in patients with hypertension, diabetes, and left ventricular hypertrophy. In the non-diabetic patients, the almost 15% reduction of the primary outcome was mostly driven by the 24% reduction of stroke (see slide 6), but in the subgroup of patients with diabetes, the 24% reduction in primary endpoint was linked with the reduction in cardiovascular and total mortality.

Slide 10:

Reduction of left ventricular mass in the subgroup of diabetic patients

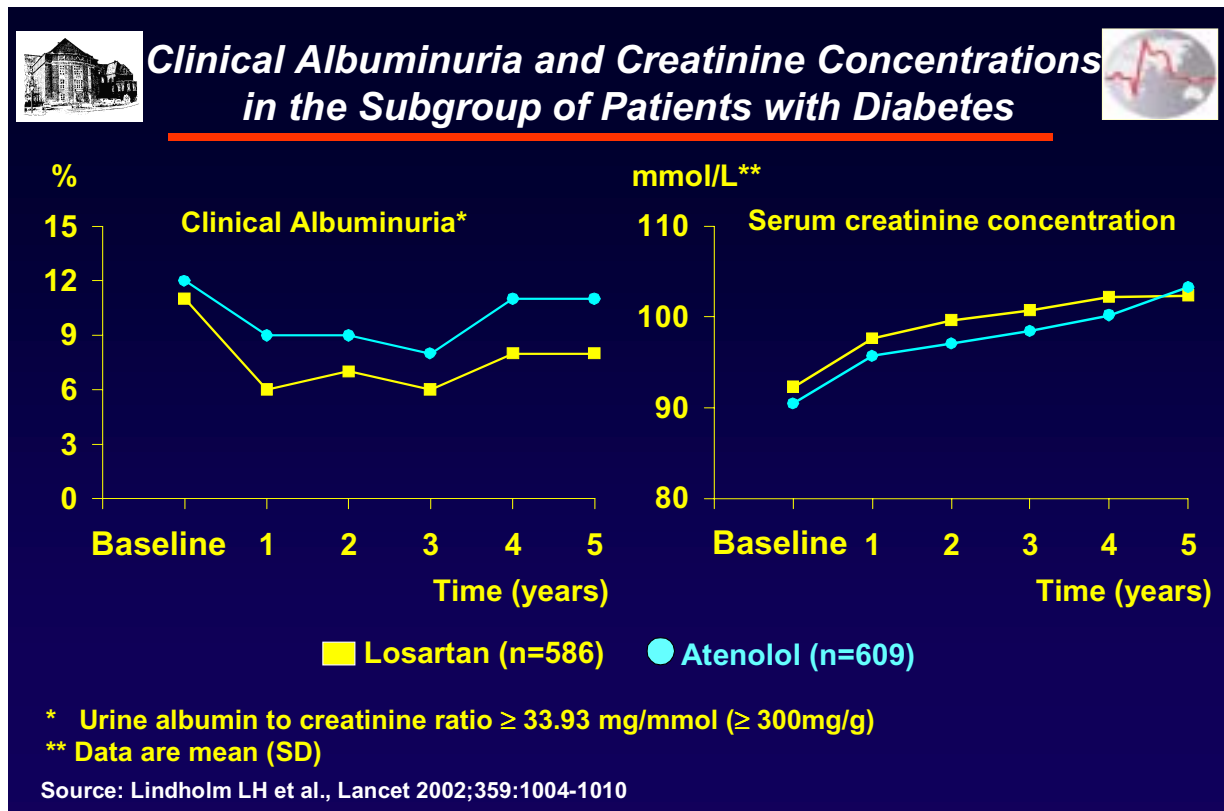


Reduction of left ventricular mass in the subgroup of diabetic patients

Losartan was more effective than atenolol in reversing left ventricular hypertrophy, which is likely to result from more complete protection against angiotensin II with losartan, whether generated by the circulating renin-angiotensin system or other mechanisms, especially since angiotensin II is a myocardial growth factor and an independent risk factor for cardiovascular disease.

Slide 11:

Clinical albuminuria and creatinine in the subgroup of patients with diabetes



Clinical albuminuria and creatinine in the subgroup of patients with diabetes

This slide shows the number (%) of diabetic patients with clinical albuminuria and mean serum creatinine concentrations (mmol/L), two markers of renal function. In this subgroup study of patients with diabetes, albuminuria was reported significantly less often in the losartan than in the atenolol group. Angiotensin II antagonists such as losartan have beneficial renal effects in patients with diabetes and nephropathy.

Slide 12:

Conclusions



Conclusions



- **Losartan prevents more cardiovascular morbidity and death than atenolol for a similar reduction in blood pressure and is better tolerated**
- **Losartan is more effective than atenolol in reversing left ventricular hypertension**
- **Losartan prevents more new-onset diabetes than atenolol**
- **Losartan has beneficial renal effects in patients with diabetes and nephropathy**

Source: Dahlöf B et al., Lancet 2002;359:995-1003
Lindholm LH et al., Lancet 2002;359:1004-1010

Conclusions

The conclusions of the LIFE study are shown in this slide.