

LIFE (LOSARTAN INTERVENTION FOR END POINT REDUCTION) STUDIES IN HYPERTENSIVE PATIENTS IN REDUCING VARIOUS CV MORBIDITIES AND MORTALITIES INCLUDING STROKE COMPARED ATENOLOL

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BACKGROUND

Stroke is the second leading cause of cardiovascular morbidity and mortality worldwide with long term disability in developed countries. Various risk factors lead to progression of stroke, they include hypertension, atrial fibrillation, new onset of diabetes, isolated systolic hypertension (ISH) & left ventricular hypertrophy. Among these risk factors, Hypertension is considered as major risk factor for myocardial infarction previously but now-a-days it is considered as the greatest risk factor for the stroke. Various antihypertensive agents which either as mono therapy or in combinations are used to reduce above cardiovascular (CV) morbidities and mortalities including different stroke outcomes.

Recently losartan, AT-2 (angiotensin-2) receptor antagonist which is acting on renin angiotensin system (RAS) is considered as first line agent to reduce different CV morbidities and mortalities compared to other conventional B-blockers and Thiazide diuretic combinations. Various "LIFE (losartan intervention for end point reduction) studies" were conducted in hypertensive patients which show better efficacy profile of losartan in reducing various CV morbidities and mortalities including stroke compared to atenolol.

INTRODUCTION OF LIFE STUDIES

LIFE studies were started in 1990. It analyzed difference between Angiotensin receptor blocker (losartan) and B-blocker (atenolol) in reducing risk of various cardiovascular morbidities and mortalities like stroke, myocardial infarction, sudden cardiac death, atrial fibrillation and new onset of diabetes as primary composite endpoint (CEP). Secondary composite endpoint of this studies include up to what extent benefits of losartan can be expanded beyond blood pressure reduction in comparison to atenolol. These LIFE studies were an investigator-initiated, multicentre, double masked, randomized between losartan and atenolol as active control.

Hypertensive patients of age between 55 to 80 having evidence of electrocardiographic left ventricular hypertrophy were included in studies. Patients with previous history of stroke or myocardial infarction (MI) in the last six months; patients using B-blockers and calcium channel blockers and patients having cardiac output of less than 40%; hepatic or renal dysfunction were excluded from the study. Anti platelets, anti coagulant and thiazide diuretics were used as supplementary therapy during study. The mean follow-up time of 4.8 years obtained in study. Analyses of cardiovascular endpoints were based on intention to treat basis which include all randomized patients. Cost hoc regression model was used to assess difference between treatment groups.

OBJECTIVE

To analyze beneficial effects of losartan Vs atenolol along with its safety and efficacy profile in different composite endpoints of CV morbidities and mortalities like MI, stroke, ISH (isolated systolic hypertension), Atrial fibrillation (AF) and new onset of diabetes and in comparison to atenolol group in hypertensive patients. Also to assess such beneficial effects in combination therapy of losartan and aspirin on the same outcomes.

LOSARTAN IN STROKE REDUCTION

“This study involved 9193 patients of ages 55 to 80 with hypertension and electrocardiographic evidence of left ventricular hypertrophy. LIFE study by Kizer et al (2004)” shows losartan attained 48% of systolic and diastolic targets compared to 46% of atenolol. In losartan group there was more reduction of 1.1 mmHg in systolic pressure compared to atenolol with almost no difference in diastolic pressure. Assessment of stroke was based on signs and symptoms, diagnostic imaging (MRI), computed tomography, or angiography, spinal fluid analysis, and autopsy. Stroke was classified into various categories which are developed in the “Framingham risk score”. There were 541 incident of first strokes noted among all the participants, out of which ischemic atherothrombotic constitutes in 395 patients, ischemic embolic in 81, 55 incidence of hemorrhagic and 10 cases of other events.

Among strokes events 76 patients shows fatality. Atrial fibrillation also occurred in 55% of patients with embolic stroke. During follow-up 72 patients had recurrent stroke events. Statically significant benefits of losartan for stroke reduction were extended to ischemic, atherothrombotic and fatal strokes. But fatal stroke is reduced significantly in losartan group while results of other two strokes were similar in both the groups. There were significantly fewer stroke events in losartan arm on the basis of “Framingham risk score” classification as compared to atenolol. All the participants have achieved follow-up of 86% & 82% in losartan and atenolol group respectively [1]. It was found that benefit of losartan versus atenolol on ECG regression of left ventricular hypertrophy and blood pressure reduction were independent which is supported by results of other LIFE studies [2-4]. Losartan shows overall 25% reduction in stroke outcomes compared to atenolol [1].

