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List of Acronyms: Clinical Studies

ANBPS	Australian National Blood Pressure Study
CAPPP	The Captopril Prevention Project Randomized Trial
LIFE	Losartan Intervention For Endpoint Reduction In Hypertension
HEP	Randomized Trial Of Treatment Of Hypertension In Elderly Patients In Primary Care
HOPE	The Heart Outcome Prevention Evaluation Study
ICARUS	Insulin Carotids United States Scandinavia
MRC	Medical Research Council Trial Of Mild Hypertension
MRC II	Medical Research Council Trial Of Treatment Of Hypertension In Older Adults**:** Principal Results
NORDIL	The Nordic Diltiazem Study
OSLO	The Oslo Hypertension Study
RENAAL	Reduction Of Endpoints In NIDDM With The Angiotensin II Antagonist Losartan
SCOPE	Study On Cognition And Prognosis In The Elderly
SHEP	Systolic Hypertension In The Elderly Program
SHEP-PS	Systolic Hypertension In The Elderly Program - Pilot Study
STOP	Swedish Trial In Old Patients With Hypertension
STOP II	Swedish Trial In Old Patients With Hypertension-2 Study
UKPDS	UK Prospective Diabetes Study Group

I. INTRODUCTION AND ORGANIZATION OF THE DOCUMENT

Use of Losartan to Reduce the Risk of Cardiovascular Morbidity and Mortality in Hypertensive Patients With Left Ventricular Hypertrophy

FDA Advisory Committee Background Information

COZAAR™[1] (losartan potassium), an angiotensin II receptor (type AT_1) antagonist (AIIA) is currently approved for the treatment of hypertension and the treatment of nephropathy in type 2 diabetic patients. COZAAR™ may be used alone or in combination with other antihypertensive agents at doses of 25, 50, and 100 mg. The usual starting dose of COZAAR™ is 50 mg daily.

Merck Research Laboratories (MRL) has submitted a supplemental NDA for the use of COZAAR™ to reduce the risk of cardiovascular morbidity and mortality as measured by the combined incidence of cardiovascular death, stroke, and myocardial infarction in patients with hypertension and left ventricular hypertrophy (LVH). This supplemental application is based on the LIFE (**L**osartan **I**ntervention **F**or **E**ndpoint reduction in hypertension) study.

As will be shown, the results of the LIFE study provide convincing evidence that a losartan-based regimen, relative to an atenolol-based regimen, reduces the risk of cardiovascular morbidity and mortality in this patient population, despite comparable blood pressure control.

Based on the data presented herein, the proposed indication for COZAAR™ is as follows:

> *COZAAR is indicated to reduce the risk of cardiovascular morbidity and mortality as measured by the combined incidence of cardiovascular death, stroke, and myocardial infarction in hypertensive patients with left ventricular hypertrophy.*

The strength of the LIFE result derives in part from the fact that the trial demonstrated the superiority of losartan to the active antihypertensive comparator atenolol, which in addition to its known antihypertensive effects, has widely accepted benefits in reducing cardiovascular morbidity and mortality, even though it does not have a specific claim for a reduction in these endpoints. Thus, the LIFE study results should be interpreted in the context of the benefits of this active comparator.

[1] COZAAR™ is a registered trademark of E.I. du Pont de Nemours and Company, Wilmington, Delaware, USA; COPYRIGHT © MERCK &CO., Inc., 1995, Whitehouse Station, NJ, USA.

The Synopsis (Section II) that immediately follows this section provides a summary intended to orient the reader to the key elements of this document. The Synopsis is cross-referenced to the Comprehensive Background (Section III) where appropriate. Citations are not provided in the Synopsis but are included in the Comprehensive Background.

A list of references follows the conclusions (references are denoted in the text by numbers within brackets [ ]). Copies of the current approved U.S. labeling for COZAAR™ and atenolol are provided in Appendices 1 and 2.

II. SYNOPSIS
Use of Losartan to Reduce the Risk of Cardiovascular Morbidity and Mortality in Hypertensive Patients With Left Ventricular Hypertrophy

FDA Advisory Committee Background Information

1. Introduction (See Section III.1)

The LIFE study was a multinational, double-blind, parallel, randomized, active-control study of 9193 patients that evaluated the long-term effects of a losartan-based regimen compared with an atenolol-based regimen in patients with documented LVH (determined by electrocardiogram [ECG]) on the combination of cardiovascular morbidity and mortality (components of the composite endpoint include: cardiovascular mortality, stroke [fatal/nonfatal], and myocardial infarction [fatal/nonfatal]). It was conducted at 945 sites in 7 countries, enrolling 9193 patients in which 1096 patients had a primary endpoint with a mean follow-up of 4.8 years.

The study was specifically designed to obtain comparable blood pressure control in the 2 treatment groups so that the results would reflect the differences in the mechanisms rather than the magnitude of blood pressure reduction.

In brief, the LIFE study demonstrated that in hypertensive patients with LVH, losartan reduced the risk of major cardiovascular morbidity and mortality compared with atenolol despite comparable blood pressure control. Treatment with losartan resulted in a 13% decrease (Hazard Ratio [HR]: 0.869 [95% CI 0.772 to 0.979], p=0.021) in the relative risk (adjusted for baseline Framingham risk score and LVH) of the primary composite endpoint of cardiovascular death, stroke, and myocardial infarction compared with atenolol. Among the components of the primary composite endpoint, losartan was associated with a significant reduction in the risk of stroke (fatal and nonfatal) by 25% (HR: 0.752 [95% CI 0.634 to 0.891], p=0.001). The reduction in the risk of cardiovascular death by 11% (HR: 0.886 [95% CI 0.734 to 1.069], p=0.206) was not significant, but was directionally consistent with the benefit of losartan on the primary composite endpoint. The incidence of myocardial infarction (fatal and nonfatal) (HR: 1.073 [95% CI 0.879 to 1.310], p=0.491) was not significantly different between treatment groups. A test for heterogeneity among the components of the primary composite endpoint was statistically significant.

The proposed indication for COZAAR™ is as follows:

> *COZAAR is indicated to reduce the risk of cardiovascular morbidity and mortality as measured by the combined incidence of cardiovascular death, stroke, and myocardial infarction in hypertensive patients with left ventricular hypertrophy.*

In considering the use of the LIFE study to support the proposed indication, the FDA and the Advisory Committee (AC) members need to evaluate the ability of this large single trial to support a new claim. Thus, it is important to consider the evidence available to provide reassurance that the results of a single trial are scientifically sound and not due to chance. During 2 recent Cardio-Renal Advisory Committee Meetings, the committee and the FDA discussed the ability of a single placebo-controlled trial with a less than highly statistically significant p-value to support a proposed claim. The utility of supporting the findings of such trials with additional data from sources internal and/or external to the trial was discussed.

The use of an active-comparator in the LIFE study, rather than placebo, provides an additional level of confidence that, compared to an atenolol-based regimen, the losartan-based regimen reduced the risk of cardiovascular morbidity and mortality in patients with hypertension and LVH.

External data from clinical, epidemiologic, and preclinical studies provide confidence that the LIFE study results demonstrate a true benefit of treatment with losartan. Specifically:

- clinical trial data provide support that a β-blocker-based regimen reduces cardiovascular events in hypertensive patients;
- epidemiologic data link left ventricular hypertrophy in hypertension with excess cardiovascular risk, and its regression with reduced risk; and
- preclinical and clinical data provide a basis for the biologic plausibility for the benefit of a losartan-based regimen on stroke in excess of the established benefit of a β-blocker-based regimen on stroke.

The LIFE study results provide compelling support for the benefit of a losartan-based regimen in patients with left ventricular hypertrophy. Although neither atenolol nor any other β-blocker has an indication for reducing cardiovascular risk in hypertensive patients, the data supporting such a benefit are persuasive, based both on efficacy in reducing blood pressure, a surrogate for cardiovascular outcomes, and clinical outcomes data. Thus, the benefit of losartan shown in this trial should be considered in the context of demonstrated superiority to an agent, and a regimen, with cardiovascular benefit.

Notably, the LIFE study demonstrated a robust and highly statistically significant benefit of losartan compared with atenolol on stroke (25% reduction, p=0.001), a medically important component of the primary composite endpoint, despite comparable blood pressure control. The strength and magnitude of this finding imply that this represents a true benefit of losartan. As will be discussed, this benefit is mechanistically consistent with losartan's specific antagonism of the effects of angiotensin II, which mediate vascular pathology known to be associated with stroke. Although not statistically significant, the reduction in the incidence of cardiovascular (CV) death by 11% with losartan was directionally consistent with the primary composite endpoint, and was largely driven by a significant 35% reduction in stroke mortality. Of note, there was no

significant difference in the incidence of the myocardial infarction (MI) component of the primary composite endpoint or in coronary heart disease (CHD) mortality between the 2 treatment groups.

As previously indicated, a test for heterogeneity among the components of the primary composite endpoint was statistically significant (p=0.023). The discordance between the stroke and myocardial infarction results is consistent with known differences in the pharmacological actions of losartan and atenolol in these pathologically distinct disease states. Specifically, the β-blocker atenolol, in addition to its antihypertensive action, is thought to attenuate myocardial ischemic events by reducing myocardial oxygen demand, whereas losartan is thought to affect both myocardial and vascular wall morphology and remodeling in addition to its antihypertensive effect. As will be discussed later, this difference provides a plausible biological basis on which to explain the finding of a similar rate of myocardial infarction but a lower rate of stroke in the losartan-treated versus atenolol-treated groups.

The treatment benefit of losartan on the primary composite endpoint was consistent among multiple prespecified demographic, geographic, medical history, and disease severity subgroups, as evidenced by the lack of significant treatment-by-subgroup interactions. However, in the predefined subgroup analyses, there was a suggestion of an interaction between ethnic background and treatment (p=0.057). Further post hoc analyses revealed a significant qualitative treatment interaction for Blacks versus non-Blacks. Non-Black patients appeared to have lower risk of experiencing an event with losartan, while Black patients, comprising 6% of the study population, appeared to have lower risk with atenolol despite comparable blood pressure reduction.

This Synopsis provides a concise review of the results of the LIFE study and the rationale for the proposed indication. Given the evidence of a significant overall treatment benefit of losartan compared with the active control agent atenolol, the data showing a significant treatment benefit of losartan on stroke, and the mechanistic consistency in the reduction of angiotensin II-mediated effects, the findings of the LIFE study provide substantial support for the benefit of losartan on the reduction of cardiovascular morbidity and mortality in patients with hypertension and LVH.

2. The Losartan LIFE Study

2.1 Overview of Study Design (See Section III.3.1)

The LIFE study was a multinational, double-blind, parallel, randomized, active-control study to evaluate the long-term effects of a losartan-based treatment regimen compared with an atenolol-based treatment regimen in hypertensive patients with ECG-documented LVH on the combined endpoint of cardiovascular morbidity and mortality. The study was designed to attain comparable blood pressure control in the 2 treatment groups. Thus, any difference in outcomes between the 2 treatment regimens would reflect the pharmacological actions of the treatments rather than the magnitude of blood pressure reduction.

The primary hypothesis of the LIFE study was that, compared with atenolol, losartan would reduce the incidence of cardiovascular morbidity and mortality in patients with essential hypertension and LVH.

The primary objective of the LIFE study was to evaluate the long-term effects (≥4 years) of losartan compared with atenolol in hypertensive patients at increased risk (as documented by the presence of LVH) of the composite endpoint of cardiovascular (CV) morbidity and mortality. The 3 components of the primary composite endpoint were cardiovascular mortality, stroke (fatal/nonfatal), and myocardial infarction (fatal/nonfatal); adjustment for baseline Framingham risk score and LVH was prespecified.

Secondary objectives of the study were to compare the effects of losartan versus atenolol on the 3 individual components of the primary composite endpoint (defined as CV mortality, stroke [fatal/nonfatal], and myocardial infarction [fatal/nonfatal]) as well as on total mortality, hospitalization for angina pectoris, hospitalization for heart failure, regression of LVH (as measured by ECG), the relationship between regression of LVH and cardiovascular morbidity and mortality (as defined for the primary endpoint), the incidence of coronary revascularization procedures, peripheral revascularization procedures, silent myocardial infarction as evaluated from serial readings of annual ECGs, and safety and tolerability based upon adverse experience profiles and the incidence of discontinuations due to adverse experiences.

Tertiary objectives included between-treatment group evaluation of: the relationship between the degree of blood pressure control and cardiovascular morbidity and mortality; assessment of the influence of various risk factors on cardiovascular event rates, including smoking, age, gender, ethnic group, alcohol, exercise, medical history of various diseases, degree of LVH at baseline (Cornell voltage and Sokolow-Lyon voltage), Framingham risk, baseline laboratory tests, level of systolic and diastolic blood pressure at randomization, and baseline body mass index; and the long-term effects on new-onset diabetes mellitus (World Health Organization [WHO] criteria).

Patients with diabetes, patients with isolated systolic hypertension (ISH), and subsets according to the country of participation were prespecified as patient populations of special interest. Prespecified analyses of primary and secondary endpoints within the population categories of diabetic patients and patients with ISH were performed, while for country, the primary composite was separately evaluated for each of the 7 countries that participated in the trial.

Patients between the ages of 55 and 80 with ECG-documented LVH, confirmed by the ECG Core Center before randomization, and with trough SiDBP 95 to 115 mm Hg and/or SiSBP 160 to 200 mm Hg (off antihypertensive medications) were eligible for participation in the study. Patients with a known history of secondary hypertension of any etiology, malignant hypertension, hypertensive encephalopathy, and increased SiDBP >115 or SiSBP >200 mm Hg during the placebo run-in period were excluded from the study. Based upon the opinion of the treating physician, patients with medical conditions requiring specific treatment with a β-blocker, diuretic, angiotensin-converting

enzyme inhibitor (ACEI), angiotensin II-receptor antagonist (AIIA), or calcium antagonist were excluded from the study. History of renal or hepatic disorders or renal transplants, and known hypersensitivity or contraindication to losartan, atenolol, or hydrochlorothiazide precluded a patient from participation. Additional key exclusion criteria included history of stroke or myocardial infarction within 6 months prior to study start or clinically significant aortic stenosis.

Following withdrawal from all antihypertensive medications, patients entered a 2-week placebo run-in period and were then randomized to study medication (losartan or atenolol) and were followed for a minimum of 4 years. The duration of the study was based upon the cumulative number of cardiovascular events, i.e., the study was to continue for at least 4 years after the last patient was entered and until 1040 patients experienced a primary cardiovascular event. Clinic visits were made each week during the placebo run-in period. Patients who were eligible were randomized in a 1:1 ratio to 50 mg of either losartan or atenolol, and during this blinded treatment period, patients were seen at the clinic at Months 1, 2, 4, and 6, and then every 6 months. An important goal of the study was to achieve comparable blood pressure control. Therefore, a titration scheme was followed until the patient reached target blood pressure (<140/90 mm Hg). The titration scheme was as follows: Step 1: study drug 50 mg→Step 2: study drug 50 mg plus HCTZ 12.5 mg→Step 3: study drug 100 mg plus HCTZ 12.5 mg→Step 4: study drug 100 mg plus HCTZ ≥25 mg or addition of other antihypertensive agents (excluding angiotensin-converting enzyme inhibitors, angiotensin II-receptor antagonists, or β-blockers). If required, HCTZ was given as open-label drug. Titration steps occurred at 2-month intervals. All patients were to remain on study therapy for the duration of the trial. Patients who discontinued early from study therapy were to be followed either by clinic visits or telephone contact every 6 months until the end of the study. The investigator continued to capture endpoint information during these follow-up visits and obtained all necessary information from the admitting physician/hospital for the endpoint package. Temporary discontinuation of study therapy was permitted and, if clinically appropriate, study drug was to be restarted.

Safety and tolerability were assessed by clinical and laboratory measurements and adverse experience reporting. Study clinical endpoints were not reported as adverse experiences, with the exception of noncardiovascular death, which was reported both as an endpoint and a serious clinical adverse experience, but was not unblinded during the study.

2.2 Summary of Statistical Methods (See Section III 3.1.7)

The primary efficacy measurement was the composite endpoint of cardiovascular morbidity and mortality. Only endpoints occurring on or before 16-Sep-2001 and confirmed by the blinded ECC before the endpoint database was locked were included in the analyses, and patients with multiple endpoints were only counted once in the analysis of the primary composite endpoint. The 3 components of the primary composite were defined as cardiovascular death, stroke (fatal/nonfatal), and myocardial infarction (fatal/nonfatal). The primary analysis of the primary composite endpoint utilized an

intention-to-treat approach. All randomized patients were included in their randomized treatment group and all available follow-up data were included from randomization through the endpoint cutoff date of 16-Sep-2001. The statistical analysis of the primary endpoint was based on survival analysis models (time to earliest confirmed event). The cumulative incidence of the primary endpoint over time was estimated by the Kaplan-Meier product-limit method. Crude event rates and event rates per 1000 patient years were also calculated. Statistical comparisons between losartan and atenolol were carried out by a Cox proportional hazards model. The Cox model included prespecified covariates for treatment group, degree of LVH at baseline (as measured by both Cornell voltage duration product and Sokolow-Lyon [S-L] voltage), and the baseline Framingham risk score. The analyses of all secondary efficacy endpoints, including the components of the composite endpoint, were based on the intention-to-treat approach. Mean changes in systolic and diastolic blood pressure, pulse pressure, and ECG measures of LVH were analyzed at each scheduled visit using a rank-transformed analysis of variance.

Safety parameters included assessment of adverse experiences, vital signs (e.g., pulse rate and weight), and laboratory values. All randomized patients (N=9193) were included in the safety analyses; the safety analyses included data obtained while on study drug or within 14 days of study drug interruption or discontinuation.

2.3 Baseline Characteristics (See Section III.3.3)

The study enrolled 9193 patients with an average age of 66.9 years; 54% were females. Baseline characteristics were similar between the 2 treatment groups. The 2 treatment groups were closely matched in prevalence of coexisting cardiovascular conditions, diabetes mellitus, and prior therapies. Baseline LVH (as estimated by both Cornell voltage product and Sokolow-Lyon voltage from ECG) were similar between the 2 treatment groups. The difference between treatment groups for baseline Framingham risk score was small (mean difference ~0.2); however, the prespecified adjustment for this difference had an influence on the analyses in this trial. Vital signs and laboratory test results were similar between the 2 treatment groups.

Since diabetic patients (defined as patients with a secondary diagnosis of diabetes mellitus, insulin-dependent diabetes mellitus, or type 2 diabetes mellitus; n=1195) and patients with isolated systolic hypertension (ISH) (defined as baseline SBP≥160 and DBP<90 mm Hg; n=1326) at baseline were prespecified to be of special interest, the baseline demographics of these patients were also evaluated. Demographics within the diabetic and ISH patients were similar between the 2 treatment groups.

2.4 Key Efficacy Results (See Section III.3.5)

2.4.1 Blood Pressure Control (See Section III.3.5.1)

One of the goals of the LIFE study was to attain comparable blood pressure reductions in both treatment arms. Sitting trough systolic blood pressure at the end of the follow-up or last visit before a primary endpoint, whichever occurred first, fell by 30.2 mm Hg in the losartan group and 29.1 mm Hg in the atenolol group (treatment difference p=0.015).

Sitting diastolic blood pressure was reduced by 16.6 mm Hg in the losartan group and 16.8 mm Hg in the atenolol group. The treatment difference between groups was not significant (p=0.345). Pulse pressure was reduced by 13.6 mm Hg in the losartan group and 12.4 mm Hg in the atenolol group (treatment difference p<0.001).

In general, systolic blood pressure tended to be lower in the losartan group while diastolic pressure tended to be lower in the atenolol group, resulting in consistently lower pulse pressure values in the losartan group. The time-averaged difference between groups in systolic blood pressure was 1.2 mm Hg favoring losartan. The time-averaged difference between groups in diastolic blood pressure was 0.8 mm Hg favoring atenolol. The time-averaged difference between groups in pulse pressure was 2.0 mm Hg favoring losartan. In a post hoc analysis, the time-averaged difference between groups in mean arterial pressure was 0.1 mm Hg in favor of atenolol.

2.4.2 Primary Composite Endpoint and Components (Intention-to-Treat) (See Section III.3.5.2)

There was a 13% risk reduction in the primary composite endpoint of cardiovascular mortality, stroke, and myocardial infarction (adjusted for baseline Framingham risk score and LVH) with losartan compared with atenolol (HR: 0.869 [95% CI 0.772 to 0.979], p=0.021) despite comparable blood pressure control. The unadjusted risk reduction was 14.6% (HR: 0.854 [95% CI 0.759 to 0.962, p=0.009]). The reduction in risk was largely due to a reduction in the risk of the stroke component of the primary endpoint relative to treatment with atenolol (25% risk reduction, p<0.001). A reduction in the incidence of cardiovascular death (11% risk reduction, p=0.206), although not statistically significant, also contributed to the benefit of losartan on the composite endpoint, largely due to the stroke mortality (35% risk reduction, p=0.032); CHD mortality was not different between treatment groups (3% risk increase, p=0.839). The risk of myocardial infarction (7% risk increase, p=0.491) did not significantly differ between the treatment groups.

2.4.3 Consistency of Effect Among Components of the Primary Composite Endpoint (See Section III.3.5.3.3)

The effect of losartan relative to atenolol appeared to vary among the 3 components of the primary composite endpoint. Since apparent variation can occur by chance alone, a prespecified formal statistical test for the homogeneity of the treatment effect among the 3 components was performed, which revealed statistically significant heterogeneity (p=0.023). Therefore, the components of the composite endpoint were evaluated separately, and these analyses and the biologic basis for the observed differences are presented in Sections III.3.5.2 and III.5.

2.4.4 Demographic Subgroup Analyses (See Section III.3.5.3.4)

In the analyses based on demographic, geographic, disease history, and disease severity subgroups, there were no treatment-by-subgroup interactions that met the prespecified test for significance (p<0.05), indicating that, with one notable exception discussed below, the effect of losartan relative to atenolol was similar among all subgroups.

Although there was not a statistically significant effect of ethnic background on the risk of an event in the prespecified groups, there was a suggestion of interaction between ethnic background and treatment (p=0.057). White patients appeared to have lower risk with losartan (hazard ratio: 0.819 [95% CI 0.724 to 0.928]), while Black patients appeared to have lower risk with atenolol (hazard ratio: 1.598 [95% CI 1.004 to 2.543]). A further exploratory analysis dichotomizing patients into Black (N=533) and non-Black (N=8660) yielded a statistically significant interaction (p=0.005). Further, a test for qualitative interaction (i.e., effect of losartan differs in direction between Blacks and non-Blacks, not just in magnitude) was also statistically significant (p=0.016). Because of the robustness of the dichotomized treatment-by-ethnicity interaction, and its qualitative nature (rarely observed in clinical trials), additional exploratory analyses were performed in these 2 groups to evaluate the possible biologic explanations for this finding. Additional analyses of changes in blood pressure, left ventricular hypertrophy, and heart rate demonstrated that Black and non-Black patients behaved similarly in their responses to treatment, and therefore, did not reveal a biologic basis for the observed interaction with treatment in Black and non-Black patients for the primary endpoint. However, as indicated by the p-value for the test of interaction (p=0.005) between treatment and the dichotomized groups (Black and non-Black), this interaction is unlikely to have occurred by chance. Thus, the benefits of losartan versus atenolol demonstrated in the LIFE study overall do not appear to apply to Black patients with hypertension and LVH.

2.4.5 Regression of Left Ventricular Hypertrophy (See Section III.3.5.4.1)

Regression of LVH as measured by ECG was a secondary endpoint of the LIFE study. Regression of LVH was significantly greater in the losartan group from 6 months ($p<0.001$), the first on-treatment measurement, and continued to be significantly greater than that of atenolol throughout the study (e.g., annually), despite comparable blood pressure reduction. At end of follow-up or at last visit before a primary endpoint occurred, if one did, Cornell product was reduced by 290 mm x msec (10.2%) in the losartan group and 124 mm x msec (4.4%) in the atenolol group, and Sokolow-Lyon voltage was reduced by 4.6 mm (15.4%) in the losartan group and 2.7 mm (9.0%) in the atenolol group.

2.4.6 Adjudicated Secondary Endpoints: Total Mortality, Hospitalizations, Revascularization (See Section III.3.5.4.2)

Other prespecified secondary clinical endpoints that were adjudicated and analyzed included total mortality, hospitalization for angina, hospitalization for heart failure, coronary revascularization, and noncoronary arterial vascular surgery. None of the differences in these secondary endpoints was statistically significant between losartan and atenolol.

2.4.7 Mortality by Causes (See Section III.3.5.4.3)

The ECC classified each death according to whether or not it was cardiovascular and into more specific categories within the general subgroups. Differences between treatment groups were compared using a survival analysis model similar to the one used for the

primary analysis. There were no significant differences between the 2 treatment groups with respect to total mortality, cardiovascular mortality, or noncardiovascular mortality. For specific causes of death, there were fewer deaths caused by stroke in the losartan group, which is consistent with the analysis of the secondary stroke endpoint. The results for cause of death should be interpreted with caution because of the limited number of such events, and because there were multiple tests performed without adjustment for multiplicity. It is important to note that the ECC did not specifically classify deaths as due to myocardial infarction. Rather, they used a classification of "coronary heart disease" death, which includes myocardial infarction and sudden cardiac death as well as coronary heart disease deaths that were not sudden. They further subclassified these deaths according to the time between the occurrence of symptoms and death: <1 hour, 1 to 24 hours, or >24 hours.

2.4.8 Patient Populations of Special Interest: Prespecified Analyses (See Section III.3.5.5)

Patients with diabetes mellitus, patients with ISH, and subsets according to the country of participation were prespecified as subgroups of special interest; the primary composite endpoint and a subset of secondary endpoints were evaluated for these groups.

In patients with diabetes, reductions in blood pressure from baseline to primary endpoint or end of study were similar in the 2 treatment groups. The overall rate of the primary endpoint was increased in patients with diabetes mellitus. Losartan significantly reduced the risk of the primary composite endpoint of cardiovascular morbidity and mortality (including adjustment for baseline measures of LVH and Framingham risk score as covariates) by 24.5% (HR: 0.755 [95% CI 0.585 to 0.975], p=0.031). The risk of cardiovascular mortality was 36.6% lower in the losartan group than in the atenolol group (HR: 0.634 [95% CI 0.422 to 0.951], p=0.028). The risks of stroke (HR: 0.788 [95% CI 0.546 to 1.138], p=0.204) and myocardial infarction (HR: 0.829 [95% CI 0.548 to 1.253], p=0.373) were not significantly different between the treatment groups, but directionally favored treatment with losartan. Consistent with the main study result, these endpoints were important contributors to the overall effect on cardiovascular morbidity and mortality observed. Total mortality was 38.7% lower (HR: 0.613 [95% CI 0.448 to 0.839], p=0.002) in the losartan group. The risk of hospitalization for heart failure was more than 40% lower in the losartan group (HR: 0.594 [95% CI 0.384 to 0.919], p=0.019). The risk of hospitalization due to angina was not different between treatment groups.

In patients with ISH (defined as baseline SBP≥160 and DBP<90 mm Hg), reductions in blood pressure from baseline to primary endpoint or end of study were similar in the 2 treatment groups. In ISH patients, the overall rate of the primary endpoint was increased. The difference between the 2 treatment groups for the primary composite (including adjustment for baseline measures of LVH and Framingham risk score as covariates) approached significance (HR: 0.750 [95% CI 0.557 to 1.011], p=0.059). Losartan significantly reduced the risk of cardiovascular mortality by 45.7% (HR: 0.543 [95% CI 0.340 to 0.867], p=0.010) and stroke by 40.5% (HR: 0.595 [95% CI 0.385 to

0.921], p=0.020); the risk of myocardial infarction was not significantly different between the 2 treatment groups (HR: 0.890 [95% CI 0.550 to 1.442], p=0.637). Losartan also significantly reduced the risk of total mortality by 27.5% (HR: 0.725 [95% CI 0.528 to 0.995], p=0.046). The risks of hospitalization due to angina and heart failure were not different between the 2 treatment groups.

2.5 Summary of Safety Results (See Section III.3.6)

The overall incidence of patients reporting at least one clinical adverse experience, regardless of relationship to study drug, was similar between losartan and atenolol (losartan: 94.7% versus atenolol: 95.0%, p=0.481). There were significantly fewer patients in the losartan group with drug-related adverse experiences (i.e., definitely, probably, or possibly drug-related as assessed by the investigator) (losartan: 37.2% versus atenolol: 45.2%, p<0.001). The difference between groups with serious adverse experiences was not significant (losartan: 37.2% versus atenolol: 36.2%, p=0.299). There were significantly fewer patients in the losartan group with adverse experiences that resulted in discontinuation of study drug (losartan: 13.1% versus atenolol: 18.1%, p<0.001).

Formal statistical testing was performed for several prespecified adverse experiences of particular interest: angioedema, bradycardia, sleep disturbance, hypotension, dizziness, sexual dysfunction, cold extremities, cough, and cancer. Significantly more patients in the atenolol group experienced bradycardia (losartan: 1.4% versus atenolol: 8.5%, p=<0.001), cold extremities (losartan: 3.9% versus atenolol: 5.9%, p=<0.001) and sexual dysfunction (losartan: 3.6% versus atenolol: 4.7%, p=0.009). Significantly more losartan patients experienced hypotension (losartan: 2.6% versus atenolol: 1.6%, p=0.001). There were no differences in the frequency of angioedema, sleep disturbance, dizziness, cough, or cancer between the treatment groups.

3. Discussion (See Section III.5)

The results of the LIFE study demonstrate that in hypertensive patients with ECG evidence of LVH, losartan reduces the incidence of major cardiovascular morbidity and mortality by 13% (p=0.021), compared with atenolol, despite comparable blood pressure control. The 3 components of the primary composite were predefined as cardiovascular death, stroke (fatal/nonfatal), and myocardial infarction (fatal/nonfatal). Among the components of the primary composite endpoint, losartan was associated with a significant reduction in the risk of stroke (fatal and nonfatal) by 25% (p<0.001). There were no significant differences in the risk of the individual components of myocardial infarction (fatal and nonfatal) or cardiovascular mortality between the treatment groups; however, the reduction in the incidence of cardiovascular mortality by 11% directionally favored losartan including a 35% reduction in stroke mortality, consistent with the primary composite results. A test for heterogeneity among the component endpoints indicated that the treatment effect differed significantly among the components (p=0.023). This is discussed in more detail in Sections III.3.5.3.3 and III.5.1.1.3.

Of the classified causes of cardiovascular death, losartan was associated with a significant reduction in the risk of fatal stroke (p=0.032). Cardiovascular death due to coronary heart disease, heart failure, vascular disease, or other causes were not significantly different between the treatment groups. Losartan did reduce ECG-LVH to a greater degree than atenolol, and this appeared to partially account for the benefit of losartan on the primary composite outcome.

Blood pressure reduction was comparable between the 2 treatment groups, with slightly greater reductions in systolic blood pressure on losartan and slightly greater reductions in diastolic blood pressure on atenolol. A post hoc analysis demonstrated a significant qualitative interaction in Black patients for the primary endpoint, although no differences between Black and non-Black patients could be discerned in their responses of blood pressure, left ventricular hypertrophy, and heart rate. In regard to safety, losartan was better tolerated than atenolol, with fewer discontinuations due to adverse experiences.

3.1 Interpretation of LIFE Results (See Section III.5.1)

Regulatory decisions sometimes must be made based primarily on the results of a single study; this often is the case with large outcomes trials where ethical and practical considerations preclude the conduct of a second, confirmatory study. In such cases, data from within and external to the single study are examined to determine if they lend confidence and support in establishing that the results are robust and unlikely to have occurred by chance. During 2 recent Cardio-Renal Advisory Committee Meetings, the committee and the FDA provided specific insight into the need to support the findings of a single placebo-controlled trial with additional data from sources internal and/or external to the trial.

There are several features of the LIFE study, as well as external to the LIFE study that provide confidence in the strength of the observed results.

Specifically, as an active-comparator trial, the LIFE study provides a level of confidence beyond that of a placebo-controlled trial in that the demonstrated benefits of the losartan-based regimen are in the context of the known benefits of the atenolol-based regimen.

The LIFE trial was designed as a large, multicenter, double-blind, active-control study; 945 clinical sites in 7 countries participated and among 9193 patients, 1096 had a primary endpoint over almost 5 years of treatment. Adherence to the protocol was high, complete follow-up was obtained for 98.8% of potential patient-days, and vital status at study end was obtained for 99.4% of potential patient-days. Overall, these study features provide support for the accuracy of the results.

The statistically significant benefit of losartan in reducing the risk of stroke by 25% (p=0.001) compared with atenolol is an important and compelling finding. Stroke is a dramatic and devastating clinical occurrence. The 25% reduction provides substantial evidence that the benefit of losartan on the primary endpoint is highly unlikely to have occurred by chance. The benefit of losartan versus atenolol on cardiovascular mortality directionally favored losartan, including a 35% benefit on stroke mortality, and contributed to the benefit of losartan on the composite endpoint, but did not reach

statistical significance. The incidence of myocardial infarction was not significantly different between the 2 groups.

A prespecified test for heterogeneity among the components of the primary composite endpoint indicated that the treatment effect differed among the components (p=0.023). Since the test for heterogeneity is statistically independent of the test for a between-group difference in the primary composite endpoint, this is independent statistical evidence that the effects of losartan and atenolol differ. The finding of heterogeneity may reflect differences in the disease states that comprise the primary composite endpoint, and in the mechanisms of action of losartan and atenolol in those disease states. Although unanticipated, the different treatment effects on the individual components are understandable. In particular, although stroke and myocardial infarction are etiologically linked to hypertension, they are unique clinical events with distinct pathophysiologic bases. Furthermore, it is not surprising that antihypertensive agents acting through different mechanisms would provide differential benefits on the end organ complications of hypertension. Although both agents reduce blood pressure to a similar degree, their actions concurrent with this hypotensive effect differ. (See Section III.3.5.1, Figure 4 and Section III.3.5.2, Figure 7).

Heart rate is a major determinant of myocardial oxygen demand and thereby cardiac ischemic events; thus, β-blockers, by reducing heart rate and myocardial contractility, have a substantial benefit in both the primary and secondary prevention of myocardial infarction. In that context, it is noteworthy that the effect of losartan on myocardial infarction is not significantly different from that of atenolol, despite the greater reduction in heart rate (~8 bpm) afforded by atenolol. Furthermore, angiotensin II (AII) produces vascular pathology that may be reversed more effectively by losartan than atenolol. In this regard it is notable that LVH, a marker of the adverse effects of AII, was reduced to a greater extent with losartan compared to atenolol. This result may in part explain the superior effect of losartan on stroke reduction.

Confidence in the overall clinical benefits of losartan, and particularly those on stroke, is supported by epidemiologic data, which demonstrate a strong relationship between LVH and both cardiovascular and cerebrovascular events. Studies show marked increases in the risk of events occurring in the presence of LVH, and reductions in the risk of events associated with regression of LVH. Consistent with the study hypothesis and rationale, the LIFE trial results demonstrated that losartan significantly decreased ECG measures of LVH to a greater degree than atenolol despite comparable blood pressure reduction, and is consistent with an additional effect of losartan on myocardial remodeling. The benefit of losartan on stroke is mechanistically consistent with losartan's specific antagonism of the effects of angiotensin II, which mediates cerebrovascular pathology known to be associated with stroke.

The treatment benefit of losartan on the primary composite endpoint was consistent among multiple demographic, geographic, medical history, and disease severity subgroups, as evidenced by the lack of significant treatment-by-subgroup interaction.

Additionally, a consistent benefit of losartan was demonstrated in the high-risk patients with diabetes or ISH.

In the predefined subgroup analyses, there was a suggestion of an interaction between ethnic background and treatment (p=0.057). When further post hoc analyses were performed to explore this finding, a significant qualitative interaction was found for Blacks versus non-Blacks. Non-Black patients appeared to have lower risk of experiencing an event with losartan, while Black patients appeared to have lower risk with atenolol despite comparable blood pressure reduction. Although Black patients comprised only 6% of the study population, the robustness and qualitative nature of this finding has led to the proposal of including information in the label describing these results.

