Note: This is a two-article spread with a shared commentary. Please scroll down for the second article.

Losartan reduced strokes and new-onset diabetes more than atenolol in essential hypertension

Dahlöf B, Devereux RB, Kjeldsen SE, et al., for the LIFE study group. **Cardiovascular morbidity and mortality in the Losartan Intervention for Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol.** Lancet. 2002 Mar 23;359:995-1003.

QUESTION

In patients with essential hypertension and signs of left ventricular hypertrophy (LVH), is losartan-based therapy more effective than atenolol-based therapy?

DESIGN

Randomized (unclear allocation concealment*), blinded (patients and monitoring committee),* controlled trial with ≥ 4 years follow-up.

SETTING

Multicenter trial in Europe and the United States.

PATIENTS

9222 patients 55 to 80 years of age (mean age 67 y, 54% women) with hypertension (sitting blood pressure [BP] after 1 to 2 wk of placebo of 160 to 200 mm Hg systolic, 95 to 115 mm Hg diastolic, or both) and electrocardiographic signs of LVH. Exclusion criteria included secondary hypertension; myocardial infarction (MI) or stroke within the previous 6 months; angina pectoris requiring treatment with β-blockers or calcium antagonists; and heart failure or left ventricular ejection fraction ≤ 40%. Follow-up was 99%.

INTERVENTION

Patients were allocated to losartan-based therapy (n = 4605) or atenolol-based therapy (n = 4588). Losartan and atenolol were started at 50 mg/d, combined with low-dose hydrochlorothiazide if needed and then increased to 100 mg/d if needed, and supplemented with other antihypertensive drugs (except β-blockers, angiotensin-converting enzyme [ACE] inhibitors, or angiotensin-receptor blockers [ARBs]) to reach a target BP < 140/90 mm Hg.

MAIN OUTCOME MEASURES

The primary end point was a composite of cardiovascular mortality, MI, and stroke. One of the secondary end points was new-onset diabetes.

MAIN RESULTS

Analysis was by intention to treat. The composite end point, fatal or nonfatal stroke and new-onset diabetes, occurred less frequently in patients assigned to losartan than in those assigned to atenolol (Table). No difference existed between the groups for cardiovascular mortality or MI. BP control, dose titration, and use of other antihypertensives were similar in both groups.

CONCLUSION

In patients with essential hypertension and signs of left ventricular hypertrophy, losartan reduced strokes and new-onset diabetes more than atenolol.

Source of funding: Merck.

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*See Glossary.

Losartan-based therapy vs atenolol-based therapy in essential hypertension with signs of left ventricular hypertrophy†

Outcomes	Losartan	Atenolol	RRR (95% CI)	NNT (CI)
Composite end point‡	11%	13%	12% (2 to 22)	64 (36 to 418)
Stroke	5%	7%	24% (11 to 36)	61 (42 to 140)
New-onset diabetes	6%	8%	24% (12 to 36)	52 (35 to 108)

†Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.
‡Cardiovascular mortality, stroke, and myocardial infarction.

COMMENTARY

Physicians can become frustrated when prescribing medications for asymptomatic patients with chronic diseases. They may doubt that the benefit of treatment exceeds the cost and risks for side effects. Patients may not comply if the cost or side effects exceed perceived benefits. As a result, therapeutic goals may be difficult to achieve.

The LIFE studies show that potentially life-threatening complications can be reduced with fewer side effects. The original, placebo-controlled public health trials of hypertension used thiazides and β-blockers. These agents successfully reduced cardiovascular disease and stroke; thus, they have been considered first-line therapy for hypertension (1). In the LIFE studies, losartan reduced stroke and combined cardiovascular end points to a greater degree than atenolol. The data indicate that cardiovascular protection by using an ARB is superior to that of a β-blocker for patients with hypertension and LVH, which are independent risk factors for cardiovascular disease. Other trials using ACE inhibitors and ARBs have shown cardiovascular and renal benefits unrelated to their effects on hypertension (2, 3). We need to reconsider the selection of first-line hypertensive therapy, particularly in patients at high risk.