LOSARTAN IN ATRIAL FIBRILLATION WITH SUBSEQUENT STROKE REDUCTION

“LIFE study by wachtell et al (2005)” was conducted to check the benefits of losartan of new AF, as it is considered as major leading factor of stroke in 9193 patients. Results show that losartan attained 33% reduction in new onset of AF with subsequent stroke as compared to atenolol [2]. The results of these study shows there were 48% reduction of composite endpoint (CEP) of CV morbidities and mortalities with 45% reduced rate of stroke events, supports the review study by Borghi et al (2007).

However, it was also found that randomization within patients with new onset of AF were might not be balanced. New-onset AF occurred in 150 patients randomized to losartan versus 221 to atenolol (6.8 vs. 10.1 per 1,000 person-years; relative risk 0.67, 95% confidence interval, $p < 0.001$) despite similar blood pressure reduction. Patients receiving losartan tended to stay in sinus rhythm longer ($1,809 \pm 225$ vs. $1,709 \pm 254$ days from baseline, $p = 0.057$) than those receiving atenolol. [2].

LOSARTAN VS ATENOLOL

LIFE study by Ruwald et al (2012) includes total of 9193 hypertensive patients with LVH aged 45-83 years were followed for a mean of 4.8 years. Patients were divided into two age groups according to the median age of 67 years and the effects of losartan versus atenolol-based antihypertensive treatment on the primary composite endpoint (CEP) consisting of cardiovascular death, nonfatal stroke or nonfatal myocardial infarction were investigated. The beneficial effect of losartan versus atenolol-based treatment was greater in the group of patients older than 67 years [hazard ratio 0.79 (0.69-0.91), $P=0.001$] compared to the group of patients younger than 67 years [hazard ratio 1.03 (0.82-1.28), $P=0.0809$], $P=0.045$ for interaction. The beneficial effects of losartan versus atenolol-based antihypertensive treatment on pulse pressure, HDL-C, UACR, and Cornell and Sokolow-Lyon voltage were not more pronounced in patients older than 67 years compared to patients younger than 67 years. Study showed a greater beneficial effect of losartan versus atenolol-based antihypertensive treatment in the group of patients older than 67 years compared to the group of patients younger than 67 years. This difference was not explained by a more pronounced effect of losartan-based treatment on any of the cardiovascular risk factors demonstrated to have independent prognostic importance.[5]

SYSTOLIC LEFT VENTRICULAR FUNCTION IN LIFE STUDY

LIFE echocardiography sub-study by Banget et al (2013) includes 939 patients had measurable LVM at enrolment. At baseline, 12% had eccentric nondilated, 20% eccentric dilated, 29% concentric nondilated, and 14% concentric dilated LVH, with normal LVM in 25%. Compared with the concentric nondilated LVH group, those with concentric dilated LVH had significantly lower pulse pressure/stroke index and ejection fraction; higher LVM index, stroke volume, cardiac output, left ventricular midwall shortening, left atrial volume and isovolumic relaxation

time; and more had segmental wall motion abnormalities (all $P < 0.05$). Similar differences existed between patients with eccentric dilated and those with eccentric nondilated LVH (all $P < 0.05$). [6]

HEMODYNAMIC MECHANISMS OF LOSARTANVS ATENOLOL

LIFE echocardiography sub-study by Greve *et al* (2012) involved 801 patients with at least two echocardiographic examinations. Atenolol- and losartan-based therapy reduced BP similarly (cumulative difference in mean brachial blood pressure 0.3 mm Hg, $P = 0.65$). After 4 years the cumulative means of SI and heart rate were 1.8 ml/m² higher and 5.7 beats/min lower on atenolol-based treatment, respectively (both $P < 0.001$). This kept CI below baseline in atenolol-treated patients, whereas in the losartan group CI was unchanged from baseline throughout the study. [7]

SAFETY AND TOLERABILITY PROFILE OF LOSARTAN

“Study by Goldberger *et al* (1995) of safety and tolerability of losartan potassium were compared with atenolol, felodipine, angiotensin converting enzyme (ACE) inhibitors” in 2900 hypertensive patients shows Increase in alanine amino transferase was the laboratory adverse event with the highest incidence of 1.9% in patients receiving losartan. But it was found that no laboratory adverse experience were unexpected or of clinical importance. Mainly dizziness was considered as “drug related adverse effect” in losartan (2.4%) compared to placebo (1.3%). Dry cough which were most significantly seen adverse effect in ACE inhibitors (8.8%) than in losartan (3.1%) & placebo group (2.6%). There were no clinically important difference in clinical or laboratory safety profiles in demographic subgroups for age, gender or race. In controlled clinical trials losartan shows excellent tolerability profile than other Antihypertensive agents which were determined by incidence of patient reporting any drug related adverse effect. [4]

COMBINATION THERAPY OF LOSARTAN WITH ASPIRIN

“LIFE study by Fossum *et al* (2005)” shows efficacy profile of losartan with aspirin group compared to losartan with atenolol group in various CV morbidities and mortalities. It was found that statistical significant interaction between losartan and aspirin shows better reduction in primary composite endpoints compared to atenolol with aspirin. Follow up in this study were 74% and 68% in losartan and atenolol group respectively. There was greater reduction in stroke, MI, cardiovascular death in losartan group receiving aspirin compared to atenolol group with aspirin [5]. The similar blood pressure reduction found in both groups [1-2, 4].