Finally, the safety of losartan in this trial was consistent with the known profile of this agent. The observed adverse experience profile in hypertensive patients with documented LVH was consistent with the currently approved U.S. labeling. Losartan was well tolerated and was associated with fewer discontinuations due to adverse experiences than atenolol.

3.2 Benefit Versus Risk Relationship (See Section III.5.2)

The results of the LIFE study clearly demonstrate that a losartan-based regimen compared with an atenolol-based regimen to control blood pressure provides cardiovascular benefit in patients with hypertension and LVH. In particular, losartan reduces the risk of stroke versus atenolol despite attainment of comparable blood pressure control.

Previous trials have demonstrated the beneficial impact on cardiovascular events of lowering blood pressure with antihypertensive therapy but have failed to distinguish among different types of therapies. Furthermore, despite treatment, the risk of cardiovascular complications in hypertensive patients remains high. Losartan treatment in hypertensive patients with ECG evidence of LVH in the LIFE study demonstrated a superior effect on cardiovascular morbidity and mortality compared with treatment with atenolol despite comparable blood pressure lowering. Losartan is established as an effective once-daily drug for the treatment of hypertension as well as for the treatment of nephropathy in type 2 diabetic patients with a history of hypertension. The potential risk associated with losartan is minimal; losartan has an excellent tolerability profile. Importantly, there is no incremental risk to the patient associated with losartan treatment with regard to the proposed new indication because losartan is already approved for patients with hypertension. However, the greater clinical benefit observed in the LIFE study is an important public health finding with direct relevance to clinical practice. Collectively, the data support a favorable benefit/risk ratio.

3.3 Overall Conclusions (See Section III.6)

Based on the LIFE study, which investigated the effect of losartan-based versus atenolol-based antihypertensive regimens on morbidity and mortality in hypertensive patients with documented LVH, the following conclusions can be drawn:

1. Losartan reduces the risk of development of the primary composite endpoint of cardiovascular mortality, stroke and myocardial infarction compared with atenolol (13% risk reduction, p=0.021), despite comparable blood pressure reduction. The reduction in risk is largely due to a reduction in the risk of the stroke component of the primary endpoint relative to treatment with atenolol (25% risk reduction, p<0.001). The benefit of losartan versus atenolol on cardiovascular mortality (11% risk reduction, p=0.206) does not significantly differ between treatment groups, but directionally favors losartan, including a benefit on stroke mortality (35% risk reduction, p=0.032), and contributes to the benefit of losartan on the composite endpoint. The incidence of myocardial infarction (7% risk increase, p=0.491) does not significantly differ between the treatment groups.
2. Losartan treatment does not differ significantly from atenolol treatment in the rate of mortality from all causes, hospitalization for heart failure or angina pectoris, coronary or peripheral revascularization procedures, or resuscitated cardiac arrest.
3. Losartan treatment reduces LVH relative to atenolol as assessed by electrocardiographic measures.
4. In diabetic patients, the primary composite endpoint result (24% risk reduction, p=0.031) is consistent with the result in the overall study population. Also, consistent with the result in the overall population, a reduction in stroke is an important contributor to the effect observed in the diabetic patients.
5. In patients with isolated systolic hypertension, the primary composite endpoint result (25% risk reduction, p=0.059) is consistent with the result in the overall study population. Also, consistent with the result in the overall population, a reduction in stroke is an important contributor to the effect observed in patients with isolated systolic hypertension.
6. In the demographic, geographic, disease history, and disease severity subgroups assessed, the treatment benefit of losartan on the primary composite endpoint is consistent as evidenced by the lack of significant treatment-by-subgroup interaction; however, in the predefined subgroup analyses, there is a suggestion of an interaction between ethnic background and treatment. A post hoc analysis revealed a qualitative interaction. Therefore, the benefits of losartan seen in the overall LIFE study do not appear to apply to Black patients with hypertension and LVH.
7. Losartan is well tolerated and is associated with fewer discontinuations due to adverse experiences than atenolol. The observed adverse experience profile of losartan in this population is consistent with the profile observed in the general hypertensive population.

Together with the data supporting the benefit of therapy with atenolol, the findings of the LIFE study provide substantial evidence for the benefit of losartan on the reduction of cardiovascular morbidity and mortality in patients with hypertension and LVH.

III. COMPREHENSIVE BACKGROUND

1. Introduction

The LIFE study was a multinational, double-blind, parallel, randomized, active-control study that evaluated the long-term effects of a losartan-based regimen compared with an atenolol-based regimen in patients with documented LVH (determined by electrocardiogram [ECG]) on the combination of cardiovascular morbidity and mortality (components of the composite endpoint included: cardiovascular mortality, stroke [fatal/nonfatal], and myocardial infarction [fatal/nonfatal]). It was conducted at 945 sites in 7 countries, enrolling 9193 patients in which 1096 patients had a primary endpoint with a mean follow-up of 4.8 years (maximum of 6.2 years).

The study was specifically designed to obtain comparable blood pressure control in the 2 treatment groups so that the results would reflect the differences in the mechanisms rather than the magnitude of blood pressure reduction.

In brief, the LIFE study demonstrated that in hypertensive patients with ECG evidence of LVH, losartan reduced the risk of major cardiovascular morbidity and mortality compared with atenolol despite comparable blood pressure control. Treatment with losartan resulted in a 13% decrease (HR: 0.869 [95% CI 0.772 to 0.979], p=0.021) in the relative risk (adjusted for baseline Framingham risk score and LVH) for the primary composite endpoint of cardiovascular death, stroke, and myocardial infarction compared with atenolol. Among the components of the primary composite endpoint, losartan was associated with a significant reduction in the risk of stroke (fatal and nonfatal) by 25% (HR: 0.752 [95% CI 0.634 to 0.891], p=0.001). The reduction in the risk of cardiovascular death (HR: 0.886 [95% CI 0.734 to 1.069], p=0.206) was not significant, but was directionally consistent with the benefit of losartan on the primary composite endpoint, largely due to a 35% benefit on stroke mortality. The incidence of myocardial infarction (fatal and nonfatal) (HR: 1.073 [95% CI 0.879 to 1.310], p=0.491) was not significantly different between treatment groups. A test for heterogeneity among the components of the primary composite endpoint was statistically significant.

The proposed indication for COZAAR™ is as follows:

> *COZAAR is indicated to reduce the risk of cardiovascular morbidity and mortality as measured by the combined incidence of cardiovascular death, stroke, and myocardial infarction in hypertensive patients with left ventricular hypertrophy.*

In considering the use of the LIFE study to support the proposed indication, the FDA and the Advisory Committee (AC) members need to evaluate the ability of a single trial to support a new claim. Thus, it is important to consider what evidence may be available to provide reassurance that the results of a single trial are scientifically sound and not due to chance. During 2 recent Cardio-Renal Advisory Committee Meetings, the committee and the FDA discussed the ability of a single placebo-controlled trial with a less than highly statistically significant p-value to support a proposed claim. The utility of supporting the

findings of such trials with additional data from sources internal and/or external to the trial was discussed.

The use of an active-comparator in the LIFE study, rather than a placebo, provides an additional level of confidence that, compared to an atenolol-based regimen, the losartan-based regimen reduced the risk of cardiovascular morbidity and mortality in patients with hypertension and left ventricular hypertrophy.

External data from clinical, epidemiologic, and preclinical studies provide confidence that the LIFE study results demonstrate a true benefit of treatment with losartan. Specifically:

- clinical trial data provide support that a β-blocker-based regimen reduces cardiovascular events in hypertensive patients;
- epidemiologic data link left ventricular hypertrophy in hypertension with excess cardiovascular risk, and its regression with reduced risk; and
- preclinical and clinical data provide a basis for the biologic plausibility for the benefit of losartan-based regimen on stroke.

The LIFE study results provide compelling support for the benefit of a losartan-based regimen in patients with left ventricular hypertrophy. Although neither atenolol nor any other β-blocker has an indication for reducing cardiovascular risk in hypertensive patients, the data supporting such a benefit are persuasive, based both on efficacy in reducing blood pressure, a surrogate for cardiovascular outcomes, and clinical outcomes data. Thus, the benefit of losartan shown in this trial should be considered in the context of demonstrated superiority to an agent, and a regimen, with cardiovascular benefit.

Notably, the LIFE study demonstrated a robust and highly statistically significant benefit of losartan compared with atenolol on stroke (25% reduction, p=0.001), a medically important component of the primary composite endpoint, despite comparable blood pressure control. The strength and magnitude of this finding imply that this represents a true benefit of losartan. As will be discussed, this benefit is mechanistically consistent with losartan's specific antagonism of the effects of angiotensin II, which mediate vascular pathology known to be associated with stroke. The reduction in the incidence of cardiovascular death by 11% was directionally consistent with the primary composite endpoint and was largely driven by a significant 35% reduction in stroke mortality. Of note, there was no significant difference in the incidence of the myocardial infarction component of the primary composite endpoint between the 2 treatment groups.

As previously indicated, a test for heterogeneity among the components of the primary composite endpoint was statistically significant (p=0.023). The discordance between the stroke and myocardial infarction results is consistent with known differences in the pharmacological actions of losartan and atenolol in these pathologically distinct disease states. Specifically, the β-blocker atenolol, in addition to its antihypertensive action, is thought to attenuate myocardial ischemic events by reducing myocardial oxygen demand, whereas losartan is thought to affect both myocardial and vascular wall morphology and

remodeling in addition to its antihypertensive effect. As will be discussed in more detail later, this difference provides a plausible biological basis on which to explain the finding of a similar rate of myocardial infarction but lower rate of stroke in the losartan-treated versus atenolol-treated groups.

The treatment benefit of losartan on the primary composite endpoint was consistent among multiple prespecified demographic, geographic, medical history, and disease severity subgroups, as evidenced by the lack of significant treatment-by-subgroup interaction. However, in the predefined subgroup analyses, there was a suggestion of an interaction between ethnic background and treatment (p=0.057). Further post hoc analyses revealed a significant qualitative interaction for Blacks versus non-Blacks. Non-Black patients appeared to have lower risk of experiencing an event with losartan, while Black patients, comprising 6% of the study population, appeared to have lower risk with atenolol despite comparable blood pressure reduction.

This Comprehensive Summary provides the results of the LIFE study as well as evidence that provides further confidence in the primary results. Given the significant overall treatment benefit of losartan compared with the active control agent atenolol, the data showing a significant treatment benefit of losartan on stroke, and the mechanistic consistency in the reduction of angiotensin II-mediated effects, the findings of the LIFE study provide substantial support for the benefit of losartan on the reduction of cardiovascular morbidity and mortality in patients with hypertension and LVH.

2. Background and Study Rationale

2.1 Epidemiology and Treatment of Hypertension

Essential hypertension is the most prevalent cardiovascular disease in the world, affecting ~20% of the world's adult population [1]. In the U.S., 24% of the adult population has hypertension. This condition has been well established as a primary risk factor for the development of cardiovascular, cerebrovascular, renovascular, and peripheral vascular diseases that make hypertension a major public health issue [2; 3]. Heart disease and stroke remain the first and third leading causes of death, respectively, in the U.S. [2]. In 1999, coronary heart disease caused 1 of every 5 deaths and stroke was responsible for 1 of every 14.3 deaths in the U.S. [4].

National guidelines from The Fifth Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC V) published in 1993 [5] were available when the LIFE trial was designed. These guidelines clearly indicated that diuretics or β-blockers were the preferred classes of drugs for initial drug therapy in patients with hypertension. This recommendation was based on evidence that diuretics or β-blockers reduced cardiovascular morbidity and mortality in controlled clinical trials [6] (see Section III.3.1.5 for a summary of the cardiovascular benefits demonstrated by β-blocker [including atenolol] treatment). Current guidelines from JNC VI (published in 1997) [2]continue to recommend diuretics or β-blockers as initial therapy in the management of hypertension unless there are specific conditions or comorbidities that indicate the need for another drug class. Neither set of treatment

guidelines provides specific therapy recommendations for patients with hypertension and LVH. In fact, JNC VI acknowledges the necessity for prospective controlled studies to demonstrate that the regression of LVH is associated with a reduction in the risk of cardiovascular events. The JNC VI guidelines (published after the initiation of the LIFE study) indicate that in older patients, thiazide diuretics or β-blockers in combination with thiazide diuretics are recommended because trials have shown these agents to be effective in reducing morbidity and mortality in the elderly [7; 8]. Additionally, the JNC VI guidelines recommend diuretics as preferred treatment for ISH in older patients but also note that calcium antagonists (excluding dihydropyridine) may be considered. The specific therapy recommendations for the elderly and patients with ISH noted in the JNC VI guidelines were not included in the JNC V guidelines.

The 1999 World Health Organization - International Society of Hypertension Guidelines for the Management of Hypertension [9] indicate that all available antihypertensive drug classes are suitable for the initiation and maintenance of therapy and recognize that drug choices will be influenced by multiple factors, including those that determine availability of drug in various countries. The guidelines recognize important differences between classes in the amount of evidence demonstrating morbidity and mortality benefits, and indicate there is a large body of evidence demonstrating the benefits of β-blockers and diuretics. The guidelines suggest that elderly patients and patients with systolic hypertension be treated with diuretics or calcium antagonists.

As noted above, treatment guidelines reflect the available long-term cardiovascular outcomes data, which indicate that reducing blood pressure results in decreases in cardiovascular morbidity and mortality including stroke, coronary events, heart failure, and progression of renal disease [9; 2]. In a meta-analysis conducted by Collins et al. involving 14 major controlled prevention trials in hypertension (comprising 37,000 middle-aged patients with an average follow-up of 5 years), the difference in diastolic blood pressure between the intervention groups (diuretic, β-blocker, or reserpine as first-line therapy) and the control groups (placebo [9 trials] or usual care [6 trials]) was 5 to 6 mm Hg. This difference in diastolic blood pressure was associated with significant reductions in all stroke events (42%), all coronary heart disease events (14%), and cardiovascular mortality (21%) [10]. A more recent meta-analysis conducted by He and Whelton [11] focused on the risk associated with elevated systolic blood pressure. In this meta-analysis, data from 10 randomized controlled trials involving 18,542 hypertensive patients were pooled. The data showed that an average reduction of 12 to 13 mm Hg in systolic blood pressure over 4 years of follow-up achieved by medical intervention (first-step agents included: diuretics, β-blocker, or calcium-channel blocker) was associated with significant reductions in stroke (37%), coronary heart disease (21%), and cardiovascular mortality (25%).

As treatment guidelines have evolved, so has the understanding of the pathophysiology of hypertension and its consequences. Specifically, the role of angiotensin II as a key mediator of hypertension and, in particular, its deleterious vascular effects, are increasingly recognized. These effects result from both hemodynamic and non-

hemodynamic actions of angiotensin II; the harmful effects of angiotensin II are considered in detail below.

2.2 Role of Angiotensin II in Hypertension and Associated Cardiovascular Morphologic and Functional Changes

Angiotensin II (AII) is the principal biologically active component of the renin angiotensin aldosterone system (RAS). It is well established that AII is a potent pressor agent acting directly as a vasoconstrictor and indirectly through its effects on sodium and water homeostasis [12].

There is also a growing body of evidence that AII is a key mediator of the adverse cardiovascular morphologic and functional changes observed in hypertensive patients *independent* of its pressor effects. A recent review [13] summarized the non-hemodynamic actions of AII: AII may induce cell growth leading to LVH and vascular remodeling; it induces fibrosis in both the cardiovascular and renal systems; it predisposes to endothelial dysfunction, vessel wall stiffness and atherosclerosis; and it contributes to the formation and instability of atherosclerotic plaques. Angiotensin II may also lead to the development of proteinuria in patients with nephropathy and is angiogenic; it may be involved in the development of microangiopathy. Importantly, almost all of these actions appear to be mediated via the AII AT_1-receptor subtype and are independent of blood pressure [13].

One of the most readily detectable and widely studied manifestations of excess circulating angiotensin II is LVH. LVH was first identified as a cardiovascular risk factor in the 1960s based on observations that hypertensive complications occurred more frequently at any given level of blood pressure in those with signs of LVH assessed by electrocardiogram (ECG) [14]. The Framingham Heart Study also reported that LVH was an independent risk factor for a wide range of cardiovascular diseases (e.g., events including coronary heart disease, congestive heart failure, stroke, myocardial infarction, and sudden death). Patients with LVH have a higher incidence of cardiac (e.g., coronary heart disease, myocardial infarction, heart failure) and non-cardiac (e.g., stroke, renal impairment) morbidity and mortality than those without LVH; based on long-term follow-up (ECG) from the Framingham Study [15; 16], the excess cardiovascular risk (depending on age and gender) for LVH is 1 to 17 times higher for cardiac consequences and 3 to 10 times higher for stroke [17]. A recent study that followed 2363 initially untreated hypertensive patients without a history of previous cardiovascular disease for a mean of 5 years found that LVH, by ECG or echocardiography, conferred an excess risk for stroke and transient ischemic attack independent of blood pressure and other risk factors [18]. After controlling for age, gender, diabetes, and ambulatory blood pressure, the relative risk for cerebrovascular events for patients with LVH assessed by ECG (Perugia score) was 1.79 (95% CI 1.17 to 2.76) and by echocardiography was 1.64 (95% CI 1.07 to 2.68).

The presence of LVH denotes a serious prognosis with an outlook closely resembling that of ECG evidence of a myocardial infarction [19]. Based on a 1983 report, one third of men and one fourth of women with ECG-LVH had died within 5 years of its appearance

(3 times the risk associated with hypertension alone) [20]. In the Framingham Study, 45% of cardiovascular deaths were preceded by ECG-LVH [16]. Taken together, these data demonstrate that LVH is a powerful risk predictor for cardiovascular disease and cardiovascular mortality [15].

Consistent with its strong association with cardiovascular disease, hypertrophied myocardium secondary to hypertension differs from normal myocardium in many respects, including its structure, mechanical properties, vascularity, biochemistry, and electrophysiology [21; 22]. Rather than representing merely a physiologic response to increased blood pressure, LVH is a pathologic response influenced by hemodynamic and non-hemodynamic factors [23; 21]. These abnormal properties of hypertrophied myocardium may be mechanistically related to adverse cardiovascular events (i.e., coronary heart disease, heart failure, myocardial infarction, and sudden death).

In addition to its non-hemodynamic effects on the myocardium, AII exerts a variety of effects on the vasculature that may, in part, be mediated by non-hemodynamic means. Studies of the structure and morphologic effects of hypertension on resistance arteries have found an increased media/lumen ratio and a smaller lumen in hypertensive patients compared with non-hypertensive patients. These changes are also associated with impaired endothelium-dependent vascular relaxation rate. In hypertensive patients, after 1 year of treatment with the angiotensin II AT_1-receptor antagonist losartan, a significant decrease in the media/lumen ratio was observed compared with treatment with atenolol [24]. In addition, endothelium-dependent relaxation was normalized in patients treated with losartan and was significantly improved compared with atenolol. Blood pressure control was equal in these groups, indicating that non-hemodynamic effects of AII may be responsible for these adverse morphologic and functional changes [13; 24].

Consistent with the findings described above, there is evidence that blockade of the renin-angiotensin-aldosterone system in hypertensive patients with ACE inhibitors and angiotensin II antagonists has a differential effect compared with other antihypertensive agents on associated cardiovascular morphologic and functional changes. Although lowering of blood pressure produces a beneficial effect on LVH, meta-analyses of clinical trials have indicated that blockade of the renin-angiotensin system with ACE inhibitors and angiotensin II receptor antagonists, including losartan, decreases LVH to a greater extent than other classes of agents including β-blockers, calcium channel antagonists, and diuretics [25; 26; 27; 28].

While no definitive study exists, there is also evidence supporting the hypothesis that regression of LVH will result in fewer cardiovascular events. In particular, studies of cardiac physiology in humans and experimental animals with and without LVH support the hypothesis that reduction of left ventricular mass during the treatment of hypertension is beneficial. Reversal of hypertrophy has been associated with reductions in arrhythmias, improved diastolic function, preservation of systolic function, and improvement in coronary reserve in both preclinical and clinical models [29]. Furthermore, in a report from the Framingham study that assessed LVH by ECG, the risk of cardiovascular events in individuals with ECG-LVH persisting for more than 4 years

was 25% greater than for subjects in whom ECG-measured LVH resolved [30]. In individuals in whom Cornell voltage increased during follow-up, the 2-year incidence of cardiovascular disease was approximately twice that of individuals in whom Cornell voltage decreased [17]. Similarly, in a small observational study, researchers from the Cornell Medical Center found that regression of LVH as compared with persistence of LVH resulted in a lower incidence of cardiovascular events (3.6% versus 25%) [31].

Thus, persistent activation of RAS may explain the excess residual cardiovascular morbidity and mortality in treated hypertensive patients, and this may be particularly evident in those selected according to the presence of LVH, a marker of the systemic effects of AII. In particular, AII effects both cardiac and vascular remodeling. Cardiac remodeling, manifested as LVH, thus serves as a marker for the presence of vascular remodeling that is causally related to stroke events.

2.3 Rationale for the LIFE Study

The hypothesis that losartan-based compared with atenolol-based antihypertensive treatment would reduce the incidence of cardiovascular morbidity and mortality in patients with essential hypertension and LVH in the setting of comparable blood pressure reduction was based on the specific actions of angiotensin II at the AT_1 receptor [12]. The following evidence was available from the clinical literature at the onset of the trial (1995): 1) Angiotensin II is a potent vasoconstrictor and in addition has non-hemodynamic effects that may adversely affect cardiovascular structure and function; 2) LVH is a significant, independent (of blood pressure, age) risk factor for cardiovascular morbidity and mortality [15] and LVH progression is associated with higher cardiovascular risk [32]; and 3) Blockade of the renin-angiotensin system causes significantly greater regression of LVH and normalization of peripheral vascular structure than β-blockade [25; 26; 24]. More recently, a diverse range of physiological and pathophysiological processes involved with the RAS has been elucidated. There is a large body of evidence demonstrating that angiotensin can cause inflammation, thrombosis, and plaque rupture, in addition to remodeling and hemodynamic effects [13]. Thus, it was postulated that there may be several different hemodynamic and non-hemodynamic mechanisms that can contribute to cardiovascular protection, with the blockade of angiotensin-induced adverse effects.

In light of the evidence of the importance of angiotensin II in hypertension-related structural and functional changes in the cardiovascular system, it was hypothesized that losartan, by directly inhibiting the effects of AII at the AT_1-receptor, would have a greater benefit on cardiovascular morbidity and mortality than conventional agents (with comparable blood pressure reduction) in patients with LVH, a marker of AII activity. Given the known benefits of treating hypertension and the desire to achieve comparable blood pressure control in the 2 groups, the use of a placebo control group in the study was not considered ethical, and consequently, identical blood pressure goals were established for the 2 groups. The choice of a β-blocker, atenolol, as the basis of the active comparator regimen will be addressed in greater detail subsequently (see Section III.3.1.5), but was based on its being among a class of effective antihypertensive

drugs with morbidity and mortality benefits in hypertensive patients, and efficacy in secondary prevention in high-risk cardiovascular patients [2; 1]. In addition, losartan and atenolol are both administered once daily with escalating dose titration that is amenable to the addition of a diuretic in patients whose blood pressure is not adequately controlled with monotherapy. The addition of a diuretic to the atenolol treatment arm mimics the regimen that has been most widely established as providing cardiovascular benefit in the treatment of hypertension. Finally, in order to test the hypothesis that specific AII blockade would mediate important benefits in the setting of comparable reductions in blood pressure, atenolol was chosen because of its previously demonstrated comparable antihypertensive efficacy versus losartan [33], and because of its different primary mechanism of action.

3. Summary of the LIFE Study

3.1 Overview of the Study

3.1.1 Study Hypothesis and Objectives

The primary hypothesis of the LIFE study was that, compared with atenolol, losartan would reduce the incidence of cardiovascular morbidity and mortality in patients with essential hypertension and LVH.

The primary objective of the LIFE study was to evaluate the long-term effects (≥4 years) of losartan compared with atenolol in hypertensive patients at increased risk of the composite endpoint of cardiovascular morbidity and mortality (because of the presence of LVH). The 3 components of the primary composite endpoint were defined as cardiovascular death, stroke (fatal/nonfatal), and myocardial infarction (fatal/nonfatal).

Secondary objectives of the study were to compare the effects of losartan versus atenolol on cardiovascular and total mortality, stroke (fatal/nonfatal), myocardial infarction (fatal/nonfatal), hospitalization for angina pectoris and heart failure, regression of LVH (as measured by ECG), the relationship between regression of LVH and cardiovascular morbidity and mortality (as defined for the primary endpoint), the incidence of coronary or peripheral revascularization procedures, silent myocardial infarction as evaluated from serial readings of annual ECGs, and safety and tolerability based upon adverse experience profiles and the incidence of discontinuations due to adverse experiences.

Tertiary objectives included the evaluation of: the relationship between blood pressure control and cardiovascular morbidity and mortality; assessment of the influence of various risk factors on cardiovascular event rates, including smoking, age, gender, ethnic group, alcohol, exercise, medical history of various diseases, degree of LVH at baseline (Cornell voltage and Sokolow-Lyon voltage), Framingham risk, baseline laboratory tests, level of systolic and diastolic blood pressure at randomization, baseline body mass index, and the long-term effects on new-onset diabetes mellitus (WHO criteria).

Patients with diabetes, patients with isolated systolic hypertension (ISH), and subsets according to the country of participation were prespecified as patient populations of special interest. Prespecified analyses of primary and secondary endpoints within the

population categories of diabetic patients and patients with ISH were performed; while for country, the primary composite was evaluated across country categories.

3.1.2 Independent Oversight Committees

The study was overseen by an independent Steering Committee (Chairman: Associate Professor Björn Dahlöf; Vice Chairman: Professor Richard Devereux), which was blinded to the data throughout the duration of the study. The Steering Committee had scientific responsibility for the study and its reports and publications. An independent, blinded Endpoint Classification Committee (ECC) (Dr. Daniel Levy and Dr. Kristian Thygesen) adjudicated all major clinical endpoints, details of which are specified in Section III.3.1.3 and Section III.3.1.4. An independent Data and Safety Monitoring Board (DSMB) (Chairman: Professor John Kjekshus), which was unblinded, monitored the safety of the study on a regular basis. The DSMB was responsible for identifying safety issues and interpreting emerging study data at 2 interim analyses.

3.1.3 Study Design

The LIFE study was a multinational, double-blind, parallel, randomized, active-control study that evaluated the long-term effects of a losartan-based regimen compared with an atenolol-based regimen in hypertensive patients with ECG-documented LVH on the composite endpoint of cardiovascular mortality, stroke, and myocardial infarction. This composite endpoint was chosen as a comprehensive reflection of the major systemic morbidity of hypertension on multiple organ systems. While it was recognized that the specific pathophysiologic mechanisms of the components differ, hypertension is known to be common to the etiology of each component.

The study randomized a total of 9222 patients from 945 investigative centers in 7 countries. All 29 patients at 1 center were discontinued from follow-up shortly after initiation of the study due to serious Good Clinical Practice (GCP) compliance issues, and were excluded from all analyses; therefore, 9193 patients were available for efficacy and safety analyses.

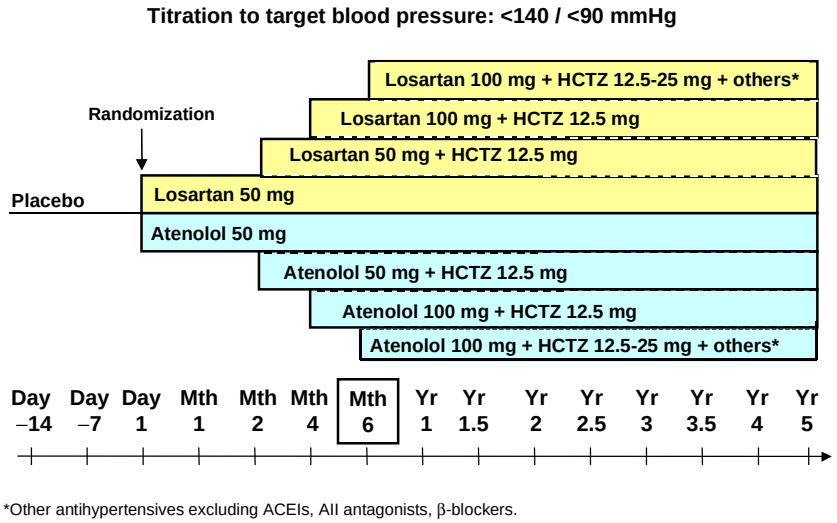
Patients between the ages of 55 and 80 with previously untreated or treated hypertension with ECG-documented LVH, confirmed by the ECG Core Center before randomization, and trough SiDBP 95 to 115 mm Hg and/or SiSBP 160 to 200 mm Hg (off all antihypertensive medications) were eligible for participation in the study. Patients with a known history of secondary hypertension of any etiology, malignant hypertension, hypertensive encephalopathy, increased diastolic BP >115, or systolic BP >200 mm Hg during the placebo run-in period were excluded from the study. Based upon the opinion of the treating physician, patients with medical conditions requiring specific treatment with a β-blocker, diuretic, angiotensin II-receptor antagonist (AIIA), angiotensin-converting enzyme inhibitor (ACEI), or calcium antagonist were excluded from the study. History of renal or hepatic disorders or renal transplants, known hypersensitivity or contraindication to losartan, atenolol, or hydrochlorothiazide precluded a patient from participation. Additional key exclusion criteria included known history of stroke or

myocardial infarction within 6 months prior to study start or significant known aortic stenosis.

After a 2-week placebo-run-in period, there was a minimum 4-year period of follow-up (Figure 1). The duration of the study was based upon the accumulation of events (until 1040 patients experienced a primary cardiovascular event) and not absolute time, with the exception that the duration of follow-up was to be at least 4 years for the last patient enrolled. Clinic visits were made each week during the placebo baseline period. Patients who were eligible were randomized in a 1:1 ratio to either 50 mg losartan or atenolol, and during this blinded treatment period, patients were seen at the clinic at Months 1, 2, 4, and 6, and then every 6 months. The LIFE study was designed with the goal of comparable blood pressure reductions in both treatment groups. Therefore, a titration scheme was used to reach a target blood pressure of <140/90 mm Hg. The titration scheme was as follows: Step 1: study drug 50 mg→Step 2: study drug 50 mg plus HCTZ 12.5 mg→Step 3: study drug 100 mg plus HCTZ 12.5 mg→Step 4: study drug 100 mg plus HCTZ ≥25 mg or addition of other antihypertensive agents (excluding angiotensin-converting enzyme inhibitors, angiotensin II-receptor antagonists, or β-blockers). Study drugs (losartan, atenolol and corresponding placebo) were blinded, whereas the other antihypertensive agents (including HCTZ) were open-label. Titration steps occurred at 2-month intervals. A diagram of the study design is in Figure 1.

Figure 1

Study Design



*Other antihypertensives excluding ACEIs, AII antagonists, β-blockers.

Patients who discontinued early from study therapy were to be followed either by clinic visits or telephone contact every 6 months until the end of the study. The investigator continued to capture endpoint information during these follow-up visits and obtained all necessary information from the admitting physician/hospital for the endpoint package. Temporary discontinuation of study therapy was permitted (as a result of adverse experiences or other reasons) and, if clinically appropriate, study drug was to be restarted.

Safety and tolerability were assessed by clinical and laboratory measurements and adverse experience reporting. Study clinical endpoints were not reported as adverse experiences, with the exception of noncardiovascular death, which was reported both as an endpoint and a serious adverse experience.

An independent, blinded ECC classified clinical endpoints using prespecified endpoint definitions and criteria determined by the Steering Committee. All cardiovascular events reported by clinical centers including the events that made up the primary composite endpoint (cardiovascular death, stroke, and myocardial infarction) as well as other secondary endpoints (total mortality, angina pectoris requiring hospitalization, heart failure requiring hospitalization, coronary or peripheral arterial revascularization procedures, and resuscitated cardiac arrest) were reviewed by the ECC, consisting of 2

experienced cardiologists, to determine if they met criteria for endpoints. The committee reviewed all potential endpoints submitted by the investigators without knowledge of the treatment groups. Disagreements about classification of endpoints were adjudicated by joint-in-person reviews for resolution. Study parameters not evaluated by the ECC included: silent myocardial infarction, regression of LVH as assessed by ECG, relationship between blood pressure control and cardiovascular morbidity and mortality, relationship between risk factors and cardiovascular event rate, and adverse experiences (including new-onset diabetes mellitus).

ECGs were submitted by the site to the ECG Core laboratory for myocardial infarction endpoints, and fatal events were also reported by the investigator directly to the Data Safety Monitoring Board (DSMB) for review. Investigators reported blood pressure readings and adverse experiences (including new-onset diabetes mellitus) directly on the case report form.

In order to monitor safety, 2 prespecified interim efficacy analyses were performed for review by the DSMB, when one-third and two-thirds of the expected number of endpoints were reached.

The study was initiated on 26-Jun-1995 and the final patient was entered into the study in May-1997. In Mar-2001, the Steering Committee set the endpoint cutoff date of 16-Sep-2001; the endpoint database was locked on 15-Nov-2001. The final study clinic visit was completed by 15-Nov-2001. Any endpoints occurring after 16-Sep-2001 or discovered after the database lock were not included in the efficacy analyses.

3.1.4 Definitions of Cardiovascular Morbidity and Mortality Endpoints

The ECC used the definitions as outlined below in the classification of cardiovascular morbidity and mortality endpoints.

Myocardial Infarction

A myocardial infarction was considered definite when any of the following conditions were present: 1) Typical rise and fall of cardiac laboratory markers with highly abnormal (i.e., greater than twice the upper limit of normal) peak values associated with typical or atypical symptoms consistent with acute myocardial infarction; 2) Serial changes in ECGs coded as definite Q/QS changes associated with typical or atypical symptoms consistent with an acute myocardial infarction; 3) Serial changes in ECGs coded as possible Q/QS changes as well as both typical or atypical symptoms of myocardial infarction *and* with a typical rise and fall of cardiac laboratory markers with abnormal (i.e., elevated but less than twice the upper limit of normal) peak values; or 4) Transient current of injury (S-T elevation) on the ECG that was reversed upon administration of thrombolytic therapy or following primary angioplasty associated with abnormal (i.e., elevated but less than twice the upper limit of normal) peak cardiac laboratory markers or typical or atypical clinical symptoms of myocardial infarction. S-T elevation had to be present on the ECG taken prior to the procedure.

The classification of definite myocardial infarction by autopsy was made when the criteria for myocardial infarction were not fulfilled during life and an autopsy revealed evidence of acute myocardial infarction.

Stroke

The diagnosis of stroke required evidence of a neurologic deficit, usually localized, lasting 24 hours or more, or until death (if death occurred <24 hours after the onset of neurologic symptoms), usually confirmed by diagnostic testing (e.g., CT scan).

The clinical characteristics of stroke included the sudden onset of a neurologic deficit typically manifested as: 1) Depression of state of consciousness; 2) Disturbance of vision; 3) Paresis or paralysis of one or more extremities; 4) Sensory impairment; 5) Speech impairment; 6) Central cranial nerve dysfunction; 7) Memory defect; 8) Ataxia; and 9) Movement disorder.

Strokes were classified into the following categories:

Ischemic: The minimal criterion for an ischemic, non-hemorrhagic stroke was a stroke as described above without evidence of primary intracranial bleeding.

Athero/Thrombotic: A diagnosis of athero/thrombotic stroke was made when an ischemic stroke occurred and there was no evidence of an embolic etiology.

Embolic: A diagnosis of embolic stroke was made when an ischemic stroke occurred and a source for embolus (e.g., chronic or paroxysmal atrial fibrillation, irrespective of anticoagulation, rheumatic heart disease with mitral stenosis, recent myocardial infarction, prosthetic heart valve, bacterial endocarditis, ulcerated carotid plaque, amaurosis fugax) was present, and the clinical course was consistent with embolic stroke (that is, rapid onset and partial clearing, slightly bloody spinal fluid, a more localized deficit), or the occurrence of associated peripheral emboli elsewhere had been noted.

Hemorrhagic: A stroke with compatible neurologic findings on examination (i.e. headache and meningeal signs in the case of subarachnoid hemorrhage) in which there was evidence of hemorrhage (bloody spinal fluid, blood on CT scan of brain, etc.) was considered to be a hemorrhagic stroke. Rupture of a vessel due to traumatic, neoplastic, or infectious processes was excluded.