Several comments should be made concerning the study methodology and results. Most patients required ≥ 2 agents to reach target-level BP, which is consistent with other trials (4). Use of multiple agents could confound the comparison between the 2 agents in reducing risk. Lower systolic pressures should have been targeted. The final mean systolic BP was 146 mm Hg in patients with diabetes and 144 mm Hg in those without. To minimize cardiovascular events, systolic pressure should be decreased to 120 mm Hg and 140 mm Hg in patients with and without diabetes, respectively (5). 16% of the patients smoked. No attempt to change dietary, exercise, or smoking habits was noted. Visits were semiannual; more frequent appointments could produce better compliance, lower BP, and more positive lifestyle changes. Aggressive antihypertensive therapy, daily aspirin administration, and lifestyle improvements could have further reduced cardiovascular events.

The cardiovascular benefits of ARBs probably resulted from interference with the deleterious effects of angiotensin II. The results should be applicable to other ARBs. Comparative studies could determine whether an ARB or ACE inhibitor is most effective. Combining ARBs and ACE inhibitors may be beneficial.

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Losartan reduced cardiovascular morbidity and mortality more than atenolol in patients with diabetes and essential hypertension

Lindholm LH, Ibsen H, Dahlöf B, et al., for the LIFE study group. **Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention for Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol.** Lancet. 2002 Mar 23;359:1004-10.

QUESTION

In patients with diabetes, essential hypertension, and signs of left ventricular hypertrophy (LVH), is losartan-based therapy more effective than atenolol-based therapy?

DESIGN

Randomized (unclear allocation concealment*), blinded (patients and monitoring committee),* controlled trial with ≥ 4 years follow-up.

SETTING

Multicenter trial in Europe and the United States.

PATIENTS

1195 patients (a predefined subgroup of patients who had diabetes mellitus at the start of the LIFE study) who were 55 to 80 years of age (mean age 67 y, 53% women) with hypertension (sitting blood pressure [BP] after 1 to 2 wk of placebo of 160 to 200 mm Hg systolic, 95 to 115 mm Hg diastolic, or both) and electrocardiographic signs of LVH. Exclusion criteria included secondary hypertension; myocardial infarction (MI) or stroke within the previous 6 months; angina pectoris requiring treatment with β-blockers or calcium antagonists; and heart failure or left ventricular ejection fraction ≤ 40%. Follow-up was 100%.

INTERVENTION

Patients were allocated to losartan-based therapy (n = 586) or atenolol-based therapy (n = 609). Losartan and atenolol were started at 50 mg/d, combined with low-dose hydrochlorothiazide if needed then increased to 100 mg/d if needed, and supplemented with other antihypertensives (except β-blockers, angiotensin-converting enzyme [ACE] inhibitors, or angiotensin-receptor blockers [ARBs]) to reach a target BP < 140/90 mm Hg.

MAIN OUTCOME MEASURES

The primary end point was a composite of cardiovascular mortality, MI, and stroke. One of the secondary end points was heart failure.

MAIN RESULTS

Analysis was by intention to treat. The composite end point, cardiovascular mortality, all-cause mortality, and heart failure, occurred less frequently in patients assigned to losartan than in those assigned to atenolol (Table).

CONCLUSION

In patients with diabetes, essential hypertension, and signs of left ventricular hypertrophy, losartan reduced cardiovascular morbidity and mortality and all-cause mortality more than atenolol.

Source of funding: Merck.

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*See Glossary.

Losartan-based therapy vs atenolol-based therapy in diabetes with essential hypertension and signs of left ventricular hypertrophy†

Outcomes	Losartan	Atenolol	RRR (95% CI)	NNT (CI)
Composite end point‡	18%	23%	22% (2 to 39)	21 (12 to 250)
Cardiovascular mortality	6%	10%	36% (5 to 57)	28 (18 to 211)
All-cause mortality	11%	17%	37% (15 to 53)	16 (12 to 40)
Heart failure	5%	9%	40% (8 to 61)	28 (19 to 145)

†Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.
‡Cardiovascular mortality, stroke, and myocardial infarction.

COMMENTARY *(continued from page 86)*

25 years ago, patients with diabetic nephropathy had little hope of averting dialysis. Risk can now be substantially decreased with better glucose control, reduction in BP to normotensive levels, and treatment with an ACE inhibitor or ARB.

The LIFE studies concluded that losartan mildly reduced cardiovascular complications more than atenolol. The reduction in side effects with ARBs was a positive step toward increasing patient satisfaction and compliance. Fewer side effects should result in greater adherence. Public programs should advertise that antihypertensive therapy is attainable with fewer unpleasant side effects.

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