REVIEW OF GIVEN ARTICLE USING ABOVE REFERRED ARTICLES

LIFE studies shows similarity in similar blood pressure reductions and all of these studies also shows beneficial effect of losartan is independent of this blood pressure reductions [1-2, 4]. Besides this study by Kizer et al (2004) shows outcomes of stroke results were independent of not only blood pressure but also on AF[1]. But study by Wachtell *et al* (2005) shows losartan shows subsequent stroke reduction events by decreasing new onset of AF. These findings might be explained by the limitation of study by Kizer *et al* (2004) which had mentioned there was not properly adjustment of baseline characteristics for stroke and LVH, this might affect the results. In the given study there were also 55% new onset of AF found but study by Wachtell *et al* (2005) shows 33% overall reduction in AF and subsequent stroke, this result can also be explained in similar manner as above [1,2].

Details of protocol and safety profile was given in study by Dahlof *et al* (2002) which was cited in the reference of given article. It shows better patient compliance in terms of safety and tolerability with less hospitalization in losartan group compared to atenolol [1]. These data of losartan's excellent safety and tolerability profile can also be supported by study of Goldberg *et al* (1995) in broader prospective. In controlled clinical trials losartan shows excellent tolerability profile than other Antihypertensive agents which were determined by incidence of patient reporting any drug related adverse effect. Rates of discontinuation of therapy were 2.3% in losartan group and 3.7% in placebo group.

In long term extension studies of 5 out of 16 double blind studies the most frequently occurring drug related clinical adverse experiences were headache (3.6%), dizziness (2.9%), and asthenia/fatigue (2.6%). These reported adverse experiences were consistent with those generally found in patients with essential hypertension. Losartan did not have any important adverse effects on lipids, glucose, or other metabolic parameters. Furthermore, the safety profile remained essentially unchanged during longer periods of treatment with losartan. Mainly dizziness was considered as "drug related adverse effect" in losartan (2.4%) compared to placebo (1.3%). Dry cough which were most significantly seen adverse effect in ACE inhibitors (8.8%) than in losartan (3.1%) & placebo group (2.6%) [4]. So in both studies losartan shows excellent safety and tolerability profile [1, 3].

In similar manner of losartan stroke reductions outcomes described in given study, Combination therapy of losartan with aspirin also shows 32% reductions in CEP compared to atenolol with aspirin. While result of Kizer *et al* (2004) shows only 13% improvements in CEP. So there might be significant interaction exist between losartan and aspirin which shows better efficacy in CEP. So combination therapy of losartan and aspirin shows more beneficial effects in different CEP. But to confirm its result which is either due to by chance or by protective action of aspirin is needs to be justified with future studies [1, 4].

Besides above review of given article few limitations of the LIFE study by Kizer *et al* (2004) also should be addressed with future research. Given study of stroke reduction shows increase in

stroke incidence in black & younger patients which could be due to salt sensitive behavior of them or through other mechanism on RAS by losartan. Another controversy exist between losartan AT-2 receptor antagonist and ACE inhibitors, “HOPE(heart outcomes prevention and evaluations)” trial shows greater reduction in stroke compared to LIFE trials. However after that another “ALLHAT (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack)” trial shows exactly opposite effect i.e. increases in stroke events noted. So controversy between such trials and molecular targets of ACE inhibitors & AT-2 antagonist along with mechanistic explanation of losartan should be justified in future trials. Another limitation is of baseline characteristics of blood pressure and LVH regression, all the results of losartan found were independent of blood pressure reduction and LVH regression. So baseline characteristics should adjust in such a manner that result will not deviate from the assessment criteria. In future rather than involving participants who are at high risk of cardiovascular events like LVH, AF selecting some baseline hypertensive patients in trials give exact picture of drug in broader view. This way data not only can be generalize to normal people but also gives better prediction of beneficial effect of drugs [1].

In addition to above studies, study by Ruwald *et al* (2012) showed greater beneficial effect of losartan versus atenolol-based antihypertensive treatment in the group of patients older than 67 years compared to the group of patients younger than 67 years. Study by Bang *et al* (2013) identifies dilated sub-groups with reduced left ventricular function among patients currently classified with eccentric or concentric LVH. Contrasting hemodynamics impacted cardiac response to similar reductions in brachial BP on losartan- vs. atenolol-based therapy in study by Greve *et al* (2012). []

CONCLUSION

LIFE studies justified efficacy and safety profile of losartan against atenolol in not only stroke but also other cardiovascular morbidities and mortalities with similar composite endpoint reduction in combination therapy of losartan with aspirin.

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