Other: This category included strokes for which a distinct etiology could not be ascertained with any degree of confidence. In the absence of information about signs and symptoms, the diagnosis may have been based on autopsy findings.

If there were co-existing evidence of ischemic athero/thrombolic and hemorrhagic stroke, the athero/thrombolic stroke was classified as being the primary criteria.

Death Due to Cardiovascular Cause

Death Due to Coronary Heart Disease: A death was considered to be due to coronary heart disease if the clinical history, autopsy results, and circumstances of death suggested this was the underlying cause of death.

Sudden death (within 1 hour) was diagnosed when: 1) A subject died within one hour from onset of symptoms; and 2) The cause of death could not reasonably be attributed on the basis of the full clinical information of some potentially lethal disease other than coronary disease (i.e. cerebral hemorrhage, ruptured aortic aneurysm, drug overdose).

Sudden death (within 24 hours) was diagnosed when 1) A subject died between one hour and 24 hours from onset of symptoms; and 2) The cause of death could not reasonably be attributed on the basis of the full clinical information to some potentially lethal disease other than coronary disease (i.e. cerebral hemorrhage, ruptured aortic aneurysm, drug overdose).

Death after 24 hours was diagnosed when: For terminal episodes that lasted longer than 24 hours, if the available information implied that the cause of death was coronary heart disease, and if no other cause was suspected, this was called non-sudden death from coronary heart disease.

Death Due to Stroke: A death clearly due to complications of stroke was coded as a stroke death. In the absence of information about signs and symptoms, the diagnosis may have been based upon autopsy findings.

Death Due to Heart Failure: Death due to heart failure required demonstration of protocol-specified signs and symptoms of heart failure along with clinical documentation of pump failure as a cause of death. Table 1 describes the protocol-specified signs and symptoms of heart failure. A definite diagnosis of heart failure required a minimum of: 1) 2 major findings or 1 major finding and two minor findings; and 2) one finding had to be clinical and one finding had to be diagnostic.

Table 1

Criteria For Diagnosis Of Heart Failure

Major Criteria:	**Minor Criteria:**
Clinical Findings	
1. Paroxysmal nocturnal dyspnea or orthopnea 2. Jugular venous distention 3. Pulmonary rales 4. Ventricular S_3 gallop 5. Hepatojugular reflux 6. Diuresis of 10 pounds or 5 kilos in response to diuretic treatment with clinical improvement in congestive symptoms	1. Night cough 2. Dyspnea on ordinary exertion 3. Bilateral ankle edema 4. Hepatomegaly
Diagnostic Findings	
Chest X-Ray	
1. Acute pulmonary edema chest x-ray	1. Pleural effusion or pulmonary vascular engorgement or redistribution on chest x-ray
Hemodynamic	
1. Pulmonary capillary wedge pressure of at least 20 mm Hg 2. Left ventricular ejection fraction less than or equal to 35% 3. Cardiac index <2.0 4. Evidence of severe valvular heart disease	1. Pulmonary capillary wedge pressure 16-19 mm Hg 2. Left ventricular ejection fraction 36-44% 3. Cardiac index 2.0-2.4 4. Evidence of moderate valvular heart
Autopsy	
1. Pulmonary edema or visceral congestion on autopsy	

Death Due to Peripheral Vascular Disease: A death that occurred in association with peripheral and aortic arterial disease including death that resulted from an aortic aneurysm (e.g., ruptured or dissecting aortic aneurysm), death that resulted from vascular insufficiency and complications thereof (e.g., gangrene or amputation), and death that occurred as a consequence of non-coronary artery revascularization procedure (e.g., bypass, angioplasty, peripheral stent placement) or abdominal aortic aneurysmectomy.

Death Due to Other Cardiovascular Disease: A death due to a cardiovascular cause not compatible with the categories above was included in this category (e.g., pulmonary embolism) and specified.

3.1.5 Active Comparator Regimen

When the LIFE trial was designed, the necessity of treating hypertension was well established, and blood pressure was a widely accepted surrogate for the risk of cardiovascular disease. It was known that reduction of elevated blood pressure was associated with a decrease in cardiovascular morbidity and mortality. In view of this

background knowledge, since the LIFE study design involved the long-term treatment in hypertensive patients, a placebo control group was not considered ethical. Furthermore, there was clear evidence that unequal blood pressure control between groups may result in differential cardiovascular benefit [10]; thus, the LIFE study was designed with the goal of comparable blood pressure reductions in both treatment groups.

The profile of an ideal comparator agent in this setting would be: 1) an agent with proven benefit in the reduction of cardiovascular morbidity and mortality in patients with hypertension (e.g., primary prevention); 2) an agent accepted as appropriate first-line therapy for hypertension; 3) an agent with a primary mechanism of action different from AII blockade; 4) an agent with blood pressure lowering efficacy comparable to losartan; 5) an agent amenable to the addition of a diuretic as a second agent; 6) an agent with demonstrated cardiovascular benefit for patients with a history of a prior cardiovascular event (e.g., secondary prevention); and 7) an agent that was widely used. Atenolol, as described below, optimally fit all of these parameters.

Importantly, when the LIFE study was designed, β-blockers, including atenolol, had been shown to improve cardiovascular morbidity and mortality in hypertensive patients, although no β-blockers had this indication. While ample data were available at the initiation of the LIFE trial to support the choice of a β-blocker-based regimen as the active comparator, the most complete assessment of the efficacy of this active control regimen is reflected by the current total available literature. A literature search from Medline, Biosis, Ringdoc, and Emed for available publications as of Jun-2002 identified studies designed to evaluate the effects of first-line β-blocker therapy on cardiovascular events (i.e., cardiovascular death, stroke and myocardial infarction) in hypertensive patients. From over 300 publications, relevant studies were selected based upon prospectively established rules as follows: hypertensive patient population; randomized, controlled trial; first-line β-blocker therapy +/- diuretic therapy; cardiovascular outcomes provided; events described per 1000 patient years; treatment duration ≥ 1 year or ≥ 1000 patient years of follow-up; primary publication in English; and comparator of placebo or no treatment. This resulted in the identification of 5 trials that fulfilled these criteria; these trials are profiled in Table 2.

Of these five trials, four compared the effect of atenolol to placebo or no treatment (usually with a diuretic as add-on therapy as in the LIFE study) on cardiovascular morbidity and mortality. In the STOP trial, where atenolol was 1 of 4 active treatment arms (3 β-blockers and 1 diuretic), there was a 40% reduction in the primary composite endpoint of cardiovascular morbidity and mortality, a 58% reduction in cardiovascular mortality, and a 47% reduction in stroke with active treatment compared with placebo [34]. In the HEP study, atenolol treatment was associated with no significant reduction in the composite endpoint of all cardiovascular endpoints, but did show a 42% reduction in the incidence of stroke relative to untreated controls [35]. In the MRC II study, there were no significant differences in the incidence of stroke and other cardiovascular endpoints between atenolol and placebo; however, in that study, 25% of patients were lost to follow-up and 63% of patients assigned to atenolol stopped taking their

randomized treatment [36]. The UKPDS trial, a study completed after the initiation of the LIFE trial, included hypertensive patients with type II diabetes and evaluated CV outcomes [37]. In the UKPDS trial, there was a 35% reduction in the composite endpoint of all cardiovascular endpoints, a 40% reduction in cardiovascular mortality, and a 47% reduction in stroke with the atenolol-based regimen involving tight blood pressure control as compared with usual care with less tight blood pressure control. In the MRC trial, propanolol treatment resulted in an 18% reduction in all cardiovascular events relative placebo [38]. The collective findings demonstrate that, in general, a β-blocker-based regimen (frequently utilizing atenolol) is statistically superior to placebo (or no treatment) with respect to all cardiovascular events and stroke, and trends toward reducing events of coronary heart disease (CHD) and cardiovascular death.

Additionally, we used a recent review of health outcomes associated with antihypertensive therapies (Psaty et al.) [39] to identify diuretic-based trials with a β-blocker as add-on therapy to further evaluate the effects of the combination of a diuretic and β-blocker regimen on cardiovascular outcomes. The Psaty review used Medline searches as well as previous meta-analyses from 1980-1995, and identified placebo-controlled, randomized trials designed to evaluate the effects of antihypertensive therapies on the occurrence of myocardial infarction and stroke. Both English and non-English abstracts were reviewed, and consideration was limited to the 4 most commonly used classes of antihypertensives (diuretics, β-blockers, calcium channel blockers, and ACE inhibitors). Psaty's search resulted in the identification of 18 long-term randomized trials meeting these criteria. Of the 18 trials, 5 trials had a diuretic-based regimen in which a β-blocker was used as add-on therapy (MRC II, ANBPS, Oslo, SHEP, and SHEP-PS) [36; 40; 41; 8; 42]. However, Merck applied an additional criterion to the selection of these trials which concerned the minimum number of patients who were known to have received β-blockers as add-on therapy (i.e., at least 20% of patients); application of this criterion resulted in 3 trials (MRC II, Oslo and SHEP) [36; 41; 8] for consideration (Table 2). Each of these studies demonstrated substantial benefit of a diuretic-based regimen, which included the addition of a β-blocker, in the reduction of cardiovascular events in patients with hypertension.

From the current body of available data, a meta-analysis estimates a 21% reduction in cardiovascular morbidity and mortality (all cardiovascular events) with a β-blocker based regimen (or a 26% reduction with diuretic- and β-blocker-based regimens) in the treatment of hypertension. This meta-analysis provides an approximation to be used as context for assessing the results of the LIFE trial's losartan-based regimen compared to the atenolol-based regimen.

Table 2

Controlled Clinical Endpoint Trials in Hypertension: β-Blocker-Based/Diuretic-Based (With Add-On β-Blocker) Regimens Compared With Placebo

	Base Therapy (N)	Mean Age (Years)	BP at Entry (mm Hg)	Treatment Δ BP (mm Hg)	All CV Events HR (95% CI) †	All CV Events p-Value	CV Death HR (95% CI) †	CV Death p-Value	Stroke HR (95% CI) †	Stroke p-Value	CHD HR (95% CI) †	CHD p-Value
β-blocker As a First-Line Therapy												
HEP‡ [35]	Atenolol (419)	68.7	196.7/99.7	-34.6/-21.9|	0.81 (0.58 to 1.13) §	0.17§	0.78 (0.51 to 1.20)	0.25§	0.58 (0.33 to 0.98) §	0.04§	1.03 (0.65 to 1.63)	1.00§
	Untreated (465)	68.8	196.1/98.8	-16/-10								
MRC [38]	Propanolol (4403)	52.0|	161.4/98.5|	-22.4/-12.5| ##	0.82 (0.67 to 0.99) §	0.034§	0.91 (0.68 to 1.22) §	0.60§	0.73 (0.5 to 1.04) §	0.14§	0.87 (0.69 to 1.10) §	0.22§
	Placebo (8654)	52.0|	161.3/98.0|	-11.8/-6.5| ##								
MRC II¶ [36]	Atenolol (1102)	70.3|	184.7/91|	-33.0/-14.6| ##	0.96 (0.77 to 1.19)	0.69	1.06 (0.81 to 1.39)	0.66	0.82 (0.6 to 1.14)	0.25	1.03 (0.77 to 1.37)	0.85
	Placebo (2213)	70.3|	184.7/90.4|	-19.3/-7.0| ##								
STOP# [34]	Atenolol/Metoprolol/ Pindolol/Diuretics (812)	75.6	195/102	-28/-15	0.60 (0.43 to 0.85)	0.003	0.42 (0.24 to 0.74) §	0.002§	0.53 (0.33 to 0.86)	0.008	0.87 (0.49 to 1.56)	0.78§
	Placebo (815)	75.7	195/102	-9/-6								
UKPDS†† [37]	Atenolol (358)	56.0	159/93	-16/-12	0.65 (0.48 to 0.89) §	0.004§	0.60 (0.39 to 0.92) §	0.01§	0.53 (0.2 to 0.94) §	0.04§	0.72 (0.50 to 1.04) §	0.07§
	Less Tight Control (390)	56.5	160/94	-6/-7								
Overall¶¶	**β-Blocker (7094) Control (12,537)**	**--**	**--**	**--**	**0.79 (0.70 to 0.89)**	**<0.001**	**0.83 (0.70 to 0.97)**	**0.022**	**0.68 (0.56 to 0.82)**	**<0.001**	**0.89 (0.77 to 1.03)**	**0.129**

Table 2 (Cont.)

Controlled Clinical Endpoint Trials in Hypertension: β-Blocker-Based/Diuretic-Based (With Add-On β-Blocker) Regimens Compared With Placebo

	Base Therapy (N)	Mean Age (Years)	BP at Entry (mm Hg)	Treatment Δ BP (mm Hg)	All CV Events HR (95% CI) †	All CV Events p-Value	CV Death HR (95% CI) †	CV Death p-Value	Stroke HR (95% CI) †	Stroke p-Value	CHD HR (95% CI) †	CHD p-Value
Diuretic-Based Regimen With β-blocker As An Add-On Agent												
MRC II[¶] [36]	HCTZ+amiloride +38% Atenolol (1081)	70.3[|]	184.7/91[|]	-33.5/-13.7[| ##]	0.69 (0.55 to 0.86)	0.001	0.74 (0.56 to 0.99)	0.040	0.68 (0.48 to 0.95)	0.023	0.61 (0.44 to 0.84)	0.002
	Placebo (2213)	70.3[|]	184.7/90.4[|]	-19.3/-7.0[| ##]								
SHEP[‡‡] [8]	Chlorthalidone + 23% Atenolol (2365)	71.6	170.5/76.7	-26.5/-9.0	0.67 (0.56 to 0.80)	--[||]	0.80 (0.60 to 1.05)	--[||]	0.64 (--)[||]	--[||]	--[||]	--[ζ]
	Placebo (2371)	71.5	170.1/76.4	-15.0/-5.3								
Oslo[§§] [41]	HCTZ + 25% Propanolol (405)	45.3	156.2/97.4	-25.2/-12.4[##]	--[||]	--[||]	--[||]	--[||]	--[||]	--[||]	--[||]	--[ζ]
	Untreated (379)	45.2	155.3/96.2	-7.3/-1.2[##]								
Grand Overall[¶¶]	**β-Blocker/Diuretic + β-Blocker (9864) Control (15,287)**	--	--	--	**0.74 (0.68 to 0.81)**	**<0.001**	**0.81 (0.71 to 0.91)**	**0.001**	**0.66 (0.57 to 0.76)**	**<0.001**	**0.80 (0.71 to 0.90)**	**<0.001**

† All hazard ratios are for β-blocker or diuretic + β-blocker relative to control.
‡ HEP - Stroke includes nonfatal major stroke, nonfatal minor stroke, and fatal stroke. All CV events include major stroke, minor stroke, nonfatal MI, and CV death.
§ P-values, hazard ratios, confidence intervals were not provided in the literature. P-values were calculated using Fisher's exact test from the crude event rates obtained from the literature. The hazard ratios and 95% confidence intervals were calculated as the ratio of reported rates of events per 1000 patient-years of follow-up provided in the literature.
| Value was calculated and weighted.
¶ MRC II - CHD includes fatal/nonfatal MI and sudden death.
# STOP- hazard ratios are based on patients on atenolol, metoprolol, pindolol, or diuretics-based therapies.
†† UKPDS- CHD includes fatal/nonfatal MI and sudden death. All CV events include fatal/nonfatal stroke, fatal/nonfatal MI, sudden death, and death from PVD. Note: This trial was not a true placebo control; instead, the control group was usual care (excluding ACE inhibitors and β-blockers) but the blood pressure goal in this arm was "less tight control" (i.e., BP <180/105 mm Hg) versus "tight control" in the atenolol arm (i.e., BP goal <150/85 mm Hg). Consequently, there were unequal blood pressure reductions between treatment groups.
‡‡ SHEP – Isolated systolic hypertensive patients
§§ Oslo study only in men.
|| The hazard ratios and 95% confidence intervals were not reported and could not be calculated because the ratio of reported rates of events per 1000 patient-years of follow-up were not provided in the literature.
¶¶ Combined hazard ratios determined by a logistic regression model with treatment group and study as class covariates; MRC II active treatment arms were combined.
Value extracted from line graph.

As a result of the pivotal outcomes trials, treatment guidelines available at the onset of the LIFE study recommended β-blockers or diuretics as first-line therapy for the treatment of hypertension [5; 2; 6]. Accordingly, at the time of protocol development for the LIFE study, there were 3 ongoing morbidity/mortality trials of antihypertensive therapy (STOP-2, CAPPP, and NORDIL) [43; 44; 45]that used a β-blocker/diuretic-based regimen as the active control agent, reflecting the acceptance of this treatment strategy as an appropriate reference standard.

Furthermore, an overview of recent randomized trials that assessed outcomes found significant benefits on stroke and major cardiovascular events with ACE inhibitors and calcium channel antagonists relative to placebo. Based on data from over 39,000 patients with hypertension, similar benefits on these endpoints were generally found between these agents and conventional treatment with diuretics and/or β-blockers [46]. The exceptions were a lower risk of stroke and a greater risk of coronary heart disease among patients assigned to calcium channel antagonists relative to β-blocker and/or diuretic therapy (stroke: HR 0.87, CI 0.77 - 0.98; coronary heart disease: HR 1.12, CI 1.00 - 1.26). In summary, a β-blocker-based regimen continues to be a well-supported and well-established choice for a comparator.

In the LIFE study, it was hypothesized that specific AII antagonism would confer greater benefit than the comparator agent, and thus, it was advantageous to compare losartan to a control agent with a primary mechanism of action which differed from losartan's, such as a β-blocker. It is important to recognize that β-blockers were originally developed as agents for the treatment of cardiac ischemia; their antihypertensive efficacy was not recognized until later in their development. The mechanism of the antihypertensive action of β-blockers is not well understood. This class of drugs blocks catecholamine binding to β-receptors, leading to a reduction in heart rate, myocardial contractility and myocardial oxygen demand. This mechanism of action is consistent with their well-established benefit in the prevention and treatment of ischemic heart disease.

Losartan, as a potent AII receptor antagonist, was hypothesized to prevent deleterious effects of excess AII. Regression of LVH, a marker of AII blockade, was postulated to be associated with improved cardiovascular benefit. In contrast, β-blockers, as adrenergic antagonists, were thought to affect the renin-aldosterone system differently. While it is well known that β-blockers inhibit renin release, only limited data are available to assess the magnitude of the effect of β-blockade on the renin-angiotensin system [47; 48]. The degree to which partial AII suppression contributes to the clinical effects of β-blockade is not well understood. However, evidence available at the time of the design of the LIFE study, and more recently, indicates that blockade of angiotensin II with receptor antagonists, including losartan, decreases LVH to a greater extent than other classes of agents (including β-blockers) that act primarily through different mechanisms [25; 26; 27; 28]. This further supports the selection of a β-blocker to best test the study hypothesis that in patients with LVH, an agent specifically blocking angiotensin II would be more efficacious in the prevention of cardiovascular morbidity

and mortality than the treatment of hypertension with an agent acting through a different primary mechanism.

Prior to the design of the LIFE trial, losartan and atenolol had demonstrated comparable blood pressure control [33], and both were effective when administered in combination with a diuretic; these features were desirable because, as previously noted, an important goal of this trial was to ensure patients in both treatment groups had comparable blood pressure control. Also, the addition of diuretics was recommended by JNC V [5] as an appropriate second step if response to initial antihypertensive therapy was inadequate. Thus, the ability to add a diuretic to the losartan and comparator arms was advantageous since β-blocker-based regimens that allowed for the addition of a diuretic to achieve optimal control of blood pressure had been demonstrated to improve cardiovascular outcomes in patients with hypertension [35; 34; 37]. Therefore, the use of this regimen as the active comparator in the LIFE study was thought to provide the most appropriate setting to assess the benefit of losartan.

Furthermore, the LIFE study proposed to enroll hypertensive patients who may have had a history of a prior cardiovascular event, and consequently, a control agent proven effective for secondary prevention of cardiovascular mortality and morbidity was advantageous. Atenolol is known to protect against cardiovascular events in patients with cardiac ischemia (Appendix 2). It is indicated for the treatment of angina pectoris due to coronary atherosclerosis, and acute myocardial infarction. Thus, because the LIFE trial was designed to evaluate cardiovascular morbidity and mortality, including occurrences of myocardial infarction, the use of a comparator agent with proven benefit to protect against further cardiovascular events was of value.

Finally, β-blockers, including atenolol, are widely used antihypertensive agents both in the U.S. and internationally and are conveniently administered once daily. Atenolol's widespread use likely reflects treatment guidelines that identified β-blockers or diuretics as first-line therapy for the treatment of hypertension [5; 2; 6].

In summary, atenolol was the appropriate comparator for the LIFE study because of the compelling evidence of morbidity/mortality benefits from β-blocker-based treatment in hypertensive patients, its effectiveness as a first-line antihypertensive agent when administered once daily, its distinct mechanism of action relative to losartan, its blood pressure lowering effects that were comparable to losartan's, its proven efficacy in combination with diuretics, its demonstrated benefit in reducing cardiovascular events in patients with a history of cardiovascular disease, and its widespread use and availability.

3.1.6 Rationale for Dose Selection in the LIFE Study

The doses selected for both losartan (starting dose 50 mg) and atenolol (starting dose 50 mg) were based on label-recommended prescribing information for the treatment of hypertension. If adequate blood pressure control was not obtained, hydrochlorothiazide (starting dose 12.5 mg) was added. This dose was in accordance with lowest usual dose range specified in JNC V [5]. Of note, adding a second drug from another class was identified in JNC V as a recommended option if initial antihypertensive therapy was

inadequate. This was based on the recognition that different modes of actions may enable lower doses of drugs to control blood pressure and thereby minimize the potential for dose-dependent side effects. Importantly, JNC V recommended diuretics as a useful second-step agent because these agents generally enhance the effects of other drugs.

3.1.7 Summary of Statistical Methods

Counting Endpoints: The primary efficacy parameter was a composite of cardiovascular mortality, stroke, or myocardial infarction. Cardiovascular mortality was defined as death due to fatal stroke, fatal myocardial infarction, sudden death, progressive heart failure, or other cardiovascular deaths. Only endpoints confirmed by the blinded ECC were included in the analyses; there were sufficient data submitted to adjudicate all potential endpoints. The treatment groups were compared with respect to the 3 individual components of the primary composite endpoint, which were also predefined as secondary endpoints of the study. While there are various ways in which the composite endpoint could be split into components, the predefined components were as follows: cardiovascular mortality, stroke (fatal/nonfatal), and myocardial infarction (fatal/nonfatal). Each of the components was analyzed independently from the others; thus, the endpoints counted in each component analysis were not necessarily mutually exclusive. Specifically, a patient with a single or multiple events was counted as having had an event in all relevant component endpoint analyses. For example, a patient who died from a stroke would count in the analysis of cardiovascular death as well as in the analysis of stroke (fatal/nonfatal), regardless of any prior nonfatal myocardial infarction. As with the primary endpoint, patients with multiple endpoints of a specific component (multiple myocardial infarctions, for example) were counted only once in the analysis of that component. The analyses of the components of the composite were based on all available adjudicated endpoints from randomization through the endpoint cutoff date of 16-Sep-2001.

Consistency of Effect Among Components of the Composite Endpoint: Since the composite endpoint consisted of 3 components, a prespecified statistical test for lack of homogeneity of the effect of losartan on reducing the incidence of each of the 3 components (cardiovascular mortality, stroke [fatal/nonfatal], and myocardial infarction [fatal/nonfatal]) of the composite endpoint was performed in order to determine if any observed heterogeneity was greater than would be expected by chance alone. The assessment of heterogeneity was based on the Wei, Lin & Weissfeld approach [49], by treating cardiovascular mortality, stroke (fatal/nonfatal), and myocardial infarction (fatal/nonfatal) as 3 separate endpoints and pooling them into a unified analysis.

Partial Follow-Up: Patients continued in follow-up after the occurrence of a nonfatal primary endpoint; therefore, with few exceptions, there is complete endpoint reporting for all patients from randomization though study termination. The exceptions are for 197 patients (i.e., partial follow-up obtained for 107 patients with vital status known at study termination and 90 patients with final status not obtained at study termination [12 patients lost to follow-up and 78 patients withdrew consent]). Of the 107 patients with vital status, 48 had died during the timeframe for follow-up. The specific cause of

death was unknown for 7 patients (4 patients in the losartan group and 3 patients in the atenolol group) and death was ascribed to non-cardiovascular cause. All other deaths were adjudicated.

Efficacy Analyses: The primary analysis of the primary endpoint utilized an intention-to-treat approach. All randomized patients were included in their randomized treatment group and all available follow-up was included from randomization through the endpoint cutoff date of 16-Sep-2001.

The statistical analysis of the primary endpoint was based on survival analysis models (i.e., time to the first confirmed adjudicated event). In addition, an exploratory analysis of investigator-reported events was performed for the primary endpoint. The cumulative incidence of the primary endpoint over time was estimated by the Kaplan-Meier product-limit method. Crude event rates and event rates per 1000 patient years were also calculated. Statistical comparisons between losartan and atenolol were carried out by a Cox proportional hazards model [50]. The Cox model included prespecified covariates for treatment group, degree of LVH at baseline (as measured by both Cornell voltage duration product and Sokolow-Lyon [S-L] voltage) and the baseline Framingham risk score [51]. The analyses of all secondary efficacy endpoints, including the components of the composite endpoint, were based on a time-to-first event approach and the intention-to-treat principal. Mean changes in systolic and diastolic blood pressure, pulse pressure, and ECG measures of LVH were analyzed at each scheduled visit using a rank-transformed analysis of variance. While analyses of all time points were prespecified, for ease of description in this document, the Year 4 results are highlighted, in addition to post hoc analyses showing the results at the end of follow-up or last visit before a primary endpoint.

Interim Analyses: An independent Data and Safety Monitoring Board (DSMB) reviewed unblinded interim results after approximately one-third and two-thirds of the expected events occurred. To adjust for the 2 interim efficacy analyses, the final analysis of the primary efficacy variable was tested at a 2-sided 4.6% significance level. All other tests were done at the 5% significance level.

Time-Varying Covariate Analyses: The impact of blood pressure and LVH changes on the effect of losartan on reduction of cardiovascular risk was assessed using time-varying covariate analyses. That is, the values of blood pressure and LVH (as measured by Cornell product and Sokolow-Lyon criterion) throughout the trial were included in Cox regression models as time-varying covariates, along with treatment group as an ordinary covariate. The impact of these covariates on the treatment effect was assessed by comparing the estimated treatment effect in models including and excluding the time-varying covariate. Note, however, that time-varying covariate analyses are not strictly protected by randomization, and there can be complex interrelationships among time-varying values, treatment, and the endpoint that can distort the interpretation. For this reason, the time-varying covariate analyses should be interpreted with caution.

Safety Analyses: Safety parameters included adverse experiences (tests were performed for adverse experiences leading to discontinuation, new-onset diabetes, and several

special interest adverse experiences including angioedema, bradycardia, sleep disturbance, hypotension, dizziness, sexual dysfunction, cold extremities, cough, and cancer), vital signs (other than blood pressure), and laboratory values. All randomized patients (N=9193) were included in the safety analyses; these analyses only included data obtained while on study drug or within 14 days of study drug interruption or discontinuation.

3.2 Patient Disposition

A total of 10,779 patients were assessed for eligibility for the LIFE study and 9222 were randomized; there were 1557 ineligible patients (1362 did not meet protocol criteria and 215 were unwilling to participate). All 29 patients at 1 center were discontinued from follow-up shortly after initiation of the study due to serious Good Clinical Practice (GCP) compliance issues, and were excluded from all analyses; therefore, 9193 patients were available for efficacy and safety analyses. Table 3 displays the number of patients entered into the study by treatment group, the number of patients with follow-up through death or 16-Sep-2001 (endpoint cutoff date), those who discontinued from follow-up, the reasons for discontinuing from study follow-up, and the reasons patients permanently discontinued study therapy prior to death or stopping study follow-up.

Fewer than 1% of patients (90) discontinued from study follow-up without final vital status being obtained. An additional 1% of patients (107 patients, 57 in the losartan group and 50 in the atenolol group) had only vital status reported at the time of death or as of 16-Sep-2001. Therefore, 8996 patients (98%) had complete follow-up for all study endpoints, and 9103 (99%) had complete follow-up for vital status. The primary reason for lack of vital status follow-up was refusal of the patient to be contacted further (78 of 90 patients).

The mean duration of follow-up from randomization through death or 16-Sep-2001 was 4.8 years (maximum 6.2 years). As shown in Table 3, overall, significantly more patients discontinued study drug in the atenolol group than in the losartan group (losartan: 22.2% versus atenolol: 26.6%, $p<0.001$). More patients in the atenolol group discontinued study therapy due to an adverse experience (losartan: 10.9% versus atenolol: 15.3%, $p<0.001$). A total of 4.4% of patients discontinued study drug due to “other administrative reason” (199 patients in the losartan group and 208 patients in the atenolol group); this category was only used if one of the other categories (endpoint other than death; required other therapy excluded by the protocol; adverse experience; death; patient withdrew consent; or lost to follow-up) was not appropriate (e.g., patient was admitted to a nursing home, non-compliance, patient moved and no longer near a participating LIFE center, etc.).

Table 3

Patient Accounting

	Losartan	Atenolol	Total
ENTERED: Total[†]	4605	4588	9193
Female (age range—years)	2487 (49 to 83)	2476 (47 to 83)	4963 (47 to 83)
Male (age range—years)	2118 (45 to 82)	2112 (48 to 80)	4230 (45 to 82)
Follow-up through death or 16-Sep-01[¶]			
All endpoints	4500 (98.0%)	4496 (98.0%)	8996 (97.9%)
Partial			
Vital status only	57 (1.0%)[‡]	50 (1.0%)[‡]	107 (1.2%)
Withdrawn consent	44 (0.9%)	34 (0.8%)	78 (0.8%)
Lost to follow-up	4 (0.1%)	8 (0.2%)	12 (0.1%)
DISCONTINUED Study Drug[§]: Total	1024 (22.2%)**	1220 (26.6%)**	2244 (24.4%)
Endpoint other than death	150 (3.3%)*	114 (2.5%)*	264 (2.9%)
Required other therapy	143 (3.1%)	168 (3.7%)	311 (3.4%)
Adverse experience[‖]	500 (10.9%)**	702 (15.3%)**	1202 (13.1%)
Patient withdrew consent	30 (0.7%)	27 (0.6%)	57 (0.6%)
Lost to follow-up	2 (0.0%)	1 (0.0%)	3 (0.0%)
Other administrative reason	199 (4.3%)	208 (4.5%)	407 (4.4%)

*,** p-Values <0.05 and <0.01, respectively, for comparison between losartan and atenolol.

† Excludes 29 patients randomized from a disqualified site.

‡ In the losartan group, 34 of these patients survived and 23 died; in the atenolol group, 25 of these patients survived and 25 died.

§ Includes reasons for discontinuing study medication prior to death, nonfatal myocardial infarction or stroke, or stopping study follow-up.

‖ If there were multiple reasons causing study drug discontinuation, the investigator was to report the first reason that applied from the following list: (1) endpoint other than death; (2) required other therapy excluded by the protocol; (3) adverse experience; (4) death; (5) patient withdrew consent; (6) other administrative reason; and (7) lost to follow-up. Therefore, the reported study drug discontinuations due to adverse experiences in this table differ from those reported in the adverse experience counts (Section 3.6).

¶ Two stroke events, which occurred prior to 16-Sep-2001 (1 randomized to losartan and 1 randomized to atenolol), were reported after 15-Nov-2001 (the endpoint database lock date); although these were reviewed by the ECC, they were not included in the efficacy analyses.

3.3 Demographic and Other Patient Baseline Characteristics

3.3.1 Patient Characteristics—Demographics

Baseline patient demographics are summarized in Table 4. Demographics were similar in the treatment groups: the average age of patients was 66.9 years, 54% of patients were female, and 92.5% of patients were White. Alcohol use, smoking history, and exercise duration were also similar between the 2 groups.

Table 4

Patient Demographics

	Losartan (N=4605)	Atenolol (N=4588)	Total (N=9193)
	n (%)	n (%)	n (%)
Age (Years)			
54 and under	58 (1.3)	52 (1.1)	110 (1.2)
55 to 59	802 (17.4)	797 (17.4)	1599 (17.4)
60 to 64	888 (19.3)	892 (19.4)	1780 (19.4)
65 to 69	1026 (22.3)	1029 (22.4)	2055 (22.4)
70 to 74	1023 (22.2)	1044 (22.8)	2067 (22.5)
75 to 80	796 (17.3)	764 (16.7)	1560 (17.0)
81 and above	12 (0.3)	10 (0.2)	22 (0.2)
Mean	66.9	66.9	66.9
SD	7.03	6.98	7.00
Median	67	67	67
Range	45 to 83	47 to 83	45 to 83
Female	49 to 83	47 to 83	47 to 83
Male	45 to 82	48 to 80	45 to 82
Gender			
Female	2487 (54.0)	2476 (54.0)	4963 (54.0)
Male	2118 (46.0)	2112 (46.0)	4230 (46.0)
Ethnic Group			
White	4258 (92.5)	4245 (92.5)	8503 (92.5)
Black	270 (5.9)	263 (5.7)	533 (5.8)
Hispanic	47 (1.0)	53 (1.2)	100 (1.1)
Asian	25 (0.5)	18 (0.4)	43 (0.5)
Other	5 (0.1)	9 (0.2)	14 (0.2)
Alcoholic Drinks			
None	2107 (45.8)	2109 (46.0)	4216 (45.9)
1 to 4/week	1779 (38.6)	1824 (39.8)	3603 (39.2)
5 to 7/week	351 (7.6)	333 (7.3)	684 (7.4)
8 to 10/week	161 (3.5)	153 (3.3)	314 (3.4)
>10/week	205 (4.5)	166 (3.6)	371 (4.0)

Table 4 (Cont.)

Patient Demographics

	Losartan (N=4605)	Atenolol (N=4588)	Total (N=9193)
	n (%)	n (%)	n (%)
Tobacco Use			
Never	2341 (50.8)	2315 (50.5)	4656 (50.6)
Ex-Smoker: longer than a year	1533 (33.3)	1500 (32.7)	3033 (33.0)
1 to 5 cigarettes/day	232 (5.0)	222 (4.8)	454 (4.9)
6 to 10 cigarettes/day	206 (4.5)	222 (4.8)	428 (4.7)
11 to 20 cigarettes/day	191 (4.1)	244 (5.3)	435 (4.7)
>20 cigarettes/day	100 (2.2)	82 (1.8)	182 (2.0)
Exercise			
Never	1024 (22.2)	996 (21.7)	2020 (22.0)
≤30 minutes twice/week	1222 (26.5)	1185 (25.8)	2407 (26.2)
>30 minutes twice/week	2356 (51.2)	2402 (52.4)	4758 (51.8)

Since patients with ISH and diabetic patients at baseline were of special interest, the baseline demographics of these patients were also evaluated.

Patients with ISH (SBP ≥160 and DBP <90) tended to be older; 58.7% were equal to or greater than age 70 (mean age 70.3 years), compared to 39.5% in all patients. There tended to be more females (60.1%) in this group than in all patients (54%). Ethnic group distribution was similar in the ISH patients as compared to all patients. In the ISH patients, 6.2% were Black compared to 5.9% patients in the overall trial. In contrast, diabetic patients tended to be more similar in age to all patients. The mean age was 67.4 years in the diabetic patients versus 66.9 years in all patients. The gender distribution was similar to all patients (53.1% of diabetic patients were female compared to 54% of all patients). In the diabetic patients, there tended to be more Black patients (11.1%) versus all patients (5.9%). Demographics within the ISH and diabetic patients were similar between the 2 treatment groups.

3.3.2 Patient Characteristics—Disease History

The 2 treatment groups were closely matched in prevalences of coexisting cardiovascular conditions and diabetes mellitus. ISH was present in 14.4% of patients (losartan: 14.3% versus atenolol: 14.5%), and diabetes was reported in 13.0% of patients (losartan: 12.7% versus atenolol: 13.3%). Both ISH and diabetes were present in 2.6% of the study population (17.7% of ISH patients were also diabetic, 19.7% of diabetic patients also had ISH). The prevalence of prior myocardial infarction was 6.7% in the losartan group and

5.7% in the atenolol group, and the prevalence of prior stroke was 4.1% in the losartan group and 4.6% in the atenolol group.

The prevalence of coronary heart disease-related diagnoses was 16.7% in the losartan group and 15.2% in the atenolol group. The prevalence of cerebrovascular-related diagnoses was 8.2% in the losartan group and 8.0% in the atenolol group.

3.3.3 Patient Characteristics—Electrocardiographic Measurements of Left Ventricular Hypertrophy and Framingham Risk Score

Baseline electrocardiographic measures of LVH and the Framingham risk score are summarized by treatment group in Table 5. Overall, 97% of the patients had complete LVH data (i.e., all voltage measures were available); 94% had complete data on all components of the Framingham risk score. Since ECG estimates of LVH and Framingham risk score were used as covariates in the primary endpoint analysis, missing baseline values were interpolated by assigning the mean value of nonmissing values. For LVH measures, the interpolation was gender specific. For the Framingham risk score, individual components of the risk score were interpolated if missing. Baseline LVH, as estimated by both Cornell voltage product and S-L voltage from ECG, was similar for the 2 treatment groups. Mean Framingham risk score was 22.271 for losartan and 22.509 for atenolol. Adjustment for the between-group risk score difference of ~0.2 had an influence on the analyses in this trial.

Table 5

Baseline Electrocardiographic Measurements of LVH and Framingham Risk Score

Event	Treatment	N	Mean	Percentiles of Distribution				
				Minimum	25%	Median	75%	Maximum
Cornell product mm x msec (all patients)	Losartan	4605	2828.0	0.0	2303.0	2668.0	3150.0	10622.0
	Atenolol	4588	2818.9	104.0	2304.0	2668.0	3150.0	14130.0
Cornell product mm x msec (men only)	Losartan	2118	2714.0	0.0	2204.0	2650.0	3120.0	10622.0
	Atenolol	2112	2713.9	104.0	2205.0	2662.5	3120.0	13552.0
Cornell product mm x msec (women only)	Losartan	2487	2925.1	480.0	2376.0	2695.0	3192.0	10400.0
	Atenolol	2476	2908.5	546.0	2365.0	2668.0	3192.0	14130.0
Sokolow-Lyon (S-L) voltage mm (all patients)	Losartan	4605	30.0	1.5	22.5	29.0	37.0	83.0
	Atenolol	4588	30.0	2.0	22.5	29.0	36.5	79.0
S-L voltage mm (men only)	Losartan	2118	32.0	3.5	24.0	31.0	39.0	83.0
	Atenolol	2112	32.2	2.5	25.0	31.0	39.5	79.0
S-L voltage mm (women only)	Losartan	2487	28.2	1.5	21.5	27.0	34.5	72.5
	Atenolol	2476	28.2	2.0	21.5	27.0	34.0	75.0
Framingham risk score	Losartan	4605	22.271	3.253	14.880	20.983	28.639	62.166
	Atenolol	4588	22.509	4.571	15.041	21.075	28.778	59.050

Note: Missing values for baseline LV Mass were imputed by corresponding means.

3.3.4 Patient Characteristics—Baseline Vital Signs

Vital signs were similar between the 2 treatment groups. Sitting systolic blood pressure was 174.3 mm Hg in the losartan group versus 174.5 mm Hg in the atenolol group; diastolic blood pressure was 97.9 mm Hg in the losartan group versus 97.7 mm Hg in the atenolol group. Mean sitting pulse pressure (systolic minus diastolic blood pressure) was 76.4 mm Hg in the losartan group and 76.9 mm Hg in the atenolol group. Mean pulse rate was 73.9 bpm in the losartan group versus 73.7 bpm in the atenolol group.

3.3.5 Patient Characteristics—Baseline Laboratory Values

All laboratory test results were similar between the 2 treatment groups, including baseline measurements of hemoglobin, creatinine, ALAT, glucose, uric acid, sodium, potassium, total cholesterol, HDL cholesterol, urine microalbumin, and urine creatinine.

3.3.6 Patient Characteristics—Prior Therapies

Approximately 75% of patients in each treatment group (losartan: 75.1% versus atenolol: 74.5%) were on some type of cardiovascular system agent prior to the study. With regard to prior antihypertensive therapies, 27.6% of losartan-treated versus 28.0% of atenolol-treated patients had no prior antihypertensive therapy; 40.2% of losartan-treated versus 40.0% of atenolol-treated patients had 1 prior antihypertensive drug; 24.5% of losartan-treated versus 24.0% of atenolol-treated patients had 2 prior antihypertensive drugs; and 7.6% of losartan-treated versus 8.0% of atenolol-treated patients had 3 or more prior antihypertensive drugs. The most common agents were diuretics (taken by 27.0% of patients in the losartan group versus 28.2% of patients in the atenolol group), β-blockers (taken by 27.6% of patients in the losartan group versus 26.6% of patients in atenolol groups), those acting on the renin-angiotensin system (AIIAs were taken by 3.8% of patients in the losartan group versus 4.1% of patients in the atenolol group, and ACE inhibitors were taken by 21.7% of patients in the losartan group versus 21.8% of patients in the atenolol group), and calcium channel blockers (taken by 25.7% of patients in the losartan group versus 25.4% of patients in the atenolol group). Analgesic use was also common in both treatment groups (26.0% in the losartan group versus 25.4% in the atenolol group). Aspirin was taken as prior therapy in 21.8% of patients in the losartan group versus 21.1% of patients in the atenolol group, and statins were taken as prior therapy in 6.2% of patients in the losartan group versus 6.2% of patients in the atenolol group.

3.3.7 Patient Characteristics—Concomitant Therapies

After randomization, the addition of antihypertensive medication was permitted by the protocol, as needed, to lower blood pressure. The distribution of protocol-permitted concomitant antihypertensive drugs, including non-study drug diuretics (losartan: 11.8% versus atenolol: 13.3%) and calcium channel blockers (losartan: 39.5% versus 40.4%), was relatively similar between groups. Refer to Table 6 for the distribution of losartan and atenolol taken with and without study-drug diuretics and other antihypertensive agents at the time of a primary endpoint or the end of follow-up. Overall, the number of patients on study drug who also received a prohibited therapy at any time was small (9.6% patients in losartan group versus 8.6% patients in atenolol group, excluding timolol maleate, with the assumption that the majority of its use was ophthalmic). Agents acting on the renin-angiotensin system were taken by 178 (3.9%) patients on study drug in the losartan group versus 195 (4.3%) in the atenolol group, or a total of 0.36% of the time while on study drug. β-blocking agents (excluding timolol) were taken by 326 (7.1%) patients in the losartan group versus 250 (5.4%) patients in the atenolol group, or a total of 0.79% of the time while on study drug. Overall, patients were on protocol-defined

prohibited therapy (ACE inhibitors, AIIAs, or β-blocking agents [excluding timolol maleate]) 0.94% of the time while on study drug.

Other concomitant therapy taken by at least 20% of patients in 1 treatment group included: serum lipid-reducing agents (taken by 20.6% of patients in the losartan group versus 22.1% of patients in the atenolol group); anti-inflammatory and antirheumatic products (taken by 23.7% of patients in the losartan group versus 23.0% of patients in the atenolol group); and analgesics (taken by 43.9% of patients in the losartan group versus 44.0% of patients in the atenolol group). Aspirin was taken as concomitant therapy in 35.7% of patients in the losartan group versus 35.4% of patients in the atenolol group, and statins were taken as concomitant therapy in 19.8% of patients in the losartan group versus 21.1% of patients in the atenolol group.

3.4 Distribution of Study Drug

Table 6 displays the distribution of study drugs at the time of a primary endpoint or the end of follow-up. The distribution of hydrochlorothiazide (HCTZ) or protocol-permitted concomitant antihypertensive drugs did not differ substantially between groups.

Table 6

Distribution of Study Drugs at the Time of a Primary Endpoint or the End of Follow-Up

Drug Doses	Losartan		Atenolol	
	n	(%)	n	(%)
50 mg with or without additional drugs†	**1278**	**(28)**	**1366**	**(30)**
Alone	434	(9)	436	(10)
With HCTZ only	624	(14)	625	(14)
With other drugs only	111	(2)	104	(2)
With HCTZ and other drugs	109	(2)	201	(4)
100 mg with or without additional drugs†	**2284**	**(50)**	**1979**	**(43)**
Alone	95	(2)	78	(2)
With HCTZ only	829	(18)	713	(16)
With other drugs only	162	(4)	172	(4)
With HCTZ and other drugs	1198	(26)	1016	(22)
Off study drugs	**1043**	**(23)**	**1243**	**(27)**

† Including hydrochlorothiazide (HCTZ).

At the time of a primary endpoint or at the end of follow-up, 2773 (60%) patients in the losartan treatment group versus 2569 (56%) patients in the atenolol group received HCTZ as part of the study treatment. The mean dose of HCTZ was ~20 mg in each treatment group and the distribution of doses was similar between the 2 treatment groups.

Considering the time on drug at the last visit before an endpoint or end of follow-up, losartan-treated patients received study drug for 86.3% of the time compared with 82.2% for atenolol-treated patients, and the mean dose for that time was 81.8 mg for the losartan group versus 79.0 mg for the atenolol group. The differences in time on drug were due to

more patients discontinuing study therapy in the atenolol group compared with the losartan group.

3.5 Efficacy Results

The primary efficacy parameter was a composite of cardiovascular mortality, stroke or myocardial infarction. Only endpoints on or before 16-Sep-2001 and confirmed by the blinded ECC were included in the analyses. The primary analysis of the primary endpoint and all analyses of other endpoints utilized an intention-to-treat approach. All randomized patients were included in their randomized treatment group and all available follow-up was included from randomization through the endpoint cutoff date of 16-Sep-2001.

Numerous procedures were undertaken to ensure the study was conducted according to Good Clinical Practices guidelines. All investigators received an instruction manual, study start-up and subsequent yearly investigators' meetings were conducted to ensure proper understanding of the protocol and all data collection procedures. Periodic newsletters were utilized to disseminate and reinforce important study administrative and procedural instructions, and regular site monitoring was conducted by the Sponsor to verify protocol adherence and to compare the accuracy of the study data against source documentation. In addition, a data review plan was prepared and utilized by the Sponsor, and all data were reviewed through the use of computer and manual queries. A random selection of both U.S. and international investigative sites was audited by the Sponsor for compliance to ICH/GCP guidelines and the Sponsor's own internal standard operating procedures. Finally, all analyses (unless otherwise specified) were prespecified in the Data Analysis Plan.

Central laboratories, Medical Research Laboratories in the United States and Nova Medical AB (formerly CALAB), Stockholm, Sweden, were utilized to ensure standardization of protocol-required laboratory screening and safety tests. Östra University Hospital ECG Core Center, Göteborg, Sweden, analyzed all screening and protocol-required ECGs.

3.5.1 Blood Pressure Control

One of the goals of the LIFE study was to attain comparable blood pressure reductions in both treatment arms. Sitting trough systolic blood pressure at the end of the follow-up or last visit before a primary endpoint, whichever occurred first, fell by 30.2 mm Hg in the losartan group and 29.1 mm Hg in the atenolol group (treatment difference $p=0.015$); sitting diastolic blood pressure was reduced by 16.6 mm Hg in the losartan group and 16.8 mm Hg in the atenolol group. The treatment difference between groups was not significant ($p=0.345$). Pulse pressure was reduced by 13.6 mm Hg in the losartan group and 12.4 mm Hg in the atenolol group (treatment difference $p<0.001$). Figure 2 presents the mean change in blood pressure from baseline to end of study or primary endpoint for each treatment group.

Figure 2

Mean Change in Blood Pressure From Baseline to End of Follow-Up or Last Visit Before a Primary Endpoint Occurred

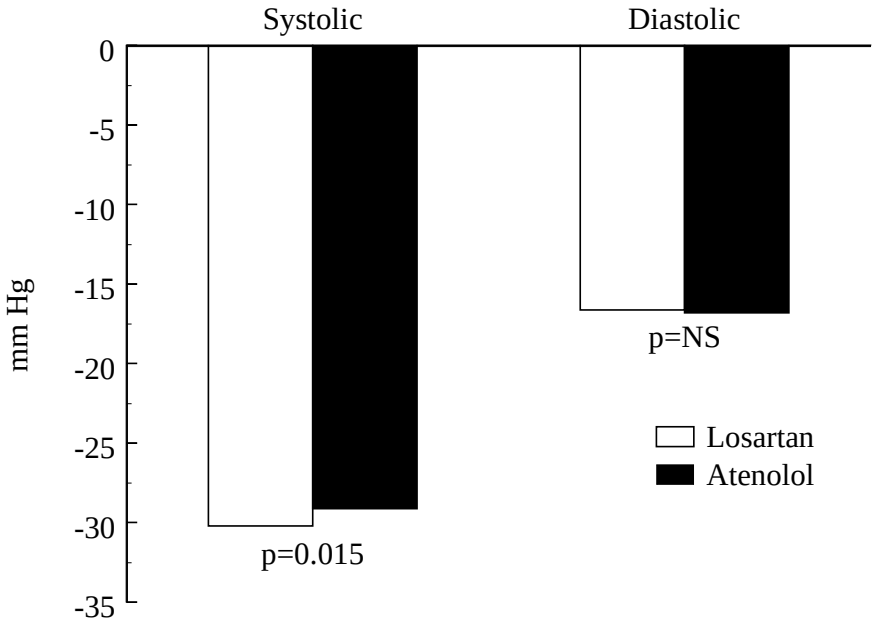


Figure 3 and Figure 4 show trough sitting systolic and diastolic blood pressures, pulse pressures, and mean arterial pressures summarized over time for both treatment groups. In general, systolic blood pressure tended to be lower in the losartan group while diastolic pressure tended to be lower in the atenolol group, resulting in consistently lower pulse pressure values in the losartan group. The time-averaged difference between groups in systolic blood pressure was 1.2 mm Hg favoring losartan. The time-averaged difference between groups in diastolic blood pressure was 0.8 mm Hg favoring atenolol. The time-averaged difference between groups in pulse pressure was 2.0 mm Hg favoring losartan. In a post hoc analysis, the time-averaged difference between groups in mean arterial pressure was 0.1 mm Hg in favor of atenolol.

Figure 3

Mean Sitting Systolic, Diastolic, Pulse, and Arterial Pressures Over Time

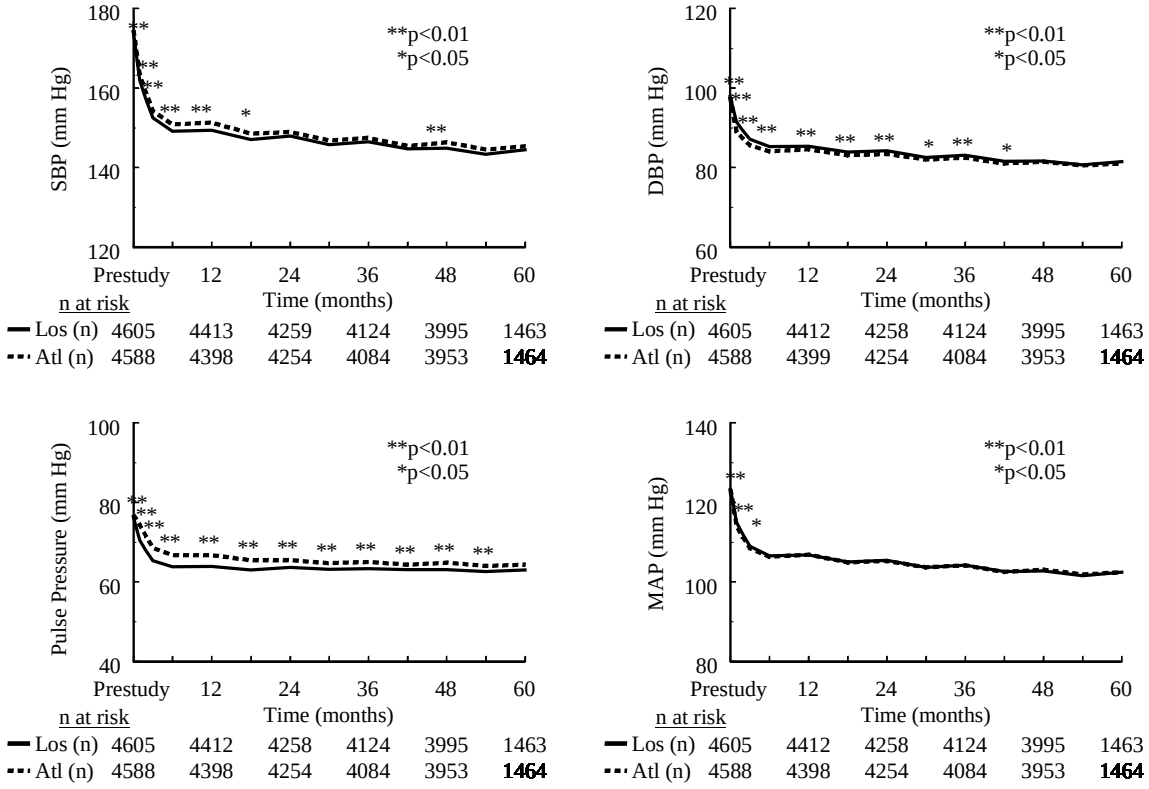
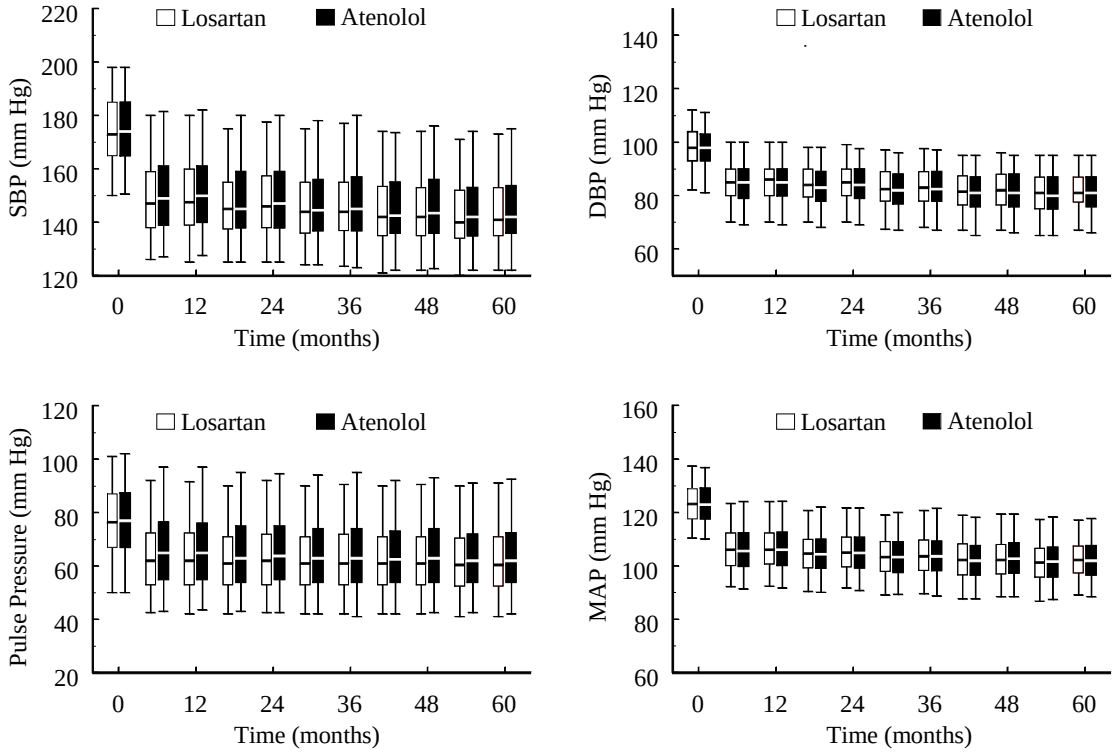


Figure 4

Box Plots: Sitting Systolic, Diastolic, Pulse, and Arterial Pressures



The box plots show the medians along with the 5th, 25th, 75th, and 95th percentiles of the pressure distributions.

Patients were also categorized based on their blood pressure response at each scheduled visit. The prespecified definitions of the categories of antihypertensive responses are shown in Table 7.

Table 7

Categories of Antihypertensive Responses

Response Category	Systolic BP (mm Hg)	Diastolic BP (mm Hg)
I	<140	<90
II	≥140 with change from baseline >20 mm Hg	<90
	OR	
	<140	≥90 with change from baseline >10 mm Hg
	OR	
	≥140 with change from baseline >20 mm Hg	≥90 with change from baseline >10 mm Hg
III	Does not qualify for category I or II	

Note that patients were considered responders if their sitting systolic and diastolic blood pressure measurements met the definition of response Category I or any of the alternatives of response Category II. Nonresponders were those patients in Category III, i.e., those who did not meet any of the definitions for Category I or II. Table 8 summarizes the distribution of blood pressure responders.

Table 8

Distribution of Blood Pressure Responders[†]

Visit	Losartan (N=4605) n/m	Losartan (N=4605) %	Atenolol (N=4588) n/m	Atenolol (N=4588) %	p-Value[‡]
Month 1	996/4545	21.9	1106/4531	24.4	0.005**
Month 2	1584/4513	35.1	1605/4472	35.9	0.433
Month 3	2126/4458	47.7	2157/4431	48.7	0.350
Month 6	2597/4447	58.4	2572/4438	58.0	0.671
Year 1	2546/4412	57.7	2413/4398	54.9	0.007**
Year 1.5	2774/4348	63.8	2679/4302	62.3	0.142
Year 2	2639/4258	62.0	2603/4254	61.2	0.455
Year 2.5	2801/4180	67.0	2745/4145	66.2	0.448
Year 3	2711/4124	65.7	2606/4084	63.8	0.068
Year 3.5	2823/4040	69.9	2771/4004	69.2	0.514
Year 4	2788/3995	69.8	2662/3953	67.3	0.019*
Year 4.5	2349/3239	72.5	2239/3130	71.5	0.379
Year 5	1061/1463	72.5	1032/1464	70.5	0.224
Year 5.5	325/440	73.9	311/426	73.0	0.775

* p-Values <0.05.
** p-Values <0.01.
[†] Responder is either:
Category I: SBP <140 mm Hg and DBP <90 mm Hg
Or
Category II: SBP ≥140 mm Hg with change from baseline >20 mm Hg and DBP <90 mm Hg;
Or SBP <140 mm Hg and DBP ≥90 mm Hg with change from baseline >10 mm Hg;
Or SBP ≥140 mm Hg with change from baseline >20 mm Hg and DBP ≥90 mm Hg with change from baseline >10 mm Hg.
[‡] p-Values are based on Chi-square Test.
n/m: Number of responders/total number of patients assessed.

At most times throughout the study, the distribution of blood pressure response was comparable between the 2 treatment groups. There were significantly more responders in the atenolol group at 1 month after study start and significantly more responders in the losartan group at Years 1 and 4. After 4 years of follow-up, 69.8% patients in the losartan group and 67.3% patients in the atenolol group were Category I or II responders, p=0.019.

At the end of follow-up or last visit before primary endpoint, blood pressure of ≤140/90 mm Hg was achieved in 2268 (49%) losartan patients and 2098 (46%) atenolol patients for systolic pressure; in 4017 (88%) losartan patients and 4067 (89%) atenolol patients for diastolic pressure; and in 2196 (48%) losartan patients and 2050 (45%) atenolol patients for both systolic and diastolic blood pressure.

These data show that blood pressure was reduced substantially in both treatment groups, and clinically comparable blood pressure reduction between treatment groups was achieved, in accordance with the study goals.

3.5.2 Primary Composite Endpoint Results and Components—Intention-to-Treat Approach

In the LIFE trial, the primary endpoint was a composite of cardiovascular morbidity and mortality. However, it is appropriate to explore the effect of treatment among the components of this composite endpoint because the events may be impacted differently by the treatment regimens. Consequently, the components were prespecified as secondary endpoints and defined as cardiovascular death, fatal/nonfatal stroke, and fatal/nonfatal myocardial infarction. The ECC classified each death according to whether or not it was cardiovascular and into more specific categories. As shown in Table 9, the primary composite endpoint occurred in 508 patients in the losartan group (23.8 per 1000 patient-years of follow-up) and in 588 patients in the atenolol group (27.9 per 1000 patient-years of follow-up). The relative risk reduction for the primary composite was 13.1 % (hazard ratio (HR): 0.869 [95% CI 0.772 to 0.979], p=0.021) for the primary analysis including adjustment for baseline measures of LVH and Framingham risk score as covariates. The unadjusted risk reduction was 14.6% (HR: 0.854 [95% CI 0.759 to 0.962, p=0.009]). Of note, in patients treated with prior angiotensin II antagonist/angiotensin-converting enzyme inhibitors or prior β-blockers, the reduction in risks for the composite endpoint were directionally consistent with the composite endpoint for the overall population.

For the components of the primary composite endpoint (secondary endpoints) in the overall population, cardiovascular mortality occurred in 204 patients in the losartan group (9.2 per 1000 patient-years of follow-up) and 234 patients in the atenolol group (10.6 per 1000 patient-years of follow-up) (See Table 9). The cardiovascular mortality HR was 0.886 (95% CI 0.734 to 1.069, p=0.206; relative risk reduction: 11.4%). Stroke occurred in 232 patients in the losartan group (10.8 per 1000 patient-years of follow-up) and 309 patients in the atenolol group (14.5 per 1000 patient-years of follow-up) (HR: 0.752 [95% CI 0.634 to 0.891], p=0.001; relative risk reduction: 24.8%). Myocardial infarction occurred in 198 patients in the losartan group (9.2 per 1000 patient-years of follow-up) and 188 patients in the atenolol group (8.7 per 1000 patient-years of follow-up) (HR: 1.073 [95% CI 0.879 to 1.310], p=0.491; relative risk reduction: -7.3%). The risks of the primary composite endpoint and stroke were significantly lower in the losartan group, and although not significant, the reduction in the incidence of cardiovascular death also contributed to the benefit of losartan on the composite endpoint.

Table 9

Summary of Intention-to-Treat Analysis of Primary Composite Endpoint and Components of Primary Composite Endpoint

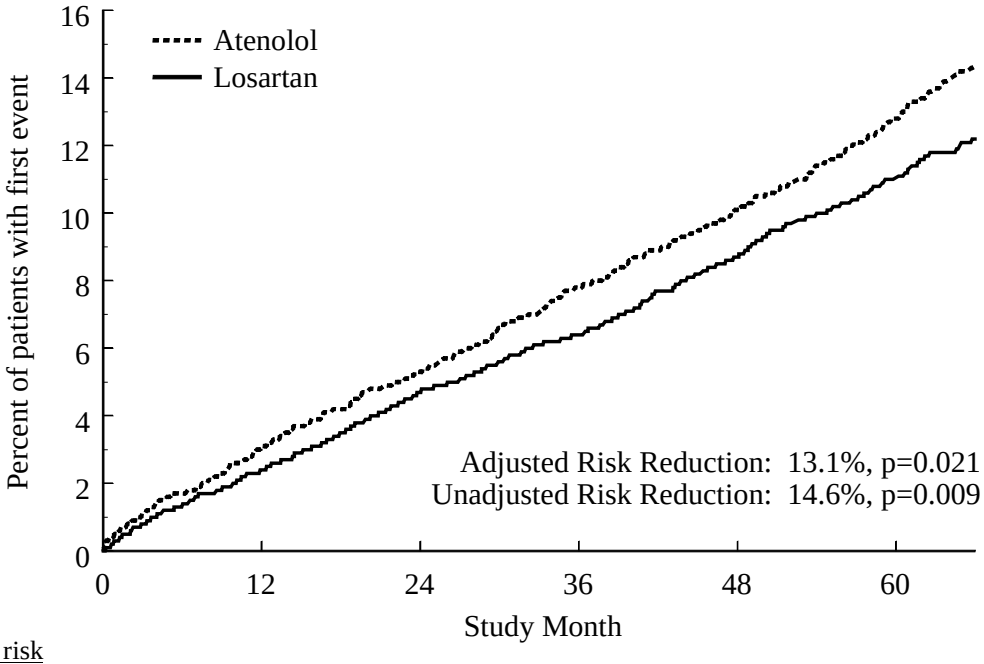
	Crude Rate						Kaplan-Meier Rates								Hazard‡	95% CI		
	Losartan (N=4605)			Atenolol (N=4588)			Losartan				Atenolol							
	Rate†	N	(%)	Rate†	n	(%)	1 Yr	2 Yr	3 Yr	4 Yr	1 Yr	2 Yr	3 Yr	4 Yr	Ratio	Lower	Upper	p-Value§
Composite	23.8	508	(11.0)	27.9	588	(12.8)	2.4	4.8	6.5	8.9	3.1	5.4	7.9	10.2	0.869	0.772	0.979	0.021*
Components																		
Cardiovascular mortality	9.2	204	(4.4)	10.6	234	(5.1)	0.7	1.6	2.2	3.3	0.9	1.8	2.9	3.7	0.886	0.734	1.069	0.206
Stroke (fatal/nonfatal)	10.8	232	(5.0)	14.5	309	(6.7)	1.1	2.3	3.1	4.1	1.9	3.1	4.2	5.7	0.752	0.634	0.891	0.001**
MI (fatal/nonfatal)	9.2	198	(4.3)	8.7	188	(4.1)	1.0	1.7	2.4	3.5	0.8	1.6	2.4	3.2	1.073	0.879	1.310	0.491

* p-Values <0.046.
** p-Values <0.01.
† Per 1000 patient-years of follow-up.
‡ Baseline left ventricular hypertrophy degree (Cornell product and Sokolow-Lyon) and baseline Framingham risk score are included in Cox proportional hazard model as covariates.
§ The p-values and estimates of hazard ratio of experiencing the endpoint on losartan compared with atenolol are based on Cox proportional hazard model.

Kaplan-Meier curves for the primary endpoint are shown in Figure 5 and the curves for the 3 components are shown in Figure 6 (Note: risk reductions are adjusted for baseline degree of LVH and Framingham risk score [FRS]). The numbers below the chart indicate the number of patients who remained at risk of a primary endpoint at the specified time point. Risk reductions for the unadjusted analyses are also provided in these figures.

Figure 5

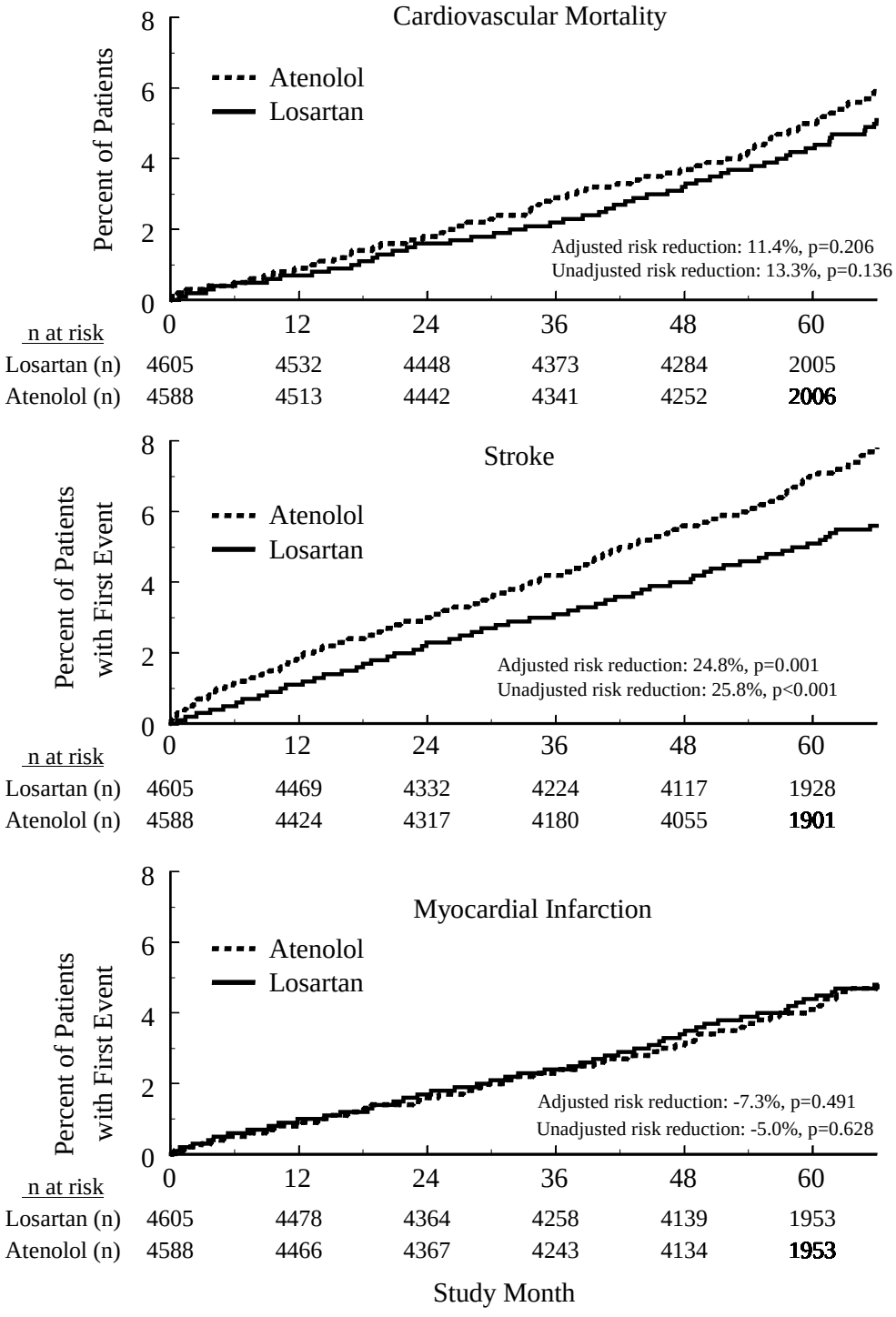
Observed Kaplan-Meier Curve—Primary Composite Endpoint



n at risk						
Losartan (n)	4605	4460	4312	4189	4045	1888
Atenolol (n)	4588	4414	4289	4135	3992	**1854**

Figure 6

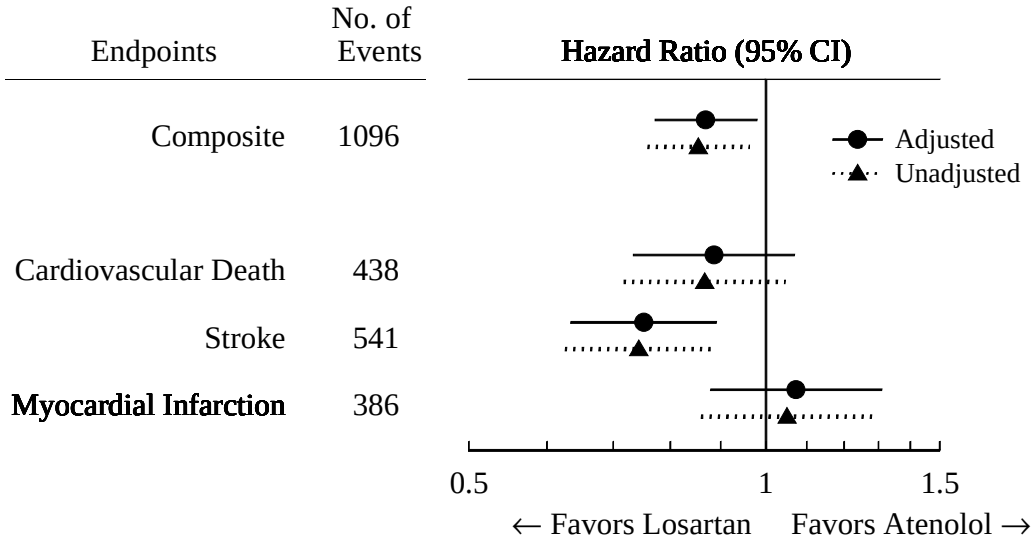
Observed Kaplan-Meier Curves—Components of Primary Composite Endpoint



Hazard ratios and 95% confidence intervals for the primary composite endpoint and components of the composite that include predefined baseline covariates (i.e., adjusted and unadjusted for baseline degree of LVH and Framingham risk score [FRS]) are shown in Figure 7. The reduction in risk for the composite endpoint of cardiovascular morbidity and mortality as well as the component endpoints of cardiovascular mortality and stroke are directionally consistent and demonstrate the cardiovascular benefit of losartan compared with atenolol.

Figure 7

Hazard Ratios for Primary Composite Endpoint and Components of Primary Composite Endpoint



3.5.3 Supportive Analyses

3.5.3.1 Primary Composite Endpoint (Per-Protocol Approach)

A per-protocol analysis of the primary endpoint was performed. This analysis excluded patients with important protocol violations identified prior to unblinding (a total of 204 patients: 101 patients in the losartan group versus 103 patients in the atenolol group) and censored patients 14 days after permanently discontinuing study medications or 14 days after starting prohibited therapy. As a result of the per protocol exclusions and censoring rules, 376 primary events were excluded: 165 events in the losartan group and 211 events in the atenolol group.

The per-protocol results are summarized in Table 10 and were supportive of the primary analysis. In the per-protocol analysis, there were approximately one-third fewer events; a primary endpoint occurred in 343 patients in the losartan group (19.4 per 1000 patient-years of follow-up) and in 377 patients in the atenolol group (22.8 per 1000 patient-years of follow-up). The adjusted hazard ratio was 0.865 (95% CI 0.748 to 1.002, p=0.053; relative risk reduction: 13.5%). Results are also included for the components. Although the overall number of events was lower in this analysis, the adjusted hazard ratio was similar to that in the intention-to-treat analysis.

Table 10

Summary of Per-Protocol Analysis of Primary Composite Endpoint and Components of Primary Composite Endpoint

	Crude Rate						Kaplan-Meier Rates											
	Losartan (N=4504)			Atenolol (N=4485)			Losartan				Atenolol				Hazard‡	95% CI		
	Rate†	n	(%)	Rate†	n	(%)	1 Yr	2 Yr	3 Yr	4 Yr	1 Yr	2 Yr	3 Yr	4 Yr	Ratio	Lower	Upper	p-Value§
Composite	19.4	343	(7.6)	22.8	377	(8.4)	2.1	4.1	5.5	7.3	2.7	4.6	6.4	8.5	0.865	0.748	1.002	0.053
Components of Primary Composite Endpoint—Secondary Endpoints																		
Cardiovascular mortality	5.4	96	(2.1)	6.2	105	(2.3)	0.6	1.1	1.4	2.0	0.5	1.1	1.8	2.2	0.879	0.667	1.160	0.362
Stroke (fatal/nonfatal)	8.7	153	(3.4)	12.7	211	(4.7)	1.0	2.1	2.6	3.3	1.8	2.8	3.7	5.0	0.687	0.558	0.845	<0.001**
MI (fatal/nonfatal)	8.4	150	(3.3)	7.2	122	(2.7)	0.9	1.7	2.3	3.3	0.7	1.4	2.0	2.7	1.178	0.927	1.496	0.180

** p-Values <0.01.

† Per 1000 patient-years of follow-up.

‡ Baseline left ventricular hypertrophy degree (Cornell Product and Sokolow-Lyon) and baseline Framingham risk score are included in Cox proportional hazard model as covariates.

§ The p-values and estimates of hazard ratio of experiencing the endpoint on losartan compared to atenolol are based on Cox proportional hazard model.

3.5.3.2 Investigator-Defined Events

An additional supportive analysis was performed for the primary composite endpoint and the components based on events as reported by the investigators (whether or not positively classified by the Endpoint Classification Committee). The results are summarized in Table 11 and were similar to those reported by the Endpoint Classification Committee.

In summary, the relative risk reduction for the primary composite was 11.1 % (hazard ratio (HR): 0.889 [95% CI 0.795 to 0.995], p=0.040) for the primary analysis including adjustment for baseline measures of LVH and Framingham risk score as covariates. The cardiovascular mortality hazard ratio was 0.842 (95% CI 0.698 to 1.015, p=0.072; relative risk reduction: 15.8%). The stroke hazard ratio was 0.805 [95% CI 0.689 to 0.941], p=0.007; relative risk reduction: 19.5%). Myocardial infarction hazard ratio was 1.044 [95% CI 0.868 to 1.256], p=0.649; relative risk reduction: -4.4%).

Table 11

Investigator-Reported Primary Composite Endpoint and Components of Primary Composite Endpoint Results

	Crude Rate						Kaplan-Meier Rates											
	Losartan (N=4605)			Atenolol (N=4588)			Losartan				Atenolol				Hazard‡	95% CI		
	Rate†	n	(%)	Rate†	n	(%)	1-Yr	2-Yr	3-Yr	4-Yr	1-Yr	2-Yr	3-Yr	4-Yr	Ratio	Lower	Upper	p-Value§
Composite	27.3	576	(12.5)	31.2	651	(14.2)	3.1	5.8	7.7	10.2	3.5	6.1	8.8	11.5	0.889	0.795	0.995	0.040*
Components of Primary Composite Endpoint—Secondary Endpoints																		
Cardiovascular mortality	9.0	200	(4.3)	11.0	241	(5.3)	0.7	1.6	2.2	3.2	0.8	1.7	3.0	3.9	0.842	0.698	1.015	0.072
Stroke	13.3	284	(6.2)	16.7	353	(7.7)	1.6	3.0	4.0	5.2	2.3	3.6	5.0	6.5	0.805	0.689	0.941	0.007**
MI	10.6	228	(5.0)	10.3	222	(4.8)	1.2	2.2	2.9	4.1	1.0	1.9	3.0	3.9	1.044	0.868	1.256	0.649

* p-Values <0.05.
** p-Values <0.01.
† Per 1000 patient-years of follow-up.
‡ Baseline left ventricular hypertrophy degree (Cornell product and Sokolow-Lyon) and baseline Framingham risk score are included in Cox proportional hazard model as covariates.
§ The p-values and estimates of hazard ratio of experiencing the endpoint on losartan compared to atenolol are based on Cox proportional hazard model.

3.5.3.3 Consistency of Effect Among Components of the Primary Composite Endpoint

The 3 components of the primary endpoint, cardiovascular mortality, fatal/nonfatal stroke, and fatal/nonfatal myocardial infarction, were not mutually exclusive. Patients with multiple primary endpoints were counted only once in the analysis of the primary composite endpoint; however, these patients were counted as having had endpoints in multiple components analyses, as appropriate. As previously shown in Section III.3.5.2 (Figure 7), the treatment effect did not appear to be consistent among the 3 components of the primary composite endpoint. The primary composite endpoint and stroke both significantly favored losartan. The direction of the treatment effect for cardiovascular mortality was consistent with the primary composite while that for the treatment effect on myocardial infarction was not. The individual treatment effects for cardiovascular mortality and myocardial infarction were not statistically significant.

The variation noted among the components of the composite endpoint can happen by chance alone, and for that reason a formal statistical test for the homogeneity of the treatment effect among the 3 components was prespecified. This test, which accounts for the correlations among components [49], found statistically significant heterogeneity ($p=0.023$). Therefore, the observed variation in the effect of losartan among the components of the composite endpoint is more than would be expected by chance, and suggests that the components should be evaluated separately. The biologic correlate of this finding is discussed in Section III.5.1.1.3.

3.5.3.4 Demographic Subgroup Analyses

To assess the influence of various risk factors on the primary composite endpoint, several prespecified subgroups were analyzed using a Cox proportional hazards model that included treatment and the risk factor of interest as covariates. Table 12 summarizes the results of the subgroup analyses. The subgroup analyses were based on the same statistical methods as the analysis of the primary endpoint, with one exception: since Framingham risk score (and its components) and degree of LVH are among the prespecified risk factors that were analyzed as subgroups, the subgroup analyses do not include Framingham risk score and degree of LVH as covariates. However, in subsequent sections (III.3.5.5.1 and III.3.5.5.2) the analyses of the populations of special interest (i.e., diabetes mellitus and ISH) did include these covariates. In the demographic, geographic, disease history, and disease severity subgroups, there were no treatment-by-subgroup interactions that met the prespecified test for significance ($p<0.05$), indicating that the effect of losartan relative to atenolol was similar among all subgroups.

Table 12

Primary Composite Endpoint—Subgroup Analyses

Subgroup	Crude Rate: Losartan Rate†	Losartan n/M	Losartan (%)	Crude Rate: Atenolol Rate†	Atenolol n/M	Atenolol (%)	Hazard Ratio*	95% CI Lower	95% CI Upper
Age (Years): Interaction Test p-Value# =0.185									
54 and under	6.9	2/ 58	(3.4)	24.9	6/ 52	(11.5)	0.274	0.055	1.359
55 to 59	13.8	53/ 802	(6.6)	13.9	53/ 797	(6.6)	0.991	0.677	1.451
60 to 64	17.8	75/ 888	(8.4)	14.3	61/ 892	(6.8)	1.238	0.883	1.735
65 to 69	21.4	102/ 1026	(9.9)	26.4	126/ 1029	(12.2)	0.812	0.625	1.054
70 to 74	27.8	129/ 1023	(12.6)	36.1	168/ 1044	(16.1)	0.774	0.616	0.974
75 to 80	40.5	143/ 796	(18.0)	51.8	171/ 764	(22.4)	0.781	0.625	0.975
81 and above	87.8	4/ 12	(33.3)	76.8	3/ 10	(30.0)	1.005	0.225	4.500
Gender: Interaction Test p-Value# =0.420									
Female	18.2	215/ 2487	(8.6)	22.5	261/ 2476	(10.5)	0.809	0.675	0.969
Male	30.8	293/ 2118	(13.8)	34.5	327/ 2112	(15.5)	0.893	0.763	1.045
Ethnic Group: Interaction Test p-Value# =0.057									
White	22.9	455/ 4258	(10.7)	27.9	548/ 4245	(12.9)	0.819	0.724	0.928
Black	41.8	46/ 270	(17.0)	25.9	29/ 263	(11.0)	1.598	1.004	2.543
Hispanic	18.8	4/ 47	(8.5)	36.9	8/ 53	(15.1)	0.523	0.157	1.737
Asian	30.6	3/ 25	(12.0)	12.3	1/ 18	(5.6)	2.428	0.252	23.356
Other	0.0	0/ 5	(0.0)	48.8	2/ 9	(22.2)	0.000	0.000	
Smoking Status: Interaction Test p-Value# =0.282									
Never	18.2	203/ 2341	(8.7)	23.1	251/ 2315	(10.8)	0.789	0.655	0.949
Ex-Smoker	25.8	180/ 1533	(11.7)	30.2	207/ 1500	(13.8)	0.854	0.700	1.043
Current Smoker	38.9	125/ 729	(17.1)	38.6	130/ 770	(16.9)	1.019	0.797	1.302
Alcohol Intake: Interaction Test p-Value# =0.420									
None	24.7	241/ 2107	(11.4)	30.1	289/ 2109	(13.7)	0.819	0.690	0.972
1 to 7/week	23.3	230/ 2130	(10.8)	25.3	255/ 2157	(11.8)	0.919	0.769	1.098
8+/week	21.7	36/ 366	(9.8)	31.3	44/ 319	(13.8)	0.693	0.446	1.076
Exercise: Interaction Test p-Value# =0.892									
Never	29.6	136/ 1024	(13.3)	35.5	158/ 996	(15.9)	0.833	0.662	1.048
≤30 min	27.1	153/ 1222	(12.5)	32.9	177/ 1185	(14.9)	0.824	0.664	1.024
>30 min	19.8	219/ 2356	(9.3)	22.5	253/ 2402	(10.5)	0.878	0.733	1.052

Table 12 (Cont.)

Primary Composite Endpoint—Subgroup Analyses

Subgroup	Crude Rate: Losartan Rate†	Losartan n/M	Losartan (%)	Crude Rate: Atenolol Rate†	Atenolol n/M	Atenolol (%)	Hazard Ratio*	95% CI Lower	95% CI Upper
Prestudy Medical History									
Myocardial Infarction‡: Interaction Test p-Value# =0.316									
Yes	54.8	70/ 305	(23.0)	54.7	61/ 262	(23.3)	1.003	0.712	1.414
No	21.9	438/ 4300	(10.2)	26.4	527/ 4326	(12.2)	0.828	0.730	0.940
Stroke: Interaction Test p-Value# =0.211									
Yes	62.4	49/ 191	(25.7)	57.2	52/ 210	(24.8)	1.105	0.748	1.632
No	22.3	459/ 4414	(10.4)	26.6	536/ 4378	(12.2)	0.841	0.743	0.953
Ischemic Heart Disease: Interaction Test p-Value# =0.209									
Yes	53.7	62/ 273	(22.7)	50.6	57/ 263	(21.7)	1.064	0.743	1.525
No	22.1	446/ 4332	(10.3)	26.6	531/ 4325	(12.3)	0.831	0.733	0.943
Angina Pectoris§: Interaction Test p-Value# =0.250									
Yes	45.2	97/ 492	(19.7)	45.8	85/ 426	(20.0)	0.989	0.739	1.323
No	21.4	411/ 4113	(10.0)	26.2	503/ 4162	(12.1)	0.819	0.719	0.933
Heart Failure: Interaction Test p-Value# =0.733									
Yes	64.5	21/ 84	(25.0)	83.0	25/ 82	(30.5)	0.796	0.445	1.422
No	23.2	487/ 4521	(10.8)	27.1	563/ 4506	(12.5)	0.856	0.758	0.967
Diabetes Mellitus‖ : Interaction Test p-Value# =0.170									
Yes	39.2	103/ 586	(17.6)	53.6	139/ 609	(22.8)	0.733	0.568	0.946
No	21.7	405/ 4019	(10.1)	24.3	449/ 3979	(11.3)	0.893	0.780	1.021
Microalbuminuria: Interaction Test p-Value# =0.383									
Yes	29.8	13/ 91	(14.3)	47.0	20/ 94	(21.3)	0.629	0.313	1.265
No	23.7	495/ 4514	(11.0)	27.5	568/ 4494	(12.6)	0.862	0.764	0.972
Degree of Left Ventricular Hypertrophy (LVH)—Cornell Voltage ¶: Interaction Test p-Value# =0.485									
Men									
Low	28.4	89/ 707	(12.6)	31.2	97/ 704	(13.8)	0.909	0.682	1.212
Middle	28.5	91/ 699	(13.0)	29.7	97/ 716	(13.5)	0.960	0.721	1.278
High	35.3	113/ 712	(15.9)	42.7	133/ 692	(19.2)	0.827	0.643	1.062
Women									
Low	13.4	52/ 811	(6.4)	20.7	82/ 844	(9.7)	0.647	0.457	0.916
Middle	17.1	68/ 835	(8.1)	17.0	66/ 819	(8.1)	1.006	0.717	1.411
High	24.1	95/ 841	(11.3)	30.2	113/ 813	(13.9)	0.800	0.609	1.052
Degree of LVH—Sokolow-Lyon Voltage ¶: Interaction Test p-Value# =0.422									
Men									
Low	25.0	87/ 763	(11.4)	32.3	106/ 727	(14.6)	0.779	0.586	1.034
Middle	31.8	97/ 669	(14.5)	37.9	119/ 696	(17.1)	0.838	0.641	1.095
High	36.4	109/ 686	(15.9)	33.3	102/ 689	(14.8)	1.091	0.833	1.429
Women									
Low	13.6	54/ 830	(6.5)	18.8	73/ 827	(8.8)	0.724	0.509	1.030
Middle	17.5	70/ 828	(8.5)	22.4	89/ 843	(10.6)	0.782	0.572	1.069
High	23.7	91/ 829	(11.0)	26.6	99/ 806	(12.3)	0.894	0.672	1.188

Table 12 (Cont.)

Primary Composite Endpoint—Subgroup Analyses

Subgroup	Crude Rate: Losartan Rate†	Losartan n/M	Losartan (%)	Crude Rate: Atenolol Rate†	Atenolol n/M	Atenolol (%)	Hazard Ratio*	95% CI Lower	95% CI Upper
Framingham Risk ¶: Interaction Test p-Value# =0.922									
Low	13.2	99/ 1565	(6.3)	15.9	113/ 1500	(7.5)	0.828	0.632	1.085
Middle	20.6	145/ 1506	(9.6)	24.4	177/ 1558	(11.4)	0.845	0.678	1.052
High	39.1	264/ 1534	(17.2)	44.5	298/ 1530	(19.5)	0.878	0.744	1.036
Baseline Lab Tests ¶									
***Total Serum** Cholesterol: Interaction Test p-Value# =0.975*									
Low	23.0	165/ 1561	(10.6)	27.0	188/ 1542	(12.2)	0.854	0.693	1.053
Middle	22.3	158/ 1526	(10.4)	26.6	186/ 1520	(12.2)	0.840	0.680	1.039
High	26.1	185/ 1518	(12.2)	30.1	214/ 1526	(14.0)	0.868	0.713	1.056
***HDL** Cholesterol: Interaction Test p-Value# =0.114*									
Low	31.3	217/ 1530	(14.2)	31.9	222/ 1542	(14.4)	0.983	0.815	1.185
Middle	21.1	154/ 1568	(9.8)	28.9	200/ 1507	(13.3)	0.730	0.592	0.901
High	19.4	137/ 1507	(9.1)	23.1	166/ 1539	(10.8)	0.838	0.669	1.051
Baseline Systolic Blood Pressure (SBP) (mm Hg): Interaction Test p-Value# =0.725									
<160	16.4	40/ 516	(7.8)	22.9	55/ 516	(10.7)	0.717	0.477	1.078
160 to 179	22.4	248/ 2386	(10.4)	25.1	269/ 2327	(11.6)	0.892	0.751	1.060
180 to 200	28.4	216/ 1664	(13.0)	33.2	259/ 1717	(15.1)	0.856	0.714	1.025
>200	21.8	4/ 39	(10.3)	38.2	5/ 28	(17.9)	0.572	0.154	2.132
Baseline Diastolic Blood Pressure (DBP) (mm Hg): Interaction Test p-Value# =0.402									
<95	25.0	148/ 1290	(11.5)	31.3	181/ 1294	(14.0)	0.801	0.645	0.995
95 to 104	24.1	253/ 2272	(11.1)	25.6	274/ 2295	(11.9)	0.939	0.792	1.114
105 to 115	21.8	105/ 1026	(10.2)	28.7	131/ 992	(13.2)	0.761	0.589	0.984
>115	25.0	2/ 17	(11.8)	65.0	2/ 7	(28.6)	0.384	0.054	2.730
Baseline Body Mass Index (BMI) ¶: Interaction Test p-Value# =0.290									
Men									
Low	27.8	85/ 672	(12.6)	38.3	125/ 744	(16.8)	0.727	0.552	0.957
Middle	33.7	110/ 731	(15.0)	30.7	95/ 680	(14.0)	1.100	0.836	1.448
High	30.5	98/ 715	(13.7)	34.1	107/ 688	(15.6)	0.897	0.682	1.180
Women									
Low	19.3	77/ 854	(9.0)	25.5	94/ 805	(11.7)	0.760	0.562	1.027
Middle	18.5	71/ 813	(8.7)	24.3	96/ 833	(11.5)	0.766	0.564	1.041
High	16.9	67/ 820	(8.2)	18.0	71/ 838	(8.5)	0.934	0.669	1.304

* Estimates of hazard ratio of experiencing the endpoint on losartan compared with atenolol are based on Cox proportional hazard model. Subgroup analysis does not adjust for left ventricular hypertrophy and Framingham risk score.

† Per 1000 patient-years of follow-up.

‡ Includes patients with a secondary diagnosis of myocardial infarction; not combined with age-indeterminate myocardial infarction as in Secondary Diagnoses.

§ Includes patients with a secondary diagnosis of angina pectoris; not combined with unstable angina as in Secondary Diagnoses.

‖ Includes patients with a secondary diagnosis of diabetes mellitus, insulin-dependent diabetes mellitus and type 2 diabetes mellitus.

¶ Based on baseline tertiles.

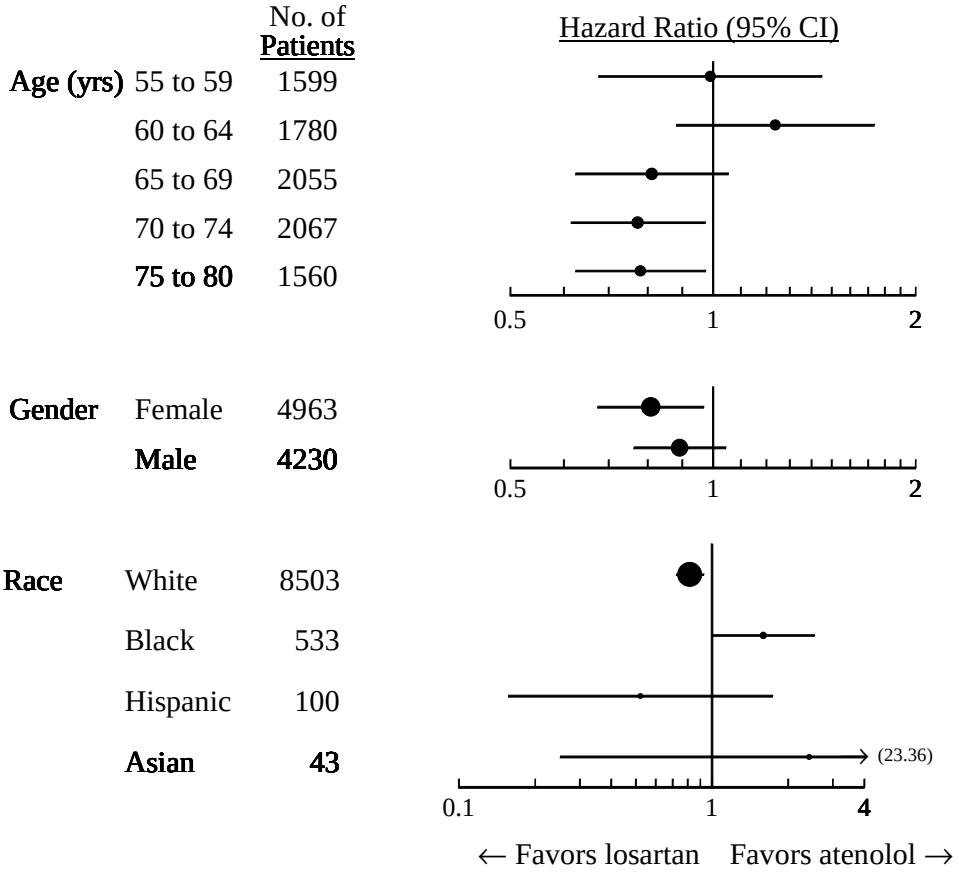
Test for interaction with treatment.

M Number of patients as denominator in the subgroup analyses.

Hazard ratios and 95% confidence intervals for the primary composite endpoint by age, gender, and ethnic groups are shown in Figure 8. Note that the size of the symbol in the figure representing the hazard ratio corresponds to the number of patients in each subgroup.

Figure 8

Hazard Ratios for the Primary Composite Endpoints by Age, Gender, and Ethnic Group



As previously stated, there were no treatment-by-subgroup interactions in the prespecified analysis; there was, however, a suggestion of an interaction between ethnic background and treatment (p=0.057). The prespecified test for the interaction between ethnic background and treatment was based on a comparison of the effect of losartan among the 5 different ethnic background categories: White (n=8503), Black (n=533), Hispanic (n=100), Asian (n=43), and Other (n=14). White patients appeared to have lower risk with losartan (hazard ratio: 0.819 [95% CI 0.724 to 0.928]; relative risk reduction: 18.1%), while Black patients appeared to have lower risk with atenolol (hazard ratio: 1.598 [95% CI 1.004 to 2.543]; relative risk reduction: -59.8% [Table 12]). The amount of data for all but the White and Black groups was very limited,

which made the prespecified test for interaction unreliable. Therefore, in view of these limitations and the borderline finding between Blacks and Whites, a post hoc test was performed. This exploratory analysis dichotomized patients into Black (N=533) and non-Black (N=8660).

It is important to note the distinction between a qualitative interaction and a quantitative interaction. A quantitative interaction refers to the situation in which the effect of the treatment differs in magnitude among 2 or more subgroup categories, but the effect is in the same direction across the subgroup categories. A qualitative interaction, on the other hand, refers to the situation in which the direction of the effect differs among subgroup categories. Of note, although statistically significant qualitative interactions are rare, there are several examples of significant interactions which are apparently qualitative in the cardiovascular outcomes trial literature [52; 53; 54]. Specifically, these trials demonstrate interactions between treatment and race [52], gender [54] and disease state [53]. These findings are not generally considered definitive. Notably, none of these trials met the criterion for a statistically significant qualitative interaction. A search of currently available literature did not reveal an example of a statistically significant qualitative interaction.

In the LIFE study, the interaction between treatment and dichotomized ethnic background (Black and non-Black) appears to be qualitative, since losartan is superior to atenolol among non-Black patients, while atenolol is superior to losartan among Black patients. However, apparent qualitative interactions can occur by chance due to small sample sizes, so it was important to evaluate the degree of statistical evidence to support it. This was done in 2 steps: First, there was a test for any interaction; this was statistically significant (p=0.005), suggesting that the effect of losartan relative to atenolol differs between Black and non-Black patients. Next, there was a test for qualitative interaction; this was also statistically significant (p=0.016), suggesting that the effect of losartan relative to atenolol differs in direction between Black and non-Black patients. In the presence of a true qualitative interaction, it would not be appropriate to pool the subgroup categories and report an overall result [55]. Although the LIFE study results suggest a true qualitative interaction, this result is not definitive given the post hoc nature of this analysis; therefore, only in this section are results for Blacks and non-Blacks considered separately.

Due to the qualitative interaction between the dichotomized groups (Black and non-Black) and treatment, additional exploratory analyses were performed in these 2 groups including analyses of the primary composite endpoint and its components (adjusted for baseline Framingham risk score and degree of LVH), to investigate a possible biologic explanation for this finding.

The hazard ratio adjusted for baseline Framingham risk score and degree of LVH for the primary composite endpoint was 1.666 (95% CI 1.043 to 2.661, p=0.033; relative risk reduction: -66.6%) in the Black patients and 0.829 (95% CI 0.733 to 0.938, p=0.003; relative risk reduction: 17.1%) in the non-Black patients.

A similar observation was noted for the components of the primary composite endpoint between the Black and non-Black patients. The results of the adjusted analysis of the primary composite endpoint and components of the primary composite endpoint for Black and non-Black patients are summarized in Table 13. A per-protocol analysis of the primary composite endpoint was performed and yielded similar findings.

In addition, analyses exploring the effect in Black versus non-Black patients in the U.S. were performed because the majority of the Black patients (523 of 533) were from this region. Overall, there was a higher incidence of diabetes (25.4%) in U.S. Black patients than in the U.S. non-Black patients (19.6%) and a lower incidence of baseline cardiovascular conditions in U.S. Black versus non-Black patients (56.8% versus 68.1%). In addition, U.S. Black patients had a higher incidence of cerebrovascular accidents (9.0% versus 5.7%) compared with U.S. non-Black patients.

Comparisons of therapies administered prior to the study and baseline laboratory test results between the 2 U.S. subgroups revealed U.S. Black patients were more likely to have received diuretics than non-Blacks (38.6% versus 31.6%); U.S. Black patients were less likely to have received agents acting on the renin-angiotensin system than non-Blacks (36.3% versus 43.2%). U.S. Black patients were also less likely to have received prior treatment with a β-blocking agent than non-Black patients (21.2% versus 27.0%). At baseline, U.S. Black patients had slightly higher serum creatinine (1.26 versus 1.18 mg/dL), glucose (117.5 versus 115.2 mg/dL), uric acid (6.1 versus 5.7 mg/dL) and urine microalbumin (16.9 versus 12.0 mg/dL) values compared with non-Black patients.

Within the U.S. Black and non-Black patient populations, the 2 treatment groups were relatively well balanced with respect to baseline characteristics; however, there were some notable differences. There was a higher prevalence of male patients in the losartan-treated U.S. Black patients (57.2%) versus the atenolol-treated U.S. Black patients (49.8%), and a higher percentage of older patients (≥65 years) in the losartan-treated U.S. Black patients (54.5%) versus the atenolol-treated U.S. Black patients (44.0%).

Additional primary composite endpoint analyses in the U.S. Black and non-Black patients were performed adjusting for: (1) age, gender, systolic blood pressure, and baseline LVH; (2) smoking; (3) prior cardiovascular disease (including prior MI, prior stroke, ischemic heart disease, peripheral vascular disease, and cerebrovascular disease); (4) prior antihypertensive treatment; and (5) prior treatment with a β-blocker. None of these adjustments accounted for the findings that Black patients had lower event rates with atenolol whereas non-Black patients responded better to losartan.

Blood pressure was reduced to a comparable level in the losartan and atenolol treatment groups in U.S. Black and non-Black patients. In U.S. Black patients, sitting trough systolic/diastolic blood pressure at the last visit before a primary endpoint occurred, or at end of follow-up, decreased by 30.3/17.3 mm Hg in the losartan group and 29.1/17.2 mm Hg in the atenolol group, and in U.S. non-Black patients, sitting trough systolic blood pressure decreased by 31.1/16.5 mm Hg in the losartan group and 30.3/17.5 mm Hg in the atenolol groups.

Treatment with losartan demonstrated a greater reduction in ECG measures of LVH in both U.S. Black and non-Black patients, similar to the results observed in the overall population (as presented in Section III.3.5.4.1), although the magnitude of the LVH regression in Black patients on losartan versus Black patients treated with atenolol was numerically smaller. In U.S. Black patients, mean Cornell voltage-duration product at last visit before a primary endpoint occurred, or at end of follow-up, was reduced by 193 mm x ms in the losartan group and 79 mm x ms in the atenolol group, whereas the corresponding numbers for U.S. non-Black patients were reductions of 233 mm x ms in the losartan group and 36 mm x ms in the atenolol group. Sokolow-Lyon voltage was reduced by 5.8 mm in the losartan group and 4.0 mm in the atenolol group in U.S. Black patients, and by 4.4 mm in the losartan group and 2.8 mm in the atenolol group in U.S. non-Black patients. Additional data relating to LVH were gathered echocardiographically in a substudy and are described in Section 3.5.7. In brief, Black patients in the atenolol group (n=71) experienced a numerically greater left ventricular mass index (LVMI) reduction compared with patients in the losartan group (n=68). In contrast, in the substudy, the reduction of ECG-LVH in Black patients was greater in the losartan group.

The physiologic benefits of the losartan-based regimen in Black patients described above, namely significant reductions in blood pressure and LVH, are noteworthy, and anticipated to result in cardiovascular benefits. Specifically, blood pressure reduction is well-known to reduce the risk of cardiovascular outcomes, and there are no data to suggest this benefit does not apply equally to Black patients. The finding of the efficacy of a losartan-based regimen in reducing blood pressure in Black patients has been observed in other trials [56]. Furthermore, data suggest that LVH regression also confers cardiovascular benefit, and this is likely to apply to Black patients as well. In addition, in the RENAAL trial, cardiovascular morbidity and mortality were reduced by a losartan-based regimen relative to placebo in Black patients (HR: 0.82 [95% CI 0.52 - 1.30; p=0.40] (data on file). Since blood pressure reduction and LVH regression are strongly

associated with reductions in cardiovascular events, it is likely that a losartan-based regimen is beneficial relative to placebo in Black patients.

In summary, the results of these additional analyses in Black and non-Black patients, did not reveal a biologic basis for the observed interaction with treatment. However, as indicated by the p-value for the test of interaction (p=0.005) between treatment and the dichotomized groups (Black and non-Black), this interaction is unlikely to have occurred by chance. Further, a test for qualitative interaction was also statistically significant (p=0.016). Therefore, based on the observed qualitative interaction, the benefits of losartan as seen in the LIFE study on cardiovascular morbidity and mortality in hypertensive patients with LVH, compared with atenolol, do not appear to apply to Black patients.

Table 13

Primary Composite Endpoint and Components of Primary Composite Endpoint by Black and Non-Black Patients

	Crude Rate						Kaplan-Meier Rates											
	Losartan (N=270)			Atenolol (N=263)			Losartan				Atenolol				Hazard‡	95% CI		
	Rate†	n	(%)	Rate†	n	(%)	1 Yr	2 Yr	3 Yr	4 Yr	1 Yr	2 Yr	3 Yr	4 Yr	Ratio	Low	Upper	p-Value§
Overall Black Patients																		
Composite	41.8	46	(17.0)	25.9	29	(11.0)	4.1	8.4	10.4	15.0	4.7	6.3	8.7	9.6	1.666	1.043	2.661	0.033 *
Components of Primary Composite Endpoint—Secondary Endpoints																		
Cardiovascular mortality	19.1	22	(8.1)	13.1	15	(5.7)	1.5	3.9	5.5	6.7	3.1	3.5	4.8	4.8	1.483	0.764	2.879	0.244
Stroke (fatal/nonfatal)	21.9	24	(8.9)	11.0	12	(4.6)	2.3	4.3	5.6	7.8	2.0	3.3	3.7	4.6	2.179	1.079	4.401	0.030 *
MI (fatal/nonfatal)	11.8	13	(4.8)	5.5	6	(2.3)	1.5	2.4	2.4	4.1	0.4	0.4	1.8	1.8	2.074	0.786	5.473	0.141
Overall Non-Black Patients																		
	Crude Rate						Kaplan-Meier Rates											
	Losartan (N=4335)			Atenolol (N=4325)			Losartan				Atenolol				Hazard‡	95% CI		
	Rate†	n	(%)	Rate†	n	(%)	1 Yr	2 Yr	3 Yr	4 Yr	1 Yr	2 Yr	3 Yr	4 Yr	Ratio	Low	Upper	p-Value§
Composite	22.8	462	(10.7)	28.0	559	(12.9)	2.2	4.6	6.2	8.5	3.0	5.3	7.8	10.3	0.829	0.733	0.938	0.003**
Components of Primary Composite Endpoint—Secondary Endpoints																		
Cardiovascular mortality	8.7	182	(4.2)	10.5	219	(5.1)	0.6	1.5	2.0	3.1	0.7	1.7	2.8	3.7	0.842	0.692	1.025	0.087
Stroke (fatal/nonfatal)	10.2	208	(4.8)	14.7	297	(6.9)	1.0	2.2	3.0	3.9	1.9	3.1	4.3	5.7	0.700	0.586	0.836	<0.001**
MI (fatal/nonfatal)	9.0	185	(4.3)	8.9	182	(4.2)	0.9	1.7	2.4	3.5	0.9	1.7	2.4	3.3	1.036	0.844	1.271	0.735

* p-Values <0.05.
** p-Values <0.01.
† Per 1000 patient-years of follow-up.
‡ Baseline LVH degree (Cornell product and Sokolow-Lyon) and baseline Framingham risk score are included in Cox proportional hazard model as covariates.
§ p-Values and estimates of hazard ratio of experiencing the endpoint on losartan compared with atenolol are based on Cox proportional hazard model.

3.5.4 Other Secondary Endpoints

3.5.4.1 Regression of Left Ventricular Hypertrophy (Including Time-Varying Covariates)

Another secondary endpoint was the regression of LVH as measured by ECG. Table 14 summarizes the mean changes for both Cornell voltage product and Sokolow-Lyon voltage from baseline to each scheduled visit at which an ECG was obtained. Regression of LVH was significantly greater in the losartan group at 6 months ($p<0.001$), the first on-treatment measurement, and continued to be significantly greater than that of atenolol throughout the study. At Year 4, the reduction from baseline in LVH as measured by Cornell voltage-duration product was 305.8 (10.9%) mm x msec in the losartan group and 162.0 (5.8%) mm x msec in the atenolol group ($p<0.001$), and Sokolow-Lyon voltage was reduced from baseline by 4.7 (15.8%) mm in the losartan group and 3.0 (10.0%) mm in the atenolol group ($p<0.001$).

Table 14

Mean Changes in ECG Measures of Estimated Left Ventricular Hypertrophy

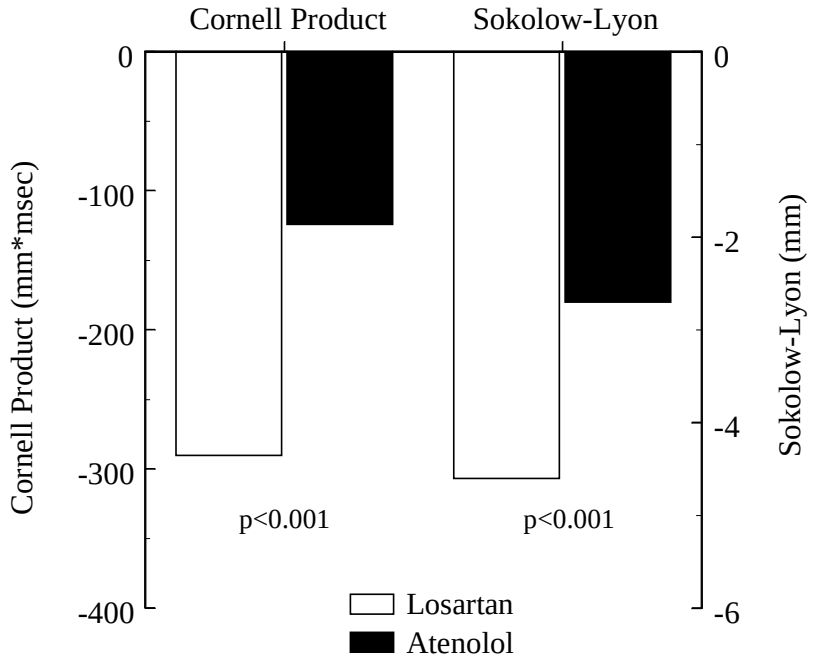
	Losartan (N=4605)				Atenolol (N=4588)				
		Mean				Mean			
	n	Baseline	Follow-up	Change	n	Baseline	Follow-up	Change	p-Value†
ECG Estimate of LVH (Cornell Product mm x msec)									
Month 6	3926	2826.4	2624.6	-201.8	3906	2804.7	2738.2	-66.6	<0.001**
Year 1	4079	2823.6	2568.1	-255.6	4042	2811.8	2702.6	-109.3	<0.001**
Year 2	3882	2817.9	2498.5	-319.4	3848	2813.5	2644.4	-169.1	<0.001**
Year 3	3731	2806.0	2492.1	-313.9	3633	2807.0	2635.6	-171.4	<0.001**
Year 4	3598	2813.4	2507.6	-305.8	3546	2797.7	2635.6	-162.0	<0.001**
Year 5	1365	2877.0	2549.9	-327.2	1365	2892.3	2710.1	-182.2	<0.001**
ECG Estimate of LVH (Sokolow-Lyon mm)									
Month 6	3964	30.0	27.4	-2.5	3960	29.9	29.2	-0.7	<0.001**
Year 1	4127	29.8	26.7	-3.1	4086	29.9	28.6	-1.3	<0.001**
Year 2	3929	29.8	25.9	-3.9	3909	29.9	27.8	-2.1	<0.001**
Year 3	3767	29.8	25.5	-4.3	3709	29.9	27.4	-2.6	<0.001**
Year 4	3638	29.8	25.1	-4.7	3596	29.9	26.9	-3.0	<0.001**
Year 5	1376	28.8	24.2	-4.6	1378	29.4	26.2	-3.2	<0.001**

** p-Values <0.01
† The p-values are based on Wilcoxon test.
n = Total number of patients with available data at each designated study time point.
ECG = electrocardiogram.
LVH = left ventricular hypertrophy.

At end of follow-up or at last visit before a primary endpoint occurred, Cornell product was reduced by 290 mm x msec in the losartan group (10.2%) and 124 mm x msec in the atenolol group (4.4%), and Sokolow-Lyon voltage was reduced by 4.6 mm in the losartan group (15.4%) and 2.7 mm in the atenolol group (9.0%) (Figure 9).

Figure 9

Change in Cornell Voltage-Duration Product and Sokolow-Lyon From Baseline to End of Follow-Up or Last Visit Before a Primary Endpoint Occurred



The relationship of LVH regression to the primary composite endpoint was explored by including both Cornell voltage product and Sokolow-Lyon voltage as time-varying covariates in a Cox regression model. Since the effects of LVH regression on outcome were similar for both treatment groups, the analysis was repeated using a model that included treatment as a standard covariate. Whether or not treatment group is included in the model, lower Cornell voltage duration and lower Sokolow-Lyon voltage were significantly associated with lower risk of the primary composite endpoint and each of the components. For the primary composite endpoint, the hazard ratio for Cornell voltage product was 1.016 (95% CI 1.011 to 1.021) per 100 mm x msec while the hazard ratio for Sokolow-Lyon voltage was 1.022 (95% CI 1.016 to 1.025) per 1 mm. This represented a significant 1.6% increase in the risk of a primary event for every 100 mm x

msec increase in Cornell Product. Accordingly, this also represented a significant 2.2% increase in the risk of an event for every mm increase in Sokolow-Lyon.

Next, the effect of losartan was evaluated in models including or excluding the LVH variables as time-varying covariates. For the composite endpoint, the adjusted hazard ratio in the time-varying covariate analysis was 0.902 (95% CI 0.801 to 1.106) while the hazard ratio for the primary analysis of the composite endpoint was 0.869 (95% CI 0.772 to 0.979). Similarly, when the same time-varying covariate analysis was applied to the components, the treatment effect was as follows: cardiovascular mortality adjusted HR was 0.936 [95% CI 0.775 to 1.130] compared with 0.886 [95% CI 0.734 to 1.069] for the primary analysis; stroke adjusted HR was 0.782 [95% CI 0.659 to 0.928] compared with 0.752 [95% CI 0.634 to 0.891] for the primary analysis; and myocardial infarction adjusted HR was 1.094 [95% CI 0.895 to 1.337] compared with 1.073 [95% CI 0.879 to 1.310] for the primary analysis. These data are consistent with a correlation between LVH and the risk of events, and suggest that regression of LVH explains a portion of the clinical benefit of losartan.

3.5.4.2 Adjudicated Secondary Endpoints: Total Mortality, Hospitalizations, Revascularization

Other prespecified secondary clinical endpoints that were analyzed included total mortality, hospitalization for angina (including probable myocardial infarction), hospitalization for heart failure, coronary revascularization and noncoronary arterial vascular surgery, and resuscitated cardiac arrest. These endpoints were based on positively adjudicated events by the ECC and the results are summarized in Table 15. None of the differences in these secondary endpoints were statistically significant between losartan and atenolol. Of note, the reduction in risk for the endpoint of total mortality directionally favored losartan (HR: 0.899 95% CI 0.783 to 1.031; p=0.128; relative risk reduction: 10.1%), largely due to a 35% benefit on stroke mortality. Note: There were 14 patients with resuscitated cardiac arrest events, 9 (0.2%) in the losartan group and 5 (0.1%) in the atenolol group. Because of the small number of patients with these events, survival analysis was not performed.

Although not adjudicated, silent myocardial infarction was also prespecified as a secondary clinical endpoint; however, a survival analysis was not performed for silent myocardial infarction because there were very few events (13 in the losartan group and 14 in the atenolol group) and because the time of the silent myocardial infarction events could not be accurately determined.

Table 15

Other Secondary Endpoints as Adjudicated by the Endpoint Classification Committee

	Crude Rate						Kaplan-Meier Rates											
	Losartan			Atenolol			Losartan				Atenolol							
	(N=4605)			(N=4588)											Hazard‡	95% CI		
	Rate†	n	(%)	Rate†	n	(%)	1 Yr	2 Yr	3 Yr	4 Yr	1 Yr	2 Yr	3 Yr	4 Yr	Ratio	Lower	Upper	p-Value§
Total mortality	17.3	383	(8.3)	19.6	431	(9.4)	1.2	2.8	4.4	6.3	1.3	2.7	4.9	6.7	0.899	0.783	1.031	0.128
Hospitalization due to angina (including probable MI)	7.4	160	(3.5)	6.6	141	(3.1)	1.1	1.8	2.5	2.9	0.9	1.5	2.0	2.7	1.155	0.921	1.449	0.212
Hospitalization due to heart failure	7.1	153	(3.3)	7.5	161	(3.5)	0.8	1.3	2.1	2.8	1.1	1.7	2.2	3.0	0.967	0.775	1.206	0.765
Coronary revascularization	7.8	169	(3.7)	7.8	168	(3.7)	0.9	1.5	2.2	3.1	0.5	1.3	2.1	2.9	1.022	0.826	1.265	0.841
Noncoronary arterial vascular surgery	4.7	102	(2.2)	6.0	129	(2.8)	0.5	0.9	1.3	1.8	0.3	1.0	1.6	2.3	0.809	0.624	1.049	0.110
Cardiac arrest, resuscitated‖		9	(0.2)		5	(0.1)												

† Per 1000 patient-years of follow-up.
‡ Baseline left ventricular hypertrophy degree (Cornell product and Sokolow-Lyon) and baseline Framingham risk score are included in Cox proportional hazard model as covariates.
§ The p-values and estimates of hazard ratio of experiencing the endpoint on losartan compared with atenolol are based on Cox proportional hazard model.
‖ Due to the small number of patients with resuscitated cardiac arrest events, survival analysis was not performed.

3.5.4.3 Mortality by Causes

The ECC classified each death according to whether or not it was cardiovascular and into more specific categories within the general subgroups. For 7 patients whose cause of death was unknown (4 patients in the losartan group and 3 patients in the atenolol group), death was ascribed to a non-cardiovascular cause. Differences between treatment groups were compared using a survival analysis model similar to the one used for the primary analysis. The results are summarized in Table 16. There were no significant differences between the 2 treatment groups with respect to total mortality, cardiovascular mortality, or noncardiovascular mortality. Note that the ECC did not specifically classify deaths as due to myocardial infarction. Rather, they used a classification of "coronary heart disease" death, which includes myocardial infarction and sudden cardiac death as well as coronary heart disease deaths that were not sudden. They further subclassified these deaths according to the time between the occurrence of symptoms and death: <1 hour, 1 to 24 hours, or >24 hours. For specific causes of death, there were fewer deaths caused by stroke in the losartan group, which is consistent with the analysis of the stroke component of the composite endpoint. The results for cause of death should be interpreted with caution because of the limited number of such events, and because there were multiple tests performed without adjustment for multiplicity.

Table 16

Mortality Results

	Crude Rate						Kaplan-Meier Rates											
	Losartan (N=4605)			Atenolol (N=4588)			Losartan				Atenolol				Hazard‡	95% CI		
	Rate†	n	(%)	Rate†	n	(%)	1 Yr	2 Yr	3 Yr	4 Yr	1 Yr	2 Yr	3 Yr	4 Yr	Ratio	Lower	Upper	p-Value§
Total mortality	17.3	383	(8.3)	19.6	431	(9.4)	1.18	2.81	4.37	6.25	1.29	2.71	4.90	6.73	0.899	0.783	1.031	0.128
Cardiovascular mortality	9.2	204	(4.4)	10.6	234	(5.1)	0.70	1.60	2.22	3.30	0.87	1.80	2.94	3.72	0.886	0.734	1.069	0.206
Coronary heart disease	5.6	125	(2.7)	5.6	124	(2.7)	0.46	1.10	1.46	2.09	0.46	0.95	1.67	2.04	1.026	0.800	1.316	0.839
Sudden death	3.7	81	(1.8)	4.4	97	(2.1)	0.31	0.68	0.89	1.32	0.35	0.73	1.32	1.59	0.852	0.634	1.144	0.287
<1 hour	1.8	40	(0.9)	2.0	45	(1.0)	0.20	0.35	0.40	0.70	0.26	0.46	0.71	0.83				
1 to 24 hours	1.9	41	(0.9)	2.4	52	(1.1)	0.11	0.33	0.49	0.63	0.09	0.27	0.61	0.77				
Non-sudden death																		
>24 hours	2.0	44	(1.0)	1.2	27	(0.6)	0.15	0.42	0.58	0.78	0.11	0.22	0.36	0.45				
Heart failure	0.7	16	(0.3)	0.8	17	(0.4)	0.00	0.04	0.16	0.23	0.07	0.07	0.18	0.27	0.987	0.498	1.956	0.971
Peripheral vascular disease	0.7	15	(0.3)	1.0	22	(0.5)	0.07	0.09	0.11	0.23	0.07	0.18	0.27	0.31	0.696	0.361	1.342	0.280
Stroke	1.8	40	(0.9)	2.8	62	(1.4)	0.15	0.31	0.45	0.68	0.24	0.55	0.76	1.03	0.647	0.434	0.962	0.032*
Other	0.4	8	(0.2)	0.4	9	(0.2)	0.02	0.07	0.07	0.11	0.04	0.07	0.09	0.11	0.912	0.351	2.366	0.850
Noncardiovascular	8.1	179	(3.9)	9.0	197	(4.3)	0.48	1.23	2.19	3.05	0.42	0.93	2.03	3.12	0.914	0.747	1.120	0.387
Accident/violent	0.3	6	(0.1)	0.4	8	(0.2)	0.00	0.04	0.07	0.11	0.04	0.04	0.11	0.11	0.745	0.258	2.148	0.586
Cancer	5.4	120	(2.6)	5.7	126	(2.7)	0.35	0.93	1.62	2.19	0.20	0.53	1.30	2.06	0.959	0.747	1.232	0.745
Infectious disease	0.6	14	(0.3)	0.9	19	(0.4)	0.02	0.07	0.09	0.16	0.04	0.09	0.13	0.23	0.742	0.372	1.479	0.396
Renal disease	0.1	3	(0.1)	0.2	4	(0.1)	0.00	0.00	0.05	0.07	0.00	0.02	0.05	0.07	0.744	0.166	3.325	0.698
Respiratory disease	0.5	10	(0.2)	0.5	12	(0.3)	0.02	0.07	0.18	0.18	0.04	0.07	0.13	0.20	0.833	0.360	1.928	0.669
Suicide	0.0	1	(0.0)	0.1	3	(0.1)	0.00	0.00	0.00	0.02	0.02	0.02	0.02	0.05	0.344	0.036	3.313	0.356
Other	1.1	25	(0.5)	1.1	25	(0.5)	0.09	0.13	0.20	0.34	0.07	0.16	0.29	0.43	1.007	0.578	1.752	0.981

* p-Values <0.05.
† Per 1000 patient-years of follow-up.
‡ Baseline left ventricular hypertrophy degree (Cornell product and Sokolow-Lyon) and baseline Framingham risk score are included in Cox proportional hazard model as covariates.
§ The p-values and estimates of risk reduction of experiencing the endpoint on losartan compared with atenolol are based on Cox proportional hazard model.

3.5.5 Patient Populations of Special Interest: Prespecified Analyses

Patients with diabetes, patients with ISH, and subsets according to the country of participation were prespecified as populations of special interest; the primary composite endpoint and a predefined subset of secondary endpoints were evaluated for these groups.

3.5.5.1 Diabetes Mellitus Patients

The baseline systolic/diastolic blood pressures for patients who were diabetic at baseline (defined as patients with a secondary diagnosis of diabetes mellitus, insulin-dependent diabetes mellitus, or type 2 diabetes mellitus) were similar in the 2 treatment groups: 176.5/96.6 mm Hg in the losartan group versus 176.7/95.8 mm Hg in the atenolol group. Reductions in blood pressure from baseline to primary endpoint or end of study were also similar in the 2 treatment groups. Systolic pressure fell by 30.7 mm Hg to 145.8 mm Hg in the losartan group and by 28.4 mm Hg to 148.3 mm Hg in the atenolol group (p=NS for between-treatment-group change from baseline). Diastolic pressure fell by 17.4 mm Hg to 79.2 mm Hg in the losartan group and by 16.6 mm Hg to 79.2 mm Hg in the atenolol group (p=NS). Regression of LVH was significantly greater in the losartan group at 6 months ($p<0.001$), the first on-treatment measurement, and continued to be significantly greater than that of atenolol throughout the study. At Year 4, the reduction from baseline in LVH as measured by Cornell voltage-duration product was 252.3 mm x msec in the losartan group and 75.1 mm x msec in the atenolol group ($p<0.001$), and Sokolow-Lyon voltage was reduced from baseline by 3.9 mm in the losartan group and 2.4 mm in the atenolol group ($p<0.001$).

Table 17 summarizes the results for diabetic patients. The overall rate of the primary endpoint was increased in patients with diabetes regardless of treatment. In diabetic patients, losartan significantly reduced the risk of the primary composite endpoint of cardiovascular morbidity and mortality (including adjustment for baseline measures of LVH and Framingham risk score as covariates) by 24.5% (HR: 0.755 [95% CI 0.585 to 0.975], p=0.031). The risk of cardiovascular mortality was 36.6% lower in the losartan group than in the atenolol group (HR: 0.634 [95% CI 0.422 to 0.951], p=0.028). The risks of stroke (HR: 0.788 [95% CI 0.546 to 1.138], p=0.204; relative risk reduction: 21.2%) and myocardial infarction (HR: 0.829 [95% CI 0.548 to 1.253], p=0.373; relative risk reduction: 17.1%) were not significantly different between the treatment groups, but directionally favored the losartan group. Total mortality was 38.7% lower (HR: 0.613 [95% CI 0.448 to 0.839], p=0.002) in the losartan group. The risk of hospitalization for heart failure was 40.6% lower in the losartan group (HR: 0.594 [95% CI 0.384 to 0.919], p=0.019). The risk of hospitalization due to angina was not different between treatment groups. These data demonstrate that the benefit of losartan seen in the overall patient population also applies to this high-risk group of diabetic patients.

Table 17

Clinical Endpoint Results—Diabetic Patients

	Crude Rate						Kaplan-Meier Rates								Hazard‡	95% CI		p-Value§
	Losartan (N=586)			Atenolol (N=609)			Losartan				Atenolol							
	Rate†	n	(%)	Rate†	n	(%)	1 Yr	2 Yr	3 Yr	4 Yr	1 Yr	2 Yr	3 Yr	4 Yr	Ratio	Lower	Upper	
Composite	39.2	103	(17.6)	53.6	139	(22.8)	3.9	7.9	9.5	14.5	6.6	9.3	14.2	18.1	0.755	0.585	0.975	0.031*
Cardiovascular mortality	13.6	38	(6.5)	21.8	61	(10.0)	0.9	1.4	2.1	4.8	1.5	3.0	5.4	6.8	0.634	0.422	0.951	0.028*
Stroke (fatal/nonfatal)	19.0	51	(8.7)	24.5	65	(10.7)	2.2	4.7	5.4	7.6	3.7	4.9	6.8	8.8	0.788	0.546	1.138	0.204
MI (fatal/nonfatal)	15.2	41	(7.0)	18.7	50	(8.2)	1.6	2.6	3.3	5.0	2.5	3.2	5.5	7.4	0.829	0.548	1.253	0.373
Total mortality	22.5	63	(10.8)	37.2	104	(17.1)	1.5	2.2	4.7	7.8	2.6	4.9	8.6	11.6	0.613	0.448	0.839	0.002**
Hospitalization due to angina	11.1	30	(5.1)	11.1	30	(4.9)	1.7	2.4	3.2	4.3	1.3	1.9	2.8	4.4	1.058	0.637	1.759	0.828
Hospitalization due to heart failure	11.8	32	(5.5)	20.7	55	(9.0)	1.0	2.3	3.5	4.8	2.5	4.6	6.5	8.4	0.594	0.384	0.919	0.019*

* p-Values <0.05.
** p-Values <0.01.
† Per 1000 patient-years of follow-up.
‡ Baseline left ventricular hypertrophy degree (Cornell product and Sokolow-Lyon) and baseline Framingham risk score are included in Cox proportional hazard model as covariates.
§ The p-values and estimates of hazard ratio of experiencing the endpoint on losartan compared with atenolol are based on Cox proportional hazard model.

3.5.5.2 Isolated Systolic Hypertension Patients

In patients with ISH (defined as baseline SBP≥160 and DBP<90 mm Hg), baseline systolic/diastolic blood pressures were similar in the 2 treatment groups: 174.2/83.0 mm Hg in the losartan group versus 174.4/82.3 mm Hg in the atenolol group. Reductions in blood pressure from baseline to primary endpoint or end of study were also similar in the 2 treatment groups. Systolic pressure fell by 28.4 mm Hg to 145.9 mm Hg in the losartan group and by 28.1 mm Hg to 146.3 mm Hg in the atenolol group (p=NS for between-treatment-group change from baseline). Diastolic pressure fell by 8.5 mm Hg to 74.5 mm Hg in the losartan group and by 8.9 mm Hg to 73.5 mm Hg in the atenolol group (p=NS). Regression of LVH was significantly greater in the losartan group at 6 months (p=0.001), the first on-treatment measurement, and continued to be significantly greater than that of atenolol throughout the study. At Year 4, the reduction from baseline in LVH as measured by Cornell voltage-duration product was 241.1 mm x msec in the losartan group and 122.0 mm x msec in the atenolol group (p=0.003), and Sokolow-Lyon voltage was reduced from baseline by 4.5 mm in the losartan group and 2.7 mm in the atenolol groups (p<0.001).

The endpoint results for the patients with baseline ISH (SBP ≥160 and DBP <90) are summarized in Table 18. The overall rate of the primary endpoint was increased in patients with ISH at baseline. In patients with ISH, the difference between the 2 treatment groups for the primary composite (including adjustment for baseline measures of LVH and Framingham risk score as covariates) approached significance (HR: 0.750 [95% CI 0.557 to 1.011], p=0.059; relative risk reduction: 25.0%); it is worth noting that the hazard ratio for the composite endpoint is lower in patients with ISH than in the overall population (ISH-HR: 0.750 versus overall population-HR: 0.869). Losartan significantly reduced the risk of cardiovascular mortality (HR: 0.543 [95% CI 0.340 to 0.867], p=0.010; relative risk reduction: 45.7%) and stroke (HR: 0.595 [95% CI 0.385 to 0.921], p=0.020; relative risk reduction: 40.5%). The risk of myocardial infarction was not significantly different between the 2 treatment groups (HR: 0.890 [95% CI 0.550 to 1.442], p=0.637; relative risk reduction: 11.0%). Losartan also significantly reduced the risk of total mortality (HR: 0.725 [95% CI 0.528 to 0.995], p=0.046; relative risk reduction: 27.5%) in ISH patients relative to atenolol. The risks of hospitalization due to angina and heart failure were not different between the 2 treatment groups. The findings in the ISH patients are consistent with the results observed in the overall population for the primary endpoint.

Table 18

Clinical Endpoint Results—Isolated Systolic Hypertension

	Crude Rate						Kaplan-Meier Rates											
	Losartan (N=660)			Atenolol (N=666)			Losartan				Atenolol				Hazard‡	95% CI		
	Rate†	n	(%)	Rate†	n	(%)	1 Yr	2 Yr	3 Yr	4 Yr	1 Yr	2 Yr	3 Yr	4 Yr	Ratio	Lower	Upper	p-Value§
Composite	25.1	75	(11.4)	35.4	104	(15.6)	2.6	5.4	7.6	9.8	4.8	7.4	11.3	13.2	0.750	0.557	1.011	0.059
Cardiovascular mortality	8.7	27	(4.1)	16.9	52	(7.8)	0.8	1.5	2.9	3.7	1.7	2.9	4.7	6.0	0.543	0.340	0.867	0.010*
Stroke (fatal/nonfatal)	10.6	32	(4.8)	18.9	56	(8.4)	1.4	2.3	3.0	3.5	3.3	4.9	6.5	7.3	0.595	0.385	0.921	0.020*
MI (fatal/nonfatal)	10.2	31	(4.7)	11.9	36	(5.4)	1.1	2.3	3.0	4.3	1.5	2.1	3.7	4.2	0.890	0.550	1.442	0.637
Total mortality	21.2	66	(10.0)	30.2	93	(14.0)	1.5	3.5	6.7	8.8	2.4	4.4	8.2	10.3	0.725	0.528	0.995	0.046*
Hospitalization due to angina	11.3	34	(5.2)	7.6	23	(3.5)	1.8	2.6	3.6	4.4	0.8	1.1	2.4	3.2	1.475	0.868	2.507	0.151
Hospitalization due to heart failure	8.5	26	(3.9)	13.3	40	(6.0)	0.9	1.7	2.7	3.5	1.5	2.4	3.9	5.4	0.665	0.405	1.093	0.107

* p-Values <0.05.
† Per 1000 patient-years of follow-up.
‡ Baseline left ventricular hypertrophy degree (Cornell product and Sokolow-Lyon) and baseline Framingham risk score are included in Cox proportional hazard model as covariates.
§ The p-values and estimates of hazard ratio of experiencing the endpoint on losartan compared with atenolol are based on Cox proportional hazard model.

3.5.5.3 Country of Participation

Table 19 shows the number of patients enrolled in each of the 7 participating countries. Figure 10 shows the hazard ratio for the primary composite endpoint by country. There were no significant interactions between treatment and country for the primary composite and the prespecified group of secondary endpoints.

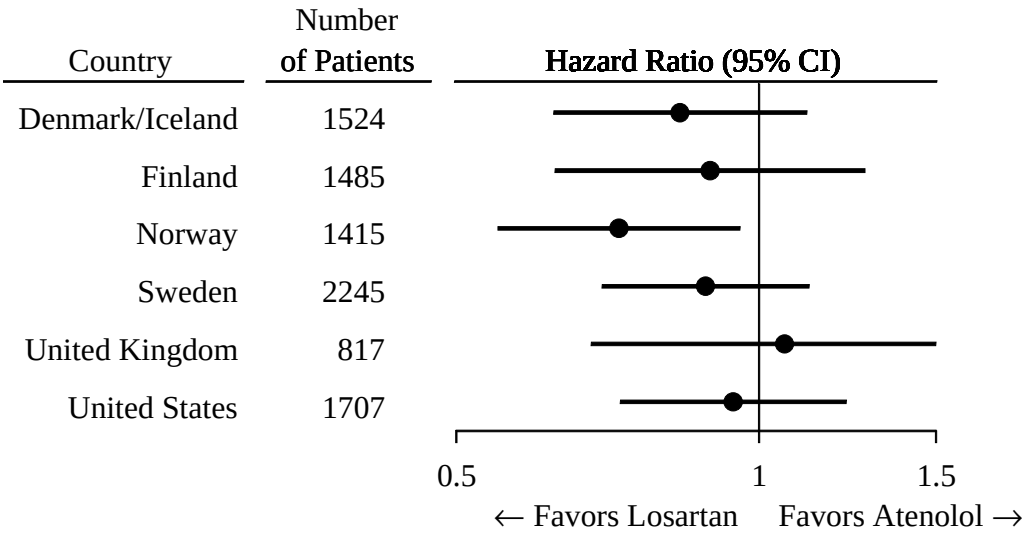
Table 19

Patient Recruitment—by Country

	n Losartan	n Atenolol	n Country	(%)
Denmark	692	699	1391	(15.1)
Iceland	65	68	133	(1.4)
Finland	748	737	1485	(16.2)
Norway	714	701	1415	(15.4)
Sweden	1112	1133	2245	(24.4)
United Kingdom	405	412	817	(8.9)
United States	869	838	1707	(18.6)

Figure 10

Hazard Ratios for the Primary Composite Endpoint by Country



3.5.6 Blood Pressure Parameters as Time-Varying Covariates on Cardiovascular Morbidity and Mortality

Although blood pressure was similar in the 2 treatment groups (the time-averaged difference between groups in systolic blood pressure was 1.2 mm Hg favoring losartan, and in diastolic blood pressure was 0.8 mm Hg favoring atenolol), analyses were performed to evaluate whether the small observed blood pressure differences during follow-up had an effect on the clinical endpoint. Systolic, diastolic, and pulse pressures were each included in separate time-varying covariate models. In each of the time-varying covariate models, the treatment effect on the risk of the primary composite endpoint and the individual components was consistent with the primary results after controlling for blood pressure differences between the groups. The adjusted hazard ratios for the primary composite endpoint were 0.861 (when including systolic as a time-varying covariate), 0.858 (when including diastolic as a time-varying covariate), and 0.871 (when including pulse pressure as a time-varying covariate). The adjusted hazard ratios for the cardiovascular death component were 0.866 (when including systolic as a time-varying covariate), 0.879 (when including diastolic as a time-varying covariate), and 0.876 (when including pulse pressure as a time-varying covariate). The adjusted hazard ratios for the stroke component were 0.755 (when including systolic as a time-varying covariate), 0.741 (when including diastolic as a time-varying covariate), and 0.765 (when including pulse pressure as a time-varying covariate). The adjusted hazard ratios for the myocardial infarction component were 1.063 (when including systolic as a time-varying covariate), 1.062 (when including diastolic as a time-varying covariate), and 1.083 (when including pulse pressure as a time-varying covariate). These data would support the position that the benefit of losartan relative to atenolol on endpoints is not explained by the differential effects of the 2 agents on blood pressure. Overall, the results of the blood pressure analyses demonstrate small differences between the treatment groups. While the importance of these differences is impossible to quantify, they do not appear to account for the differences in outcomes between the treatment groups.

3.5.7 Echocardiographic Substudy Results

There are various methods for diagnosing LVH based on both electrocardiographic and echocardiographic criteria. The ECG is a readily accessible diagnostic tool; however, the echocardiogram has emerged as the accepted standard in the assessment of LVH.

Both the ECG and echocardiogram have high specificity but differ in sensitivity. Sokolow-Lyon criteria have 22% sensitivity with a 79% specificity [57]. The Cornell method has a reported sensitivity of 31% with a specificity of 87% [57]. In comparison to ECG criteria, echocardiographic criteria are deemed more reliable due to their ability to detect LVH with a sensitivity of 85 to 100% [57].

A total of 965 patients from 47 sites from all participating countries were enrolled in the LIFE Echocardiographic Substudy (losartan [n=481] and atenolol [n=484]). LVH was measured as left ventricular mass index (LVMI) at baseline and annually. The primary objectives of the Echocardiographic Substudy were to: (1) investigate whether losartan

reduced LVMI more effectively than atenolol independent of blood pressure lowering; and (2) whether the clinical endpoint as defined in the main study was affected by LVH lowering, independent of antihypertensive treatment and blood pressure values during follow-up.

Demographic characteristics and baseline vital signs for patients participating in the Echocardiographic Substudy were similar between the losartan and atenolol groups. The mean age for substudy patients was ~66 years in each treatment group. Approximately 58% (losartan) and 59% (atenolol) of the patients were men, and 84% (losartan) and 83% (atenolol) were White. This represents fewer female patients and fewer White patients than the population in the main study. Baseline vital signs including sitting systolic and diastolic blood pressure, pulse rate, height, weight, and body surface area were similar between the treatment groups.

Table 20 summarizes the primary results for the substudy. The reduction in LVMI at Year 4 and last visit was significantly greater in the losartan group than in the atenolol group and the effect was independent of blood pressure values during the follow-up. The analysis from the last available echocardiographic showed a decrease from baseline of 21.7 g/m^2 in the losartan group and 17.7 g/m^2 in the atenolol groups (p=0.011).

In addition, when pooling both treatment arms, lower LVMI was associated with a lower risk of a clinical endpoint, independent of blood pressure levels at baseline and during follow-up. The hazard ratio for the composite endpoint was 1.010 with a 95% confidence interval of 1.002 to 1.017, p=0.009. This represented a significant 1% greater risk of an event for every 1 g/m^2 greater LVMI during the trial.

Table 20

Change in Echocardiographic Left Ventricular Mass Index (LVMI)

	Losartan				Atenolol				Primary Mixed Model p-Value[†]	Adjusted Mixed Model p-Value[‡]
		Mean				Mean				
	N	Pre	Post	Change	N	Pre	Post	Change		
LV Mass Index (g/m^2)										
Year 1	414	124.6	108.7	-15.9	411	122.0	109.0	-13.0	0.096	0.126
Year 2	380	124.7	102.8	-21.8	375	121.6	103.3	-18.3	0.071	0.083
Year 3	361	124.4	102.2	-22.2	353	121.5	102.9	-18.5	0.060	0.086
Year 4	333	123.4	99.3	-24.1	345	122.0	101.6	-20.4	0.020*	0.033*
Year 5	171	122.8	99.2	-23.6	159	118.4	99.3	-19.1	0.242	0.380
Last	457	124.6	102.9	-21.7	459	122.5	104.8	-17.7	0.011*	0.027*
									Primary Mixed Model (Repeated) p-Value[§]	Adjusted Mixed Model (Repeated) p-Value[‖]
LV Mass Index (g/m^2)										
Over All Visits	1659	124.1	103.1	-21.1	1647	121.4	103.9	-17.5	0.013*	0.016*

* p-Values <0.05.
[†] Model includes treatment as main effect with baseline LVMI and baseline blood pressure as covariates.
[‡] Model with additional annual blood pressure measured at time of latest echocardiogram.
[§] Mixed Model with repeated measures includes all measurements of LVMI changes for each patient.
[‖] Mixed Model with repeated measures includes all measurements of LVMI changes and blood pressure values for each patient.

As a result of the positive qualitative interaction on the risk of an event between Black and non-Black patients in the main study, post hoc exploratory analyses of the Echocardiographic Substudy by ethnic background were performed. The subgroups of the Echocardiographic Substudy population evaluated included: all patients (losartan: 481 and atenolol: 484), all Black patients (losartan: 68 and atenolol: 71), all non-Black patients (losartan: 413 and atenolol: 413), all U.S. patients (losartan: 119 and atenolol: 127), and U.S. non-Black patients (losartan: 51 and atenolol: 56). Note that all Black patients in the Echocardiographic Substudy were enrolled in the United States. These subgroups within the Echocardiographic Substudy were analyzed for patterns in the effect of treatment on the primary composite endpoint, the components of the primary composite endpoint, and changes in LVMI, blood pressure, heart rate, and ECG-LVH measurements from baseline. With only 965 patients, the substudy was underpowered to detect any effect on these parameters.

In contrast to the overall result of the Echocardiographic Substudy, Black patients in the atenolol group experienced a numerically greater LVMI reduction compared with patients in the losartan group. In the overall Black population, the analysis from the last available echocardiographic showed a decrease from baseline of 15.56 g/m^2 in the losartan group and 19.04 g/m^2 in the atenolol group (p=NS). Non-Black patients overall had greater reduction in LVMI on losartan (22.67 g/m^2) than atenolol (17.51 g/m^2) as did U.S. non-Black patients (on losartan 19.36 versus on atenolol 16.46 g/m^2).

However, as reviewed previously in Section III.3.5.3.4, a similar pattern of change in the ECG measures of LVH (Cornell product and Sokolow-Lyon voltage) was seen in Black and non-Black Echocardiographic Substudy patients, and was consistent with the results in Black and non-Black patients in the main LIFE population; the reduction of ECG-LVH was greater in the losartan group. The differences between the measures of LVH by ECG and echocardiography in the Black patients, and their relationship to clinical events, is not well understood. Changes in blood pressure and heart rate from baseline in Black and non-Black Echocardiographic Substudy patients were similar to the reductions noted in the overall study population.

In summary, the Echocardiographic substudy showed that independent of blood pressure reduction, there were greater reductions in LVMI with losartan than with atenolol. This finding is consistent with LVH regression assessed by ECG measurements.

3.5.8 Summary of Efficacy Results

The findings in this trial clearly indicate that losartan offers cardiovascular protection by reducing the risk of cardiovascular morbidity (defined as stroke and myocardial infarction) and mortality compared with atenolol in patients with hypertension and LVH. The risk reduction is largely due to the benefit of losartan in reducing stroke. The incidence of cardiovascular death, although not significantly different, directionally favored losartan. The incidence of myocardial infarction did not significantly differ between treatment groups. Losartan did not significantly differ from atenolol in the rate of all-cause mortality, hospitalization for heart failure or angina pectoris, coronary or

peripheral revascularization procedures, or resuscitated cardiac arrest. Consistent with the hypothesis of the trial, losartan reduced LVH relative to atenolol and this may partially explain the reduction of cardiovascular morbidity and mortality with losartan relative to atenolol. However, it is possible that other as yet undefined mechanisms account for some of the differences between treatments. In the demographic, geographic, disease history, and disease severity subgroups assessed, the treatment benefit of losartan on the primary composite endpoint was consistent as evidenced by the lack of significant treatment-by-subgroup interaction; however, in the predefined subgroup analyses, there was a suggestion of an interaction between ethnic background and treatment. Based on the observed qualitative interaction, the benefits of losartan seen in the LIFE study do not appear to apply to Black patients with hypertension and LVH.

3.6 Summary of Safety

3.6.1 Summary of Adverse Experiences

Adverse event data were collected throughout the follow-up period. All adverse experience categories (Clinical, Laboratory, Other examinations) were reported on a single case report form and were analyzed as one overall category. Study clinical endpoints, death, stroke, myocardial infarction, hospitalization for angina pectoris and heart failure, coronary revascularization, noncoronary arterial vascular surgery, and resuscitated cardiac arrest were not reported as adverse experiences from the time of randomization through the endpoint cutoff date of 16-Sep-2001. The one exception was noncardiovascular death, which was reported both as an endpoint and a serious adverse experience. Since patients who discontinued blinded study medication often took another antihypertensive medication that had its own set of potential adverse experiences, the adverse experiences that occurred during the period following discontinuation would tend to obscure the true differences between losartan and atenolol. For this reason, the adverse experience results summarized below do not include adverse experiences that occurred more than 14 days after the patient discontinued study medication or more than 14 days after the start of a gap in study therapy.

Table 21 provides a summary of the overall adverse experiences. The treatment groups were compared with respect to the percentage of patients with any adverse experience, with any drug-related adverse experience, with any serious adverse experience, and those who discontinued due to an adverse experience. Risk differences, confidence intervals, and p-values for a test of the difference between treatments are included. Additional categories are summarized but no statistical tests were performed. Most patients in the study experienced at least one adverse experience during the adverse experience reporting period previously described and the proportion of patients with any adverse experience was similar between the 2 groups (losartan: 94.7% versus atenolol: 95.0%, p=0.481).

Table 21

Overall Adverse Experiences

	Losartan (N=4605)		Atenolol (N=4588)		Losartan – Atenolol			
					Risk	95% CI		
	n	(%)	n	(%)	Difference	Lower	Upper	p-Values†
Number (%) of patients:								
with one or more adverse experiences	4359	(94.7)	4358	(95.0)	-0.0033	-0.0123	0.0058	0.481
with no adverse experience	246	(5.3)	230	(5.0)	0.0033	-0.0058	0.0123	
with drug-related adverse experiences‡	1715	(37.2)	2073	(45.2)	-0.0794	-0.0995	-0.0594	<0.001**
with serious adverse experiences	1715	(37.2)	1660	(36.2)	0.0106	-0.0091	0.0303	0.299
with serious drug-related adverse experiences	139	(3.0)	159	(3.5)	-0.0045	-0.0117	0.0028	
who died	122	(2.6)	118	(2.6)	0.0008	-0.0057	0.0073	
discontinued due to adverse experiences	604	(13.1)	831	(18.1)	-0.0500	-0.0648	-0.0352	<0.001**
discontinued due to drug-related adverse experiences	281	(6.1)	493	(10.7)	-0.0464	-0.0578	-0.0351	
discontinued due to serious adverse experiences	177	(3.8)	210	(4.6)	-0.0073	-0.0155	0.0009	
discontinued due to serious drug-related adverse experiences	24	(0.5)	52	(1.1)	-0.0061	-0.0098	-0.0024	

** p-Values <0.01.
† p-Values are based on Fisher's exact test.
‡ Possibly, probably, or definitely drug related as assessed by the investigator.

3.6.1.1 Most Common and Prespecified Adverse Experiences

Adverse experiences with a frequency of more than 5% in at least one treatment group and with a difference of 1% or greater between the groups included albuminuria (losartan: 4.6% versus atenolol: 6.4%), hyperglycemia (losartan: 5.2% versus atenolol: 6.5%), asthenia/fatigue (losartan: 15.0% versus atenolol: 17.5%), palpitation (losartan: 5.5% versus atenolol: 3.2%), peripheral vascular disorder (losartan: 3.7% versus atenolol: 5.6%), back pain (losartan: 12.3% versus atenolol: 10.4%), chest pain (losartan: 11.3% versus atenolol: 10.1%), dyspnea (losartan: 9.9% versus atenolol: 14.1%), lower extremity edema (losartan: 11.7% versus atenolol: 13.9%) and pneumonia (losartan: 4.7% versus atenolol: 5.9%).

A group of adverse experiences was prespecified as being of particular interest: angioedema, bradycardia, sleep disturbance, hypotension, dizziness, sexual dysfunction, cold extremities, cough, and cancer. Significantly more patients in the atenolol group experienced bradycardia (losartan: 1.4% versus atenolol: 8.5%, p=<0.001), cold extremities (losartan: 3.9% versus atenolol: 5.9%, p=<0.001) and sexual dysfunction (losartan: 3.6% versus atenolol: 4.7%, p=0.009). Significantly more losartan patients experienced hypotension (losartan: 121 (2.6%) versus atenolol:

75 (1.6%), p=0.001). Approximately 10% of these patients (losartan: 13 versus atenolol: 7) had hypotension that was considered serious and the incidence of serious adverse experiences of hypotension did not differ between treatment groups. There were no differences in the frequency of angioedema (losartan: 0.1% versus atenolol: 0.2%), sleep disturbance (losartan: 0.7% versus atenolol: 0.8%), dizziness (losartan: 16.7% versus atenolol: 15.8%), cough (losartan: 2.9% versus atenolol: 2.5%), or cancer (losartan: 7.8% versus atenolol: 7.0%) between the treatment groups.

3.6.1.2 Drug-Related Adverse Experiences

Table 22 presents the number and percent of patients with specific drug-related adverse experiences (incidence ≥0.5% in 1 or more treatment groups) by body system. There were significantly fewer patients in the losartan group with drug-related adverse experiences (i.e., definitely, probably, or possibly drug related as assessed by the investigator) (losartan: 37.2% versus atenolol: 45.2%, p<0.001). The most common drug-related adverse experiences in the losartan group included dizziness (5.3%), asthenia/fatigue (5.0%), and vertigo (3.1%). The most common drug-related adverse experiences in the atenolol group included asthenia/fatigue (8.7%), bradycardia (6.4%), and dizziness (5.3%).

Table 22

Number (%) of Patients With Specific Drug-Related† Adverse Experiences (Incidence ≥0.5% in One or More Treatment Groups) by Body System

	Losartan (N=4605)		Atenolol (N=4588)	
	n	(%)	n	(%)
Patients with one or more drug-related† adverse experiences	1715	(37.2)	2073	(45.2)
Patients with no drug-related adverse experience	2890	(62.8)	2515	(54.8)
Body as a Whole/Site Unspecified	**727**	**(15.8)**	**879**	**(19.2)**
Asthenia/fatigue	228	(5.0)	401	(8.7)
Chest pain	40	(0.9)	37	(0.8)
Dizziness	244	(5.3)	243	(5.3)
Drug overdose	82	(1.8)	65	(1.4)
Edema	12	(0.3)	32	(0.7)
Lower extremity edema	63	(1.4)	77	(1.7)
Perspiration	18	(0.4)	28	(0.6)
Syncope	36	(0.8)	50	(1.1)
Cardiovascular System	**419**	**(9.1)**	**712**	**(15.5)**
Bradycardia	35	(0.8)	292	(6.4)
Hypotension	34	(0.7)	22	(0.5)
Intermittent claudication	16	(0.3)	25	(0.5)
Orthostatic hypotension	26	(0.6)	22	(0.5)
Palpitation	58	(1.3)	32	(0.7)
Peripheral vascular disorder	133	(2.9)	211	(4.6)
Sinus bradycardia	7	(0.2)	33	(0.7)
Tachycardia	29	(0.6)	15	(0.3)
Digestive System	**184**	**(4.0)**	**225**	**(4.9)**
Diarrhea	33	(0.7)	40	(0.9)
Dry mouth	30	(0.7)	39	(0.9)
Dyspepsia	7	(0.2)	24	(0.5)
Nausea	56	(1.2)	70	(1.5)
Endocrine System	**27**	**(0.6)**	**34**	**(0.7)**
Eyes, Ears, Nose, and Throat	**65**	**(1.4)**	**77**	**(1.7)**
Metabolism and Nutrition	**231**	**(5.0)**	**281**	**(6.1)**
Alanine aminotransferase increased	16	(0.3)	23	(0.5)
Hyperglycemia	15	(0.3)	28	(0.6)
Hyperuricemia	10	(0.2)	29	(0.6)
Hypokalemia	43	(0.9)	62	(1.4)
Serum creatinine increased	60	(1.3)	36	(0.8)
Uric acid increased	44	(1.0)	72	(1.6)
Musculoskeletal System	**142**	**(3.1)**	**190**	**(4.1)**
Gout	16	(0.3)	36	(0.8)
Muscular cramp	27	(0.6)	19	(0.4)
Muscular weakness	30	(0.7)	81	(1.8)

Table 22 (Cont.)

Number (%) of Patients With Specific Drug-Related† Adverse Experiences
(Incidence ≥0.5% in One or More Treatment Groups) by Body System

	Losartan (N=4605)		Atenolol (N=4588)	
	n	(%)	n	(%)
Nervous System	**370**	**(8.0)**	**401**	**(8.7)**
Dream abnormality	20	(0.4)	26	(0.6)
Headache	125	(2.7)	131	(2.9)
Insomnia	29	(0.6)	36	(0.8)
Vertigo	141	(3.1)	157	(3.4)
Psychiatric Disorder	**66**	**(1.4)**	**69**	**(1.5)**
Depression	28	(0.6)	26	(0.6)
Respiratory System	**191**	**(4.1)**	**327**	**(7.1)**
Cough	57	(1.2)	39	(0.9)
Dyspnea	106	(2.3)	235	(5.1)
Skin and Skin Appendages	**91**	**(2.0)**	**120**	**(2.6)**
Eczematous dermatitis	15	(0.3)	23	(0.5)
Rash	21	(0.5)	28	(0.6)
Urogenital System	**156**	**(3.4)**	**205**	**(4.5)**
Albuminuria	24	(0.5)	37	(0.8)
Impotence	51	(1.1)	86	(1.9)

† Possibly, probably, or definitely drug related as assessed by the investigator.
Although a patient may have had 2 or more drug-related adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

3.6.1.3 Serious Adverse Experiences

The difference between groups with respect to serious adverse experiences was not significant (losartan: 37.2% versus atenolol: 36.2%, p=0.299). The most common serious adverse experiences included atrial fibrillation (losartan: 2.1% versus atenolol: 2.0%), pneumonia (losartan: 1.6% versus atenolol: 2.1%), drug overdose (losartan: 1.9% versus atenolol: 1.4%), basal cell carcinoma (losartan: 1.4% versus atenolol: 1.3%), syncope (losartan: 1.3% versus atenolol: 1.1%), and cholelithiasis (losartan: 1.1% versus atenolol: 1.0%).

3.6.1.4 Discontinuations Due to Adverse Experiences

There were significantly fewer patients in the losartan group with adverse experiences that resulted in discontinuation of study drug (losartan: 13.1% versus atenolol: 18.1%, p<0.001). The most common adverse experiences leading to discontinuation included asthenia/fatigue (losartan: 0.7% versus atenolol: 1.7%), bradycardia (losartan: 0.2% versus atenolol: 2.7%), and dyspnea (losartan: 0.5% versus atenolol: 1.7%).

3.6.2 Adverse Experiences in Special Populations

3.6.2.1 Analysis of Adverse Experiences by Age

The proportions of patients with any adverse experience was similar between the 2 treatment groups in all age categories and, as expected, patients in the ≥65-year-old age category experienced more serious adverse experiences than younger patients. There were fewer patients in the losartan group across all age categories with drug-related adverse experiences and with adverse experiences that resulted in discontinuation of study drug.

3.6.2.2 Analysis of Adverse Experiences by Gender

Proportions of patients with any adverse experience were similar between the 2 treatment groups in both male (losartan: 93.6% versus atenolol: 94.1%) and female populations (losartan: 95.6% versus atenolol: 95.7%). As in the overall population, fewer male and female patients in the losartan group experienced drug-related adverse experiences and study drug discontinuations related to adverse experiences.

3.6.2.3 Analysis of Adverse Experiences by Ethnic Background

White patients in the losartan treatment group experienced fewer drug-related adverse experiences (losartan: 37.2% versus atenolol: 45.6%) and study drug discontinuations related to adverse experiences (losartan: 13.0% versus atenolol: 18.4%) compared with White patients in the atenolol treatment group. White patients comprised 92.5% of the overall population. This trend is similar for other ethnic backgrounds except for Black patients. Black patients who comprised 5.8% of the overall patient population had a similar rate of drug-related adverse experiences (losartan: 38.9% versus atenolol: 39.5%) between groups, whereas study drug discontinuations related to adverse experiences occurred less in the atenolol group (losartan: 15.6% versus atenolol: 12.9%). Serious adverse experiences occurred more frequently in Black patients in the losartan group (40.0%) than in the atenolol group (28.1%); however, the rate of serious adverse experiences in the losartan group was similar to that observed in the overall losartan population (40.0% in losartan-treated Black patients versus 37.2% in all losartan-treated patients).

3.6.3 Clinical Evaluation of Laboratory Safety Tests

As with all safety data, the analysis of laboratory data only included values obtained on study drug or within 14 days of study therapy interruption or discontinuation.

3.6.3.1 Changes in Laboratory Measures (Predefined Limits of Change)

The number and proportion of patients with changes in laboratory values outside predefined limits of change were summarized by treatment group. All patients with a valid prestudy value and a valid poststudy value were included in the analysis and all changes from baseline to any valid treatment value were considered. Statistical significance of differences between treatment groups was not assessed. A summary of the patients with values exceeding predefined limits is included in Table 23. A larger

proportion of patients with a change in uric acid above the predefined limit of change (>60 μmol/L or >1.0 mg/dL) was observed in the atenolol group (67.2%) than in the losartan group (41.7%). There also was a greater proportion of patients with glucose values above the predefined limit of change (>3.33 mmol/L or >60 mg/dL) in the atenolol group (13.3%) than in the losartan group (10.1%). The proportion of patients with a serum creatinine value above the predefined limit of change (>35 μmol/L or >0.40 mg/dL) was larger in the losartan group (10.5%) than in the atenolol group (8.6%).

Table 23

Patients Exceeding Predefined Limits of Change in Laboratory Tests (International Units and Standard Units)

Predefined Laboratory Test	Limit of Change (International Units)	Converted to Standard Units	Treatment	Number[†]/Total[‡] (%)	
Hemoglobin	Decrease ≥35 g/L	3.5 gm/dL	Atenolol	52/3480	(1.5)
			Losartan	100/3636	(2.8)
Creatinine	Increase >35 μmol/L	0.40 mg/dL	Atenolol	363/4202	(8.6)
			Losartan	451/4277	(10.5)
SGPT (ALT)	Increase >1.0 μkat/L	N/A	Atenolol	87/3058	(2.8)
			Losartan	74/3149	(2.3)
SGPT (ALT)—US	Increase >25 mU/mL	N/A	Atenolol	22/633	(3.5)
			Losartan	29/711	(4.1)
Glucose	Increase >3.33 mmol/L	60 mg/dL	Atenolol	496/3734	(13.3)
			Losartan	394/3897	(10.1)
Uric acid	Increase >60 μmol/L	1.0 mg/dL	Atenolol	2480/3691	(67.2)
			Losartan	1610/3862	(41.7)
Sodium	Increase >10 mmol/L	10 mEq/L	Atenolol	21/4105	(0.5)
			Losartan	14/4209	(0.3)
	Decrease >10 mmol/L	10 mEq/L	Atenolol	61/4105	(1.5)
			Losartan	57/4209	(1.4)
Potassium	Increase >1.0 mmol/L	1 mEq/L	Atenolol	125/4094	(3.1)
			Losartan	155/4195	(3.7)
	Decrease >1.0 mmol/L	1 mEq/L	Atenolol	185/4094	(4.5)
			Losartan	132/4195	(3.1)
Total cholesterol	Increase >1.0 mmol/L	38.7 mg/dL	Atenolol	708/3695	(19.2)
			Losartan	601/3861	(15.6)
HDL cholesterol	Decrease >0.25 mmol/L	9.7 mg/dL	Atenolol	1933/3691	(52.4)
			Losartan	1643/3856	(42.6)

[†] Number of patients with both a valid prestudy and poststudy value.

[‡] Total number of patients with changes in laboratory values that exceeded predefined limits.

Changes from baseline were limited only to valid treatment values, which were from laboratory records on drug or off drug no more than 14 days.

3.6.3.2 New-Onset Diabetes Mellitus

Hypertension and diabetes are common comorbidities; however, the risk of new-onset diabetes in patients with hypertension treated with different blood pressure lowering agents is unclear. As a result, new-onset diabetes was prespecified as a tertiary objective in the LIFE trial. New-onset diabetes mellitus was reported as an adverse event by investigators during the study in patients with no prior history of diabetes mellitus, based on diagnostic fasting serum glucose levels, defined according to the 1985 WHO criteria. Laboratory safety tests, including fasting serum glucose, were drawn on Day -14, Day 1, Month 1, and then yearly. After 2 fasting serum glucose values of ≥140 mg/dL (≥7.8 mmol/L), at least 1 week apart, a diagnosis of new-onset diabetes was reported. If the repeat fasting serum glucose was <140 mg/dL (<7.8 mmol/L), the patient underwent a 2-hour oral glucose tolerance test. A diagnosis of new-onset diabetes was reported if the result of the 2-hour oral glucose tolerance test was ≥200 mg/dL (≥11.1 mmol/L). In a predefined analysis, the incidence of new-onset diabetes mellitus and the difference between treatment groups, using a Cox proportional hazards model similar to the one used for the primary composite and secondary endpoints, is summarized in Table 24. The incidence of new-onset diabetes mellitus was lower in the losartan group (6%) than in the atenolol group (8%) (HR: 0.749 [95% CI 0.634 to 0.885, p<0.001]). Whether this difference represents a benefit of losartan or a deleterious effect of atenolol is unknown; however, data suggest that long-term use of ACE inhibitors and AII antagonists may be associated with a lower incidence of new-onset diabetes (HOPE [58] and SCOPE [data unpublished but presented at the 2002 Joint Meeting of the European and International Societies of Hypertension]), and that long-term treatment with a β-blocker may increase the incidence of new-onset diabetes [59]. Prospective trials are needed to confirm these observations.

Table 24

New Onset of Diabetes Mellitus

	Crude Rate						Kaplan-Meier Rates											
	Losartan ($N^{\dagger}$=4019)			Atenolol ($N^{\dagger}$=3979)			Losartan				Atenolol				Hazard[§]	95% CI		
	Rate[‡]	n	(%)	Rate[‡]	n	(%)	1 Yr	2 Yr	3 Yr	4 Yr	1 Yr	2 Yr	3 Yr	4 Yr	Ratio	Lower	Upper	p-Value[‖]
New-Onset Diabetes Mellitus	13.0	242	(6.0)	17.4	320	(8.0)	1.1	2.7	3.9	4.9	1.0	3.1	4.9	6.5	0.749	0.634	0.885	<0.001**

** p-Values <0.01.
† N = Patients without prior history of diabetes.
‡ Per 1000 patient-years of follow-up.
§ Baseline left ventricular hypertrophy degree (Cornell product and Sokolow-Lyon) and baseline Framingham risk score are included in Cox proportional hazard model as covariates.
‖ The p-values and estimates of hazard ratio of experiencing the endpoint on losartan compared to atenolol are based on Cox proportional hazard model.

3.6.3.3 Vital Signs and Other Physical Observations Related to Safety

Changes in blood pressure and pulse pressure over time were included as part of the efficacy analysis. The remaining vital signs analyzed primarily for safety were pulse rate and weight. Mean changes in pulse rate and weight were calculated from prestudy to each follow-up visit. All patients with a valid prestudy value and a valid poststudy value were included. Consistent with the rest of the safety analyses, valid poststudy values were those measured up to 14 days after permanent discontinuation or study drug interruption. Mean changes in vital signs are presented in Table 25.

Table 25

Mean Changes in Vital Signs

	Losartan (N=4605)				Atenolol (N=4588)				
		Mean				Mean			
	N	Baseline	Follow-up	Change	N	Baseline	Follow-up	Change	p-Value†
Pulse Rate (/min)									
Month 1	4463	73.9	73.4	-0.5	4382	73.8	65.4	-8.3	<0.001**
Month 2	4363	73.9	73.4	-0.5	4237	73.8	65.6	-8.1	<0.001**
Month 3	4233	73.8	73.2	-0.7	4097	73.8	65.3	-8.5	<0.001**
Month 6	4157	73.8	72.6	-1.3	3998	73.9	64.6	-9.3	<0.001**
Year 1	4032	73.8	72.3	-1.6	3838	73.9	64.5	-9.4	<0.001**
Year 1.5	3851	73.8	72.4	-1.4	3612	74.0	64.9	-9.0	<0.001**
Year 2	3721	73.8	72.1	-1.8	3505	73.9	64.5	-9.5	<0.001**
Year 2.5	3591	73.8	72.3	-1.5	3358	74.0	64.9	-9.1	<0.001**
Year 3	3520	73.7	72.0	-1.8	3303	73.9	64.5	-9.4	<0.001**
Year 3.5	3410	73.8	72.2	-1.6	3206	73.9	64.8	-9.1	<0.001**
Year 4	3336	73.7	71.9	-1.9	3134	73.9	64.5	-9.4	<0.001**
Year 4.5	3226	73.6	72.2	-1.4	2991	73.8	65.0	-8.7	<0.001**
Year 5	2361	73.3	71.3	-2.0	2158	73.4	64.1	-9.3	<0.001**
Year 5.5	1102	73.5	72.3	-1.2	1062	74.2	64.2	-10.1	<0.001**
Weight (kg)									
Year 1	3702	78.8	78.7	-0.1	3494	78.7	79.3	0.6	<0.001**
Year 2	3453	78.8	78.7	-0.1	3213	78.9	79.6	0.7	<0.001**
Year 3	3302	78.8	78.7	-0.1	3058	78.7	79.1	0.4	<0.001**
Year 4	3102	78.8	78.5	-0.3	2904	78.5	79.0	0.4	<0.001**
Year 5	2244	78.7	78.3	-0.4	2033	78.2	78.6	0.4	<0.001**

** p-Values <0.01.
† The p-values are based on Wilcoxon test.

3.6.4 Summary of Safety Results

The observed adverse experience profile in hypertensive patients with documented LVH was consistent with the profile described in the currently approved U.S. labeling. Losartan was well tolerated and was associated with fewer discontinuations due to adverse experiences than atenolol.

4. Postmarketing Experience With Losartan in Patients With Hypertension and Left Ventricular Hypertrophy

The Merck & Co., Inc. Worldwide Adverse Experience System (WAES) database was searched to identify spontaneous reports from a patient population with LVH who were treated with losartan, similar to the patients enrolled in the LIFE Study. The time frame of the search extended from the grant of licensure for sale of losartan potassium (02-Sep-1994) through 31-Mar-2002. Of the 56 reports identified, there were no unexpected adverse experiences.

5. Discussion

The results of the LIFE study demonstrate that in hypertensive patients with ECG evidence of LVH, losartan reduces the risk of major cardiovascular morbidity and mortality, compared with atenolol. This study showed that with comparable blood pressure control, one specific antihypertensive treatment reduces the incidence of cardiovascular morbidity and mortality in hypertensive patients relative to another active antihypertensive treatment.

The risk of the primary endpoint, a composite of cardiovascular mortality, stroke, and myocardial infarction, was significantly reduced by 13% ($p=0.021$) with losartan as compared with atenolol, in the primary analysis that adjusts for Framingham risk score and degree of ECG-LVH at baseline. Among the components of the primary composite endpoint, losartan was associated with a significant reduction in the risk of stroke (fatal and nonfatal) by 25% ($p<0.001$). Furthermore, the relative risk reduction of the component endpoint of cardiovascular mortality was not significantly different between the losartan and atenolol groups but was directionally consistent with the composite endpoint and favored losartan. There was no significant difference in the risk of the individual component of myocardial infarction (fatal and nonfatal) between the treatment groups. A test for heterogeneity among the components of the primary composite endpoint was statistically significant, suggesting that the components should be evaluated separately.

Of the classified causes of cardiovascular death, losartan was associated with a significant reduction in the risk of fatal stroke ($p=0.032$). Cardiovascular death due to coronary heart disease, heart failure, vascular disease, or other causes was not significantly different between the treatment groups. Losartan did reduce ECG-LVH to a greater degree than atenolol, and the results of a time-varying covariate analysis suggest that LVH reduction appeared to partially account for the benefit of losartan on the primary composite outcome.

Blood pressure reduction was comparable between the 2 treatment groups, with slightly greater reductions in systolic blood pressure with losartan and slightly greater reductions in diastolic blood pressure with atenolol. A post hoc analysis demonstrated a significant qualitative interaction in Black patients, for which no biologic basis could be discerned from the available data. Losartan was better tolerated than atenolol, with fewer discontinuations due to adverse experiences.

5.1 Interpretation of LIFE Results

Regulatory decisions have been made based primarily on information from a single study. This is often the case for large outcomes trials, when ethical and practical considerations make it impossible and/or impractical to conduct a second confirmatory study to provide independent substantiation of the first study. In such cases, it is important to consider what supportive evidence may be available to provide reassurance that the results of the single trial are scientifically sound and not due to chance alone. During 2 recent Cardio-Renal Advisory Committee Meetings, the committee and the FDA discussed the ability of a single placebo-controlled trial without a highly significant p-value to support a proposed claim. The need to support the findings of such trials with additional data from sources internal and/or external to the trial was discussed, but as an active-comparator trial, the LIFE study provides an additional level of confidence that the demonstrated benefits of a losartan-based regimen represent a true finding.

In considering the use of the LIFE study to support the proposed indication, there are several features of the trial as well as additional scientific data that provide confidence in the strength of the results. These will be considered in detail in the sections that follow.

5.1.1 Strength of the Results

5.1.1.1 Study Conduct Features

Characteristics of the design and execution of the LIFE study itself provide support for the accuracy of the results. The LIFE trial was a large, multicenter, multinational, double-blind study that enrolled 9193 patients from 945 sites in 7 countries, with a mean follow-up of 4.8 years (maximum 6.2 years) and over 1000 primary composite endpoints evaluated. Despite the size and duration of the trial, adherence to the protocol was high, complete follow-up was obtained for 98.8% of potential patient-days, and vital status at study end was obtained for 99.4% of potential patient-days. All morbidity and mortality endpoints were adjudicated by an independent blinded ECC. Overall, these study conduct features provide strong evidence in support of the accuracy of the results.

An important aspect of the study conduct that strengthens confidence in the findings is the use of an active comparator. In the LIFE trial, atenolol substantially and significantly reduced blood pressure by 29.1/16.8 mm Hg. Blood pressure reduction is a well-accepted surrogate for cardiovascular benefit; accordingly, atenolol served as an active antihypertensive agent in this trial. Additional evidence for a benefit of β-blockers in general, and atenolol specifically, in the treatment of hypertension is reviewed below.

5.1.1.2 Atenolol as an Active Control

As described in detail in Section III.3.1.5, prior to the initiation of the LIFE trial, 2 pivotal outcomes trials in hypertensive patients independently and unequivocally demonstrated significant cardiovascular benefit with a β-blocker-based regimen (in which atenolol was a first-line treatment) compared with placebo or no treatment [35; 34]. In total, the available data on the efficacy of a first-line β-blocker based-regimen for the reduction of cardiovascular events suggest a treatment effect of 21% (26% reduction

with diuretic- and β-blocker-based regimens). Based on outcomes data, initial antihypertensive therapy with a β-blocker was incorporated into the JNC V guidelines [5], and a number of trials of newer antihypertensive agents (including CAPPP, STOP II, and NORDIL) were initiated using β-blocker-based regimens as the established treatment reference standard [44; 43; 45]. These studies, which compared β-blocker-based regimens with ACE inhibitors or calcium channel antagonists, did not detect differences between the active regimens, and concluded that, in general, these agents have similar efficacy in preventing cardiovascular morbidity and mortality.

Additionally, Psaty et al. [39]performed a meta-analysis of placebo-controlled, randomized long-term outcome trials to evaluate the effects of antihypertensive therapies on the occurrence of stroke and myocardial infarction. Based on the analysis of 4 trials involving 12,147 patients treated with β-blocker and 6736 patients treated with placebo, β-blocker therapy as compared with placebo was found to be effective in preventing stroke (RR 0.71; CI 0.59-0.86) and congestive heart failure (RR 0.58; CI 0.40 - 0.84). Three of these 4 trials included atenolol as a first-line agent. The 29% risk reduction for stroke provides a historical reference for the risk reduction achieved with the atenolol-based regimen in the LIFE trial.

Furthermore, an overview of recent randomized trials that assessed outcomes found significant benefits on stroke and major cardiovascular events with ACE inhibitors and calcium channel antagonists relative to placebo, and, based on data from over 39,000 patients with hypertension, generally found similar benefits on these endpoints between these agents and conventional treatment with diuretics and/or β-blockers [46]. The exceptions were a lower risk of stroke and a greater risk of coronary heart disease among patients assigned to calcium channel antagonists relative to β-blocker and/or diuretic therapy (stroke: HR 0.87, CI 0.77 - 0.98; coronary heart disease: HR 1.12, CI 1.00 - 1.26).

Although neither atenolol nor any other β-blocker has an indication for reducing cardiovascular risk in hypertensive patients, the data supporting such a benefit are compelling. Importantly, the JNC VI guidelines [2] recognize that numerous randomized controlled trials have shown a reduction in morbidity and mortality with diuretics or β-blockers (results detailed above for β-blockers) and continue to recommend either of these drugs as initial drug therapy to treat uncomplicated hypertension. Of note, guidelines do not provide specific treatment recommendations for patients with hypertension and LVH, although it is likely that a proportion of the patients enrolled in these studies had LVH. Thus, by using a β-blocker-based regimen in which diuretics were added as needed to control blood pressure, the LIFE trial demonstrated the benefits of losartan versus an active treatment regimen. Furthermore, atenolol is well known to prevent cardiac ischemic events, mediated by its reduction in heart rate and myocardial oxygen consumption. This benefit derives from the specific mechanism of action of atenolol, and is concurrent with its antihypertensive effects.

5.1.1.3 Clinically Important Benefits

The primary composite endpoint of the LIFE trial was chosen as a comprehensive reflection of the major cardiovascular consequences of hypertension. Collectively, the events that comprise this composite are a major public health issue worldwide [2]. While the effective treatment of hypertension is known to confer benefit on cardiovascular outcomes, it has long been hypothesized that the means by which blood pressure is reduced may allow for incremental treatment benefit [46]. However, several trials designed to evaluate particular benefits from ACE inhibitors or calcium channel blockers showed no therapeutic benefits compared with the already accepted β-blocker- and/or diuretic-based regimens [44; 43; 45]. A meta-analysis of available trials did not suggest substantial differences between therapeutic classes of antihypertensive agents and β-blocker- and/or diuretic-based regimens [46]. Thus, the LIFE study demonstrates a benefit of losartan on cardiovascular outcomes in high-risk patients with hypertension, versus an active control. This result has the potential to provide important clinical benefits, particularly with regard to stroke reduction.

Worldwide, stroke is the second leading cause of mortality. In the U.S., stroke is the third leading cause of death. Approximately 1 of every 14 deaths in the U.S. in 1999 was due to stroke [4]. Stroke is also a leading cause of serious, long-term disability with direct and indirect economic burden resulting from functional limitations and interference with the activities of daily living. The JNC-VI guidelines summarize the important public health benefits that have been observed in the United States with increasing awareness and treatment of hypertension from the period of 1976 to 1991. In this period, the effective treatment of patients with hypertension resulted in a decline in the age-adjusted death rates from stroke of nearly 60% [2], but the incidence of stroke remains of substantial clinical concern. Thus, the incremental benefit of losartan over the established benefits of conventional antihypertensive therapy has important public health implications.

In the LIFE study, the secondary endpoint of stroke reduction significantly favored losartan (HR 0.752, CI 0.634-0.891, p=0.001). While the benefit of losartan on stroke was substantial, the differences between the treatments in the incidence of cardiovascular death was not significant but was directionally consistent with the composite endpoint and stroke. Myocardial infarction was not significantly different between treatment groups, nor were there significant differences in the rates of hospitalization for angina pectoris or heart failure, or in the rates of coronary or non-coronary artery vascular surgery. Of note, a test for heterogeneity among the components of the primary composite endpoint was performed, and indicated that the treatment effect differed significantly among the components (p=0.023). Since the test for heterogeneity is statistically independent of the test for a between-group difference in the primary composite endpoint, this is independent statistical evidence that the effects of losartan and atenolol differ.

The finding of heterogeneity may reflect differences in the disease states that comprise the primary composite endpoint, and/or in the mechanisms of action of losartan and

atenolol in those disease states. In particular, although stroke and myocardial infarction are etiologically linked to hypertension, they are unique diseases with distinct pathophysiologic bases. The determinants of cerebrovascular and cardiovascular blood flow, and of the oxygen requirements of the heart and brain, differ substantially, as do the mechanisms and treatment of ischemic events in the 2 organ systems [60; 61]. As such, it is not surprising that antihypertensive agents acting through different mechanisms would provide differential benefits on the end organ complications of hypertension, even in the setting of similar blood pressure reduction, as was seen in recent trials in hypertensive patients with diabetic nephropathy [62; 63; 64]. Specifically, losartan blocks the deleterious effects of AII at the AT_1 receptor, resulting in an increase in AII levels, and increased binding of AII at the AT_2 receptor. The net effect of these actions is vasodilation, blood pressure reduction, regression of vascular and myocardial hypertrophy, and normalization of vascular endothelial function. In contrast, β-blockers prevent catecholamine binding to β-receptors, reducing heart rate and myocardial contractility, resulting in a decrease in blood pressure, regression of LVH, and a reduction in myocardial oxygen consumption.

Although both agents reduce blood pressure to a similar degree, their actions concurrent with this hypotensive effect differ. Thus, in considering the comparative effects of the chronic use of these agents on cardiac and cerebral ischemic events, it is important to integrate both the pathophysiologic and drug mechanism differences. Heart rate is an important modulator of myocardial oxygen demand, and in turn, myocardial oxygen demand is a key determinant of cardiac ischemia [65]. Thus, it is not surprising that β-blockers are well-known to have a substantial benefit in both the primary and secondary prevention of myocardial ischemia and infarction. In that context, it is noteworthy that the effect of losartan on myocardial infarction is not significantly different from that of atenolol, despite the greater reduction in heart rate afforded by atenolol. Alternatively, AII produces vascular pathology that may be reversed more effectively by losartan than atenolol; losartan's greater regression of LVH, a marker of the adverse cardiovascular effects of AII, is a reflection of this benefit, and may, in part, explain the superior effect of losartan on stroke reduction.

Confidence in the overall clinical benefits of losartan, and particularly those on stroke, is provided by epidemiologic data, which support a strong relationship between LVH and both cardiovascular and cerebrovascular events [18; 66]. Studies show marked increases in the risk of events occurring in the presence of LVH, and reductions in the risk of events associated with regression of LVH [17; 31; 30; 29]. Framingham data suggest ~25% risk reduction in patients whose LVH regresses compared with those with persistent LVH for 4 years [30]. Consistent with the study hypothesis and rationale, the LIFE trial results demonstrated that losartan significantly decreased ECG measures of LVH to a greater degree than atenolol; the differential effects of losartan on ECG measures of LVH appear to be in addition to the beneficial effect of blood pressure lowering on LVH. Furthermore, the 965-patient echocardiography substudy was consistent with the ECG-LVH findings. The substudy showed a greater reduction in left ventricular mass index (LVMI) with losartan than with atenolol. The substudy also

showed that lower LVMI was associated with a lower risk of a clinical endpoint, independent of blood pressure.

The potential clinical impact of the LIFE study result is further demonstrated in prespecified analyses of the morbidity and mortality endpoints in 2 high-risk populations of hypertensive patients, diabetic patients (n=1195; 13% of population) and patients with ISH (n=1326; 14% of population). As expected, both of these populations had an increased rate of events in comparison to the overall population in the LIFE study. For the primary composite endpoint, the results seen in these populations were consistent with the benefit of therapy with losartan seen in the overall study population. In diabetic patients, a 24% risk reduction (p=0.03) was observed and in patients with ISH, a 25% risk reduction (p=0.06) was observed. Consistent with the results seen in the overall population, a reduction in stroke was an important contributor to the benefit observed in patients with diabetes or ISH. Coupled with the recent finding among type 2 diabetics with nephropathy [62], these data suggest that losartan may be especially well-suited for use in patients with diabetes.

5.1.1.4 Potential Mechanisms of Benefit

In considering the strength of the observation of a significant reduction in the occurrence of cardiovascular events with losartan, it is important to note that the LIFE trial was not designed to determine the mechanism of demonstrated clinical benefits. Thus, potential explanations must be considered to be hypothetical. In that context, there is particular interest in exploring the data that provide mechanistic support for the finding of the benefit of losartan on stroke reduction.

Preclinical data from the stroke-prone spontaneously hypertensive rat support the hypothesis that there are non-hemodynamic benefits of AII antagonism. In this model, chronic treatment with losartan has been shown to improve cerebral arterial vascular smooth muscle and endothelial cell function in conjunction with prevention of stroke and mortality [67]. Furthermore, losartan has been shown to prevent the occurrence of cerebral lesions in these animals in the absence of a fall in blood pressure [68]. Importantly, treatment with beta-blockade in this model did not result in normalization of structural arterial abnormalities beyond those associated with non-specific blood pressure reduction [69]. In the Dahl salt-sensitive rat, blood pressure increases were only transiently attenuated by losartan, but nonetheless, losartan treatment reduced the incidence of stroke and dramatically increased survival; 74 of 91 (81%) losartan-treated rats survived as compared with 54 of 95 (57%) untreated rats that survived. At 8 weeks, only 1 of 12 (8%) losartan-treated rats showed evidence of cerebrovascular lesions, whereas 7 of 11 (64%) untreated rats had multiple lesions. In this study, blood pressure did not correlate with stroke incidence [70].

Clinical data are limited but generally support the hypothesis of the non-hemodynamic benefits of AII antagonism [71; 24; 72]. Schiffrin et al. demonstrated a significant decrease in the media/lumen ratio in hypertensive patients after 1 year of treatment with losartan compared with atenolol, and endothelium-dependent relaxation was normalized in patients treated with losartan, but not with atenolol, despite comparable blood pressure

control [24]. Within the LIFE trial, the ICARUS substudy (n=57 entered) evaluated intima-media thickness and lumen in the common carotid arteries which were measured by ultrasound at or near baseline and at 1, 2, and 3 years of treatment with either a losartan-based or atenolol-based regimen. There was a relative reduction in the intima-media thickness of the common carotid artery relative to atenolol after 3 years of treatment (-7.9% versus -1.7%, $p<0.05$) [71]. Mean intima-media cross-sectional area indexed by height (mm^2/m) did not decrease significantly in patients treated with atenolol (baseline: 11.9; Year 1: 11.6, p=NS; Year 2: 11.2, $p<0.05$; Year 3: 11.4, p = NS), whereas it did in patients treated with losartan (baseline: 11.2; Year 1: 10.6; Year 2: 10.2; Year 3: 10.1, all within treatment changes: $p<0.01$) [71].

Another potential mechanism by which losartan might have conferred greater benefit than atenolol in the reduction of stroke may be through differential reductions in elevated aortic (central) blood pressure, which has been correlated more closely with cardiovascular risk, particularly stroke, than peripheral blood pressure. Studies have shown that conventional brachial artery measurements of blood pressure are an imperfect surrogate for central blood pressure [73; 74]. Limited data suggest that agents from different antihypertensive classes have different effects on reductions in central hypertension [75; 76]. In fact, antihypertensive therapy with β-blockers, by virtue of associated reductions in heart rate, lead to increases in stroke volume, and thus smaller reductions in central blood pressure than other agents such as those that act through the angiotensin system [75; 76]. However, it is not known whether a difference between the effects of antihypertensive medications on elevated central blood pressure might account for observed differences in the prevention of cardiovascular events. It is possible that in the LIFE study, differences in effects on central hypertension contributed to the differences in the occurrence of stroke.

Although peripheral blood pressure was lowered substantially in both the losartan and atenolol arms, there were small differences in systolic blood pressure (1.1 mm Hg, $p=0.015$) and pulse pressure (1.2 mm Hg, $p<0.001$) favoring losartan. Although systolic and pulse pressures have been linked to the occurrence of cardiovascular disease [9; 77; 78] [7], it is unlikely that differences of this magnitude contributed to the observed benefit of losartan.

5.1.2 Qualitative Interaction

An analysis of the primary composite endpoint data in a number of demographic, geographic, disease history, and disease severity subgroups (including the prespecified high-risk patients with diabetes or ISH) showed that the results were generally consistent with one notable exception. Although the study population consisted almost entirely of White patients, there appeared to be an interaction between treatment and ethnic background. This observation was further explored with a post hoc analysis that dichotomized ethnic background to Black and non-Black patients and showed a significant qualitative interaction with treatment. Due to the qualitative interaction, it was reasonable to look at the treatment difference separately between Black and non-Black patients. In Black patients (N=533), atenolol demonstrated a reduction in the

risk of the primary composite endpoint relative to losartan (p=0.033). In non-Black patients (N=8660), losartan demonstrated a reduction in the risk of the primary composite endpoint relative to atenolol (p=0.003). Because almost all Black patients were enrolled in the United States (523 of 533 Black patients), analyses comparing U.S. Blacks and non-Blacks were undertaken. These analyses revealed the same finding favoring atenolol over losartan among Black patients, despite the fact that blood pressure lowering in this subgroup was comparable and ECG-measured LVH was reduced more with losartan than atenolol. Further exploration of differences in baseline risk parameters and blood pressure and LVH changes in U.S. Blacks and non-Blacks failed to reveal any biologic basis for the interaction. The effect of a losartan-based regimen on blood pressure reduction and LVH regression suggest that it is likely to be beneficial relative to placebo in Black patients.

5.1.3 Safety

In the LIFE Study, the adverse experience profiles observed were consistent with the known properties of losartan and atenolol. Significantly more patients assigned to atenolol treatment reported adverse experiences that led to discontinuation of therapy (13.1% of patients in the losartan group and 18.1% of patients in the atenolol group; p<0.001) and adverse experiences that were considered drug related by the investigator (37.2% in the losartan group and 45.2% in the atenolol group; p<0.001). For the adverse experiences occurring in more than 5% of patients in both treatment groups with at least a 1% difference between treatments, only back pain, palpitation, and chest pain occurred more frequently in the patients assigned to treatment with losartan. A similar pattern was observed in the demographic subgroups of age, gender, and ethnic background, with the exception of Black patients. In Black patients (5.8% of study population), a similar rate of drug-related adverse experiences was observed between treatment groups, and study drug discontinuations related to adverse experiences occurred less in the atenolol group (15.6% for the losartan group versus 12.9% for the atenolol group). Serious adverse experiences occurred more frequently in Black patients in the losartan group (40.0%) than in the atenolol group (28.1%); however, the rate of serious adverse experiences in the losartan group was similar to that observed in the overall population (40.0% in losartan-treated Black patients versus 37.2% in the overall losartan-treated group and 36.2% in the overall atenolol-treated group).

5.2 Benefit Versus Risk Relationship

The results of the LIFE study clearly demonstrate that losartan compared with atenolol provides cardiovascular and cerebrovascular benefit in patients with hypertension and LVH.

Previous trials have demonstrated the beneficial impact of lowering blood pressure with antihypertensive therapy but have failed to distinguish among different therapies and, despite treatment, the risk of cardiovascular complications in hypertensive patients remains high. Losartan treatment in hypertensive patients with ECG evidence of LVH in the LIFE study demonstrated a superior effect on cardiovascular morbidity and mortality compared with treatment with atenolol despite comparable blood pressure lowering,

although the benefit of losartan shown in the LIFE trial does not appear to apply to Black patients. Losartan has already been established as an effective once-daily drug for the treatment of hypertension as well as for the treatment of nephropathy in type 2 diabetic patients with a history of hypertension [62]. The potential risk associated with the losartan safety profile is minimal; losartan has an excellent tolerability profile. Importantly, there is no incremental risk to the patient associated with losartan treatment in regards to the proposed new indication because losartan is already approved for patients with hypertension. However, the greater clinical benefit observed in the LIFE study is an important public health finding with direct relevance to clinical practice. Collectively, the data strongly support a favorable benefit/risk ratio.

6. Overall Conclusions

Based on the LIFE study, which investigated the effect of losartan-based versus atenolol-based antihypertensive regimens on morbidity and mortality in hypertensive patients with documented LVH, the following conclusions can be drawn:

1. Losartan reduces the risk of development of the primary composite endpoint of cardiovascular mortality, stroke and myocardial infarction compared with atenolol (13% risk reduction, p=0.021), despite comparable blood pressure reduction. The reduction in risk is largely due to a reduction in the risk of the stroke component of the primary endpoint relative to treatment with atenolol (25% risk reduction, p<0.001). The benefit of losartan versus atenolol on cardiovascular mortality (11% risk reduction, p=0.206) does not significantly differ between treatment groups, but directionally favors losartan, including a benefit on stroke mortality (35% risk reduction, p=0.032), and contributes to the benefit of losartan on the composite endpoint. The incidence of myocardial infarction (7% risk increase, p=0.491) does not significantly differ between the treatment groups.
2. Losartan treatment does not differ significantly from atenolol treatment in the rate of mortality from all causes, hospitalization for heart failure or angina pectoris, coronary or peripheral revascularization procedures, or resuscitated cardiac arrest.
3. Losartan treatment reduces LVH relative to atenolol as assessed by electrocardiographic measures.
4. In diabetic patients, the primary composite endpoint result (24% risk reduction, p=0.031) is consistent with the result in the overall study population. Also, consistent with the result in the overall population, a reduction in stroke is an important contributor to the effect observed in the diabetic patients.
5. In patients with isolated systolic hypertension, the primary composite endpoint result (25% risk reduction, p=0.059) is consistent with the result in the overall study population. Also, consistent with the result in the overall population, a reduction in stroke is an important contributor to the effect observed in patients with isolated systolic hypertension.

6. In the demographic, geographic, disease history, and disease severity subgroups assessed, the treatment benefit of losartan on the primary composite endpoint is consistent as evidenced by the lack of significant treatment-by-subgroup interaction; however, in the predefined subgroup analyses, there is a suggestion of an interaction between ethnic background and treatment. A post hoc analysis revealed a qualitative interaction. Therefore, the benefits of losartan seen in the overall LIFE study do not appear to apply to Black patients with hypertension and LVH.
7. Losartan is well tolerated and is associated with fewer discontinuations due to adverse experiences than atenolol. The observed adverse experience profile of losartan in this population is consistent with the profile observed in the general hypertensive population.

Together with the data supporting the benefit of therapy with atenolol, the findings of the LIFE study provide substantial evidence for the benefit of losartan on the reduction of cardiovascular morbidity and mortality in patients with hypertension and LVH.

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MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

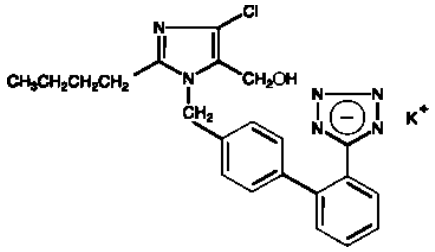
COZAAR®
(LOSARTAN POTASSIUM TABLETS)

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, COZAAR should be discontinued as soon as possible. See WARNINGS: *Fetal/Neonatal Morbidity and Mortality*.

DESCRIPTION

COZAAR* (losartan potassium) is an angiotensin II receptor (type AT_1) antagonist. Losartan potassium, a non-peptide molecule, is chemically described as 2-butyl-4-chloro-1-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]imidazole-5-methanol monopotassium salt.
Its empirical formula is $C_{22}H_{22}ClKN_6O$, and its structural formula is:



Losartan potassium is a white to off-white free-flowing crystalline powder with a molecular weight of 461.01. It is freely soluble in water, soluble in alcohols, and slightly soluble in common organic solvents, such as acetonitrile and methyl ethyl ketone. Oxidation of the 5-hydroxymethyl group on the imidazole ring results in the active metabolite of losartan.

COZAAR is available as tablets for oral administration containing either 25 mg, 50 mg or 100 mg of losartan potassium and the following inactive ingredients: microcrystalline cellulose, lactose hydrous, pregelatinized starch, magnesium stearate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, titanium dioxide, D&C yellow No. 10 aluminum lake and FD&C blue No. 2 aluminum lake.

COZAAR 25 mg, 50 mg and 100 mg tablets contain potassium in the following amounts: 2.12 mg (0.054 mEq), 4.24 mg (0.108 mEq) and 8.48 mg (0.216 mEq), respectively.

CLINICAL PHARMACOLOGY

Mechanism of Action

Angiotensin II [formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kininase II)], is a potent vasoconstrictor, the primary vasoactive hormone of the renin-angiotensin system and an important component in the pathophysiology of hypertension. It

* Registered trademark of E.I. du Pont de Nemours and Company, Wilmington, Delaware, USA

also stimulates aldosterone secretion by the adrenal cortex. Losartan and its principal active metabolite block the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor found in many tissues, (e.g., vascular smooth muscle, adrenal gland). There is also an AT_2 receptor found in many tissues but it is not known to be associated with cardiovascular homeostasis. Both losartan and its principal active metabolite do not exhibit any partial agonist activity at the AT_1 receptor and have much greater affinity (about 1000-fold) for the AT_1 receptor than for the AT_2 receptor. *In vitro* binding studies indicate that losartan is a reversible, competitive inhibitor of the AT_1 receptor. The active metabolite is 10 to 40 times more potent by weight than losartan and appears to be a reversible, non-competitive inhibitor of the AT_1 receptor.

Neither losartan nor its active metabolite inhibits ACE (kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin); nor do they bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Pharmacokinetics

General

Losartan is an orally active agent that undergoes substantial first-pass metabolism by cytochrome P450 enzymes. It is converted, in part, to an active carboxylic acid metabolite that is responsible for most of the angiotensin II receptor antagonism that follows losartan treatment. The terminal half-life of losartan is about 2 hours and of the metabolite is about 6-9 hours. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan doses up to 200 mg and do not change over time. Neither losartan nor its metabolite accumulate in plasma upon repeated once-daily dosing.

Following oral administration, losartan is well absorbed (based on absorption of radiolabeled losartan) and undergoes substantial first-pass metabolism; the systemic bioavailability of losartan is approximately 33%. About 14% of an orally-administered dose of losartan is converted to the active metabolite. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. While maximum plasma concentrations of losartan and its active metabolite are approximately equal, the AUC of the metabolite is about 4 times as great as that of losartan. A meal slows absorption of losartan and decreases its C_{max} but has only minor effects on losartan AUC or on the AUC of the metabolite (about 10% decreased).

Both losartan and its active metabolite are highly bound to plasma proteins, primarily albumin, with plasma free fractions of 1.3% and 0.2%, respectively. Plasma protein binding is constant over the concentration range achieved with recommended doses. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

Losartan metabolites have been identified in human plasma and urine. In addition to the active carboxylic acid metabolite, several inactive metabolites are formed. Following oral and intravenous administration of ^{14}C-labeled losartan potassium, circulating plasma radioactivity is primarily attributed to losartan and its active metabolite. *In vitro* studies indicate that cytochrome P450 2C9 and 3A4 are involved in the biotransformation of losartan to its metabolites. Minimal conversion of losartan to the active metabolite (less than 1% of the dose compared to 14% of the dose in normal subjects) was seen in about one percent of individuals studied.

The volume of distribution of losartan is about 34 liters and of the active metabolite is about 12 liters. Total plasma clearance of losartan and the active metabolite is about 600 mL/min and 50 mL/min, respectively, with renal clearance of about 75 mL/min and 25 mL/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine and about 6% is excreted in urine as active metabolite. Biliary excretion contributes to the elimination of losartan and its metabolites. Following oral ^{14}C-labeled losartan, about 35% of radioactivity is recovered in the urine and about 60% in the feces. Following an intravenous dose of ^{14}C-labeled losartan, about 45% of radioactivity is recovered in the urine and 50% in the feces.

Special Populations

Pediatric: Losartan pharmacokinetics have not been investigated in patients <18 years of age.

Geriatric and Gender: Losartan pharmacokinetics have been investigated in the elderly (65-75 years) and in both genders. Plasma concentrations of losartan and its active metabolite are

similar in elderly and young hypertensives. Plasma concentrations of losartan were about twice as high in female hypertensives as male hypertensives, but concentrations of the active metabolite were similar in males and females. No dosage adjustment is necessary (see DOSAGE AND ADMINISTRATION).

Race: Pharmacokinetic differences due to race have not been studied.

Renal Insufficiency: Plasma concentrations of losartan are not altered in patients with creatinine clearance above 30 mL/min. In patients with lower creatinine clearance, AUCs are about 50% greater and they are doubled in hemodialysis patients. Plasma concentrations of the active metabolite are not significantly altered in patients with renal impairment or in hemodialysis patients. Neither losartan nor its active metabolite can be removed by hemodialysis. No dosage adjustment is necessary for patients with renal impairment unless they are volume-depleted (see WARNINGS, *Hypotension — Volume-Depleted Patients* and DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency: Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were, respectively, 5-times and about 1.7-times those in young male volunteers. Compared to normal subjects the total plasma clearance of losartan in patients with hepatic insufficiency was about 50% lower and the oral bioavailability was about 2-times higher. A lower starting dose is recommended for patients with a history of hepatic impairment (see DOSAGE AND ADMINISTRATION).

Drug Interactions

Losartan, administered for 12 days, did not affect the pharmacokinetics or pharmacodynamics of a single dose of warfarin. Losartan did not affect the pharmacokinetics of oral or intravenous digoxin. Coadministration of losartan and cimetidine led to an increase of about 18% in AUC of losartan but did not affect the pharmacokinetics of its active metabolite. Coadministration of losartan and phenobarbital led to a reduction of about 20% in the AUC of losartan and that of its active metabolite. Conversion of losartan to its active metabolite after intravenous administration is not affected by ketoconazole, an inhibitor of P450 3A4. There is no pharmacokinetic interaction between losartan and hydrochlorothiazide.

Pharmacodynamics and Clinical Effects

Hypertension: Losartan inhibits the pressor effect of angiotensin II (as well as angiotensin I) infusions. A dose of 100 mg inhibits the pressor effect by about 85% at peak with 25-40% inhibition persisting for 24 hours. Removal of the negative feedback of angiotensin II causes a 2-3 fold rise in plasma renin activity and consequent rise in angiotensin II plasma concentration in hypertensive patients. Losartan does not affect the response to bradykinin, whereas ACE inhibitors increase the response to bradykinin. Aldosterone plasma concentrations fall following losartan administration. In spite of the effect of losartan on aldosterone secretion, very little effect on serum potassium was observed.

In a single-dose study in normal volunteers, losartan had no effects on glomerular filtration rate, renal plasma flow or filtration fraction. In multiple dose studies in hypertensive patients, there were no notable effects on systemic or renal prostaglandin concentrations, fasting triglycerides, total cholesterol or HDL-cholesterol or fasting glucose concentrations. There was a small uricosuric effect leading to a minimal decrease in serum uric acid (mean decrease <0.4 mg/dL) during chronic oral administration.

The antihypertensive effects of COZAAR were demonstrated principally in 4 placebo-controlled 6-12 week trials of dosages from 10 to 150 mg per day in patients with baseline diastolic blood pressures of 95-115. The studies allowed comparisons of two doses (50-100 mg/day) as once-daily or twice-daily regimens, comparisons of peak and trough effects, and comparisons of response by gender, age, and race. Three additional studies examined the antihypertensive effects of losartan and hydrochlorothiazide in combination.

The 4 studies of losartan monotherapy included a total of 1075 patients randomized to several doses of losartan and 334 to placebo. The 10 and 25 mg doses produced some effect at peak (6 hours after dosing) but small and inconsistent trough (24 hour) responses. Doses of 50, 100 and 150 mg once daily gave statistically significant systolic/diastolic mean decreases in blood

pressure, compared to placebo in the range of 5.5-10.5/3.5-7.5 mmHg, with the 150 mg dose giving no greater effect than 50-100 mg. Twice-daily dosing at 50-100 mg/day gave consistently larger trough responses than once-daily dosing at the same total dose. Peak (6 hour) effects were uniformly, but moderately, larger than trough effects, with the trough-to-peak ratio for systolic and diastolic responses 50-95% and 60-90%, respectively.

Addition of a low dose of hydrochlorothiazide (12.5 mg) to losartan 50 mg once daily resulted in placebo-adjusted blood pressure reductions of 15.5/9.2 mmHg.

Analysis of age, gender, and race subgroups of patients showed that men and women, and patients over and under 65, had generally similar responses. COZAAR was effective in reducing blood pressure regardless of race, although the effect was somewhat less in black patients (usually a low-renin population).

The effect of losartan is substantially present within one week but in some studies the maximal effect occurred in 3-6 weeks. In long-term follow-up studies (without placebo control) the effect of losartan appeared to be maintained for up to a year. There is no apparent rebound effect after abrupt withdrawal of losartan. There was essentially no change in average heart rate in losartan-treated patients in controlled trials.

Nephropathy in Type 2 Diabetic Patients: The Reduction of Endpoints in NIDDM with the Angiotensin II Receptor Antagonist Losartan (RENAAL) study was a randomized, placebo-controlled, double-blind, multicenter study conducted worldwide in 1513 patients with type 2 diabetes with nephropathy (defined as serum creatinine 1.3 to 3.0 mg/dl in females or males ≤60 kg and 1.5 to 3.0 mg/dl in males >60 kg and proteinuria [urinary albumin to creatinine ratio ≥300 mg/g]).

Patients were randomized to receive COZAAR 50 mg once daily or placebo on a background of conventional antihypertensive therapy excluding ACE inhibitors and angiotensin II antagonists. After one month, investigators were instructed to titrate study drug to 100 mg once daily if the trough blood pressure goal (140/90 mmHg) was not achieved. Overall, 72% of patients received the 100 mg daily dose more than 50% of the time they were on study drug. Because the study was designed to achieve equal blood pressure control in both groups, other antihypertensive agents (diuretics, calcium-channel blockers, alpha- or beta-blockers, and centrally acting agents) could be added as needed in both groups. Patients were followed for a mean duration of 3.4 years.

The study population was diverse with regard to race (Asian 16.7%, Black 15.2%, Hispanic 18.3%, White 48.6%). Overall, 63.2% of the patients were men, and 66.4% were under the age of 65 years. Almost all of the patients (96.6%) had a history of hypertension, and the patients entered the trial with a mean serum creatinine of 1.9 mg/dl and mean proteinuria (urinary albumin/creatinine) of 1808 mg/g at baseline.

The primary endpoint of the study was the time to first occurrence of any one of the following events: doubling of serum creatinine, end-stage renal disease (need for dialysis or transplantation), or death. Treatment with COZAAR resulted in a 16% risk reduction in this endpoint (see Figure 1 and Table 1). Treatment with COZAAR also reduced the occurrence of sustained doubling of serum creatinine by 25% and ESRD by 29% as separate endpoints, but had no effect on overall mortality (see Table 1).

The mean baseline blood pressures were 152/82 mmHg for COZAAR plus conventional antihypertensive therapy and 153/82 mmHg for placebo plus conventional antihypertensive therapy. At the end of the study, the mean blood pressures were 143/76 mmHg for the group treated with COZAAR and 146/77 mmHg for the group treated with placebo.

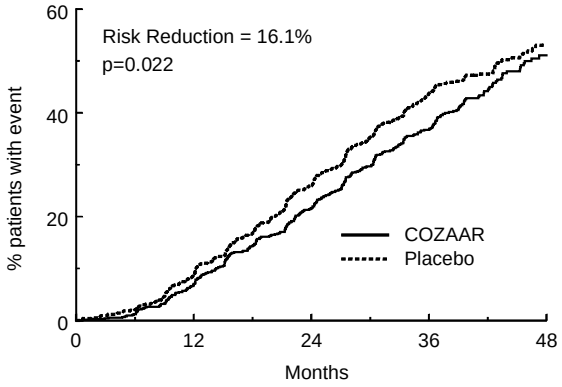


FIGURE 1: Kaplan-Meier curve for the primary composite endpoint of doubling of serum creatinine, end stage renal disease (need for dialysis or transplantation) or death.

Table 1 Incidence of Primary Endpoint Events

	Incidence		Risk Reduction	95% C.I.	p-Value
	Losartan	Placebo			
Primary Composite Endpoint	43.5%	47.1%	16.1%	2.3% to 27.9%	0.022
Doubling of Serum Creatinine, ESRD and Death Occurring as a First Event					
Doubling of Serum Creatinine	21.6%	26.0%			
ESRD	8.5%	8.5%			
Death	13.4%	12.6%			
Overall Incidence of Doubling of Serum Creatinine, ESRD and Death					
Doubling of Serum Creatinine	21.6%	26.0%	25.3%	7.8% to 39.4%	0.006
ESRD	19.6%	25.5%	28.6%	11.5% to 42.4%	0.002
Death	21.0%	20.3%	-1.7%	-26.9% to 18.6%	0.884

The secondary endpoints of the study were change in proteinuria, change in the rate of progression of renal disease, and the composite of morbidity and mortality from cardiovascular causes (hospitalization for heart failure, myocardial infarction, revascularization, stroke, hospitalization for unstable angina, or cardiovascular death). Compared with placebo, COZAAR significantly reduced proteinuria by an average of 34%, an effect that was evident within 3 months of starting therapy, and significantly reduced the rate of decline in glomerular filtration rate during the study by 13%, as measured by the reciprocal of the serum creatinine concentration. There was no significant difference in the incidence of the composite endpoint of cardiovascular morbidity and mortality.

The favorable effects of COZAAR were seen in patients also taking other anti-hypertensive medications (angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors were not allowed), oral hypoglycemic agents and lipid-lowering agents.

For the primary endpoint and ESRD, the effects of COZAAR in patient subgroups defined by age, gender and race are shown in Table 2 below. Subgroup analyses can be difficult to interpret and it is not known whether these represent true differences or chance effects.

Table 2 Efficacy Outcomes within Demographic Subgroups

		Primary Composite Endpoint			ESRD		
	No. of Patients	COZAAR Event Rate %	Placebo Event Rate %	Hazard Ratio (95% CI)	COZAAR Event Rate %	Placebo Event Rate %	Hazard Ratio (95% CI)
Overall Results	1513	43.5	47.1	0.839 (0.721, 0.977)	19.6	25.5	0.714 (0.576, 0.885)
Age							
<65 years	1005	44.1	49.0	0.784 (0.653, 0.941)	21.1	28.5	0.670 (0.521, 0.863)

≥65 years	508	42.3	43.5	0.978 (0.749, 1.277)	16.5	19.6	0.847 (0.560, 1.281)
Gender							
Female	557	47.8	54.1	0.762 (0.603, 0.962)	22.8	32.8	0.601 (0.436, 0.828)
Male	956	40.9	43.3	0.892 (0.733, 1.085)	17.5	21.5	0.809 (0.605, 1.081)
Race							
Asian	252	41.9	54.8	0.655 (0.453, 0.947)	18.8	27.4	0.625 (0.367, 1.066)
Black	230	40.0	39.0	0.983 (0.647, 1.495)	17.6	21.0	0.831 (0.456, 1.516)
Hispanic	277	55.0	54.0	1.003 (0.728, 1.380)	30.0	28.5	1.024 (0.661, 1.586)
White	735	40.5	43.2	0.809 (0.645, 1.013)	16.2	23.9	0.596 (0.427, 0.831)

INDICATIONS AND USAGE

Hypertension

COZAAR is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

Nephropathy in Type 2 Diabetic Patients

COZAAR is indicated for the treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria (urinary albumin to creatinine ratio ≥300 mg/g) in patients with type 2 diabetes and a history of hypertension. In this population, COZAAR reduces the rate of progression of nephropathy as measured by the occurrence of doubling of serum creatinine or end stage renal disease (need for dialysis or renal transplantation) (see CLINICAL PHARMACOLOGY, *Pharmacodynamics and Clinical Effects*).

CONTRAINDICATIONS

COZAAR is contraindicated in patients who are hypersensitive to any component of this product.

WARNINGS

Fetal/Neonatal Morbidity and Mortality

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors. When pregnancy is detected, COZAAR should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester.

Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of COZAAR as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to an angiotensin II receptor antagonist will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, COZAAR should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical

profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

Losartan potassium has been shown to produce adverse effects in rat fetuses and neonates, including decreased body weight, delayed physical and behavioral development, mortality and renal toxicity. With the exception of neonatal weight gain (which was affected at doses as low as 10 mg/kg/day), doses associated with these effects exceeded 25 mg/kg/day (approximately three times the maximum recommended human dose of 100 mg on a mg/m^2 basis). These findings are attributed to drug exposure in late gestation and during lactation. Significant levels of losartan and its active metabolite were shown to be present in rat fetal plasma during late gestation and in rat milk.

Hypotension — Volume-Depleted Patients

In patients who are intravascularly volume-depleted (e.g., those treated with diuretics), symptomatic hypotension may occur after initiation of therapy with COZAAR. These conditions should be corrected prior to administration of COZAAR, or a lower starting dose should be used (see DOSAGE AND ADMINISTRATION).

PRECAUTIONS

General

Hypersensitivity: Angioedema. See ADVERSE REACTIONS, *Post-Marketing Experience.*

Impaired Hepatic Function

Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, a lower dose should be considered for patients with impaired liver function (see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY, *Pharmacokinetics*).

Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function have been reported in susceptible individuals treated with COZAAR; in some patients, these changes in renal function were reversible upon discontinuation of therapy.

In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar outcomes have been reported with COZAAR.

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or BUN have been reported. Similar effects have been reported with COZAAR; in some patients, these effects were reversible upon discontinuation of therapy.

Electrolyte Imbalance

Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. In a clinical study conducted in type 2 diabetic patients with proteinuria, the incidence of hyperkalemia was higher in the group treated with COZAAR as compared to the placebo group; however, few patients discontinued therapy due to hyperkalemia (see ADVERSE REACTIONS).

Information for Patients

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug

exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Potassium Supplements: A patient receiving COZAAR should be told not to use potassium supplements or salt substitutes containing potassium without consulting the prescribing physician (see PRECAUTIONS, *Drug Interactions*).

Drug Interactions

No significant drug-drug pharmacokinetic interactions have been found in interaction studies with hydrochlorothiazide, digoxin, warfarin, cimetidine and phenobarbital. (See CLINICAL PHARMACOLOGY, *Drug Interactions*.) Potent inhibitors of cytochrome P450 3A4 and 2C9 have not been studied clinically but *in vitro* studies show significant inhibition of the formation of the active metabolite by inhibitors of P450 3A4 (ketoconazole, troleandomycin, gestodene), or P450 2C9 (sulfaphenazole) and nearly complete inhibition by the combination of sulfaphenazole and ketoconazole. In humans, ketoconazole, an inhibitor of P450 3A4, did not affect the conversion of losartan to the active metabolite after intravenous administration of losartan. Inhibitors of cytochrome P450 2C9 have not been studied clinically. The pharmacodynamic consequences of concomitant use of losartan and inhibitors of P450 2C9 have not been examined.

As with other drugs that block angiotensin II or its effects, concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium.

As with other antihypertensive agents, the antihypertensive effect of losartan may be blunted by the non-steroidal anti-inflammatory drug indomethacin.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Losartan potassium was not carcinogenic when administered at maximally tolerated dosages to rats and mice for 105 and 92 weeks, respectively. Female rats given the highest dose (270 mg/kg/day) had a slightly higher incidence of pancreatic acinar adenoma. The maximally tolerated dosages (270 mg/kg/day in rats, 200 mg/kg/day in mice) provided systemic exposures for losartan and its pharmacologically active metabolite that were approximately 160- and 90-times (rats) and 30- and 15-times (mice) the exposure of a 50 kg human given 100 mg per day.

Losartan potassium was negative in the microbial mutagenesis and V-79 mammalian cell mutagenesis assays and in the *in vitro* alkaline elution and *in vitro* and *in vivo* chromosomal aberration assays. In addition, the active metabolite showed no evidence of genotoxicity in the microbial mutagenesis, *in vitro* alkaline elution, and *in vitro* chromosomal aberration assays.

Fertility and reproductive performance were not affected in studies with male rats given oral doses of losartan potassium up to approximately 150 mg/kg/day. The administration of toxic dosage levels in females (300/200 mg/kg/day) was associated with a significant ($p<0.05$) decrease in the number of corpora lutea/female, implants/female, and live fetuses/female at C-section. At 100 mg/kg/day only a decrease in the number of corpora lutea/female was observed. The relationship of these findings to drug-treatment is uncertain since there was no effect at these dosage levels on implants/pregnant female, percent post-implantation loss, or live animals/litter at parturition. In nonpregnant rats dosed at 135 mg/kg/day for 7 days, systemic exposure (AUCs) for losartan and its active metabolite were approximately 66 and 26 times the exposure achieved in man at the maximum recommended human daily dosage (100 mg).

Pregnancy

Pregnancy Categories C (first trimester) and D (second and third trimesters). See WARNINGS, *Fetal/Neonatal Morbidity and Mortality.*

Nursing Mothers

It is not known whether losartan is excreted in human milk, but significant levels of losartan and its active metabolite were shown to be present in rat milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Use in the Elderly

Of the total number of patients receiving COZAAR in controlled clinical studies for hypertension, 391 patients (19%) were 65 years and over, while 37 patients (2%) were 75 years and over. In a controlled clinical study for renal protection in type 2 diabetic patients with proteinuria, 248 patients (33%) were 65 years and over. No overall differences in effectiveness or safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Hypertension

COZAAR has been evaluated for safety in more than 3300 patients treated for essential hypertension and 4058 patients/subjects overall. Over 1200 patients were treated for over 6 months and more than 800 for over one year. In general, treatment with COZAAR was well-tolerated. The overall incidence of adverse experiences reported with COZAAR was similar to placebo.

In controlled clinical trials, discontinuation of therapy due to clinical adverse experiences was required in 2.3 percent of patients treated with COZAAR and 3.7 percent of patients given placebo.

The following table of adverse events is based on four 6-12 week placebo-controlled trials involving over 1000 patients on various doses (10-150 mg) of losartan and over 300 patients given placebo. All doses of losartan are grouped because none of the adverse events appeared to have a dose-related frequency. The adverse experiences reported in ≥1% of patients treated with COZAAR and more commonly than placebo are shown in the table below.

	Losartan (n=1075) Incidence %	Placebo (n=334) Incidence %
Musculoskeletal		
Cramp, muscle	1	0
Pain, back	2	1
Pain, leg	1	0
Nervous System/Psychiatric		
Dizziness	3	2
Respiratory		
Congestion, nasal	2	1
Infection, upper respiratory	8	7
Sinusitis	1	0

The following adverse events were also reported at a rate of 1% or greater in patients treated with losartan, but were as, or more frequent, in the placebo group: asthenia/fatigue, edema/swelling, abdominal pain, chest pain, nausea, headache, pharyngitis, diarrhea, dyspepsia, myalgia, insomnia, cough, sinus disorder.

Adverse events occurred at about the same rates in men and women, older and younger patients, and black and non-black patients.

A patient with known hypersensitivity to aspirin and penicillin, when treated with COZAAR, was withdrawn from study due to swelling of the lips and eyelids and facial rash, reported as angioedema, which returned to normal 5 days after therapy was discontinued.

Superficial peeling of palms and hemolysis was reported in one subject.

In addition to the adverse events above, potentially important events that occurred in at least two patients/subjects exposed to losartan or other adverse events that occurred in <1% of patients in clinical studies are listed below. It cannot be determined whether these events were causally related to losartan: *Body as a Whole:* facial edema, fever, orthostatic effects, syncope;

Cardiovascular: angina pectoris, second degree AV block, CVA, hypotension, myocardial infarction, arrhythmias including atrial fibrillation, palpitation, sinus bradycardia, tachycardia, ventricular tachycardia, ventricular fibrillation; *Digestive:* anorexia, constipation, dental pain, dry mouth, flatulence, gastritis, vomiting; *Hematologic:* anemia; *Metabolic:* gout; *Musculoskeletal:* arm pain, hip pain, joint swelling, knee pain, musculoskeletal pain, shoulder pain, stiffness, arthralgia, arthritis, fibromyalgia, muscle weakness; *Nervous System/Psychiatric:* anxiety, anxiety disorder, ataxia, confusion, depression, dream abnormality, hypesthesia, decreased libido, memory impairment, migraine, nervousness, paresthesia, peripheral neuropathy, panic disorder, sleep disorder, somnolence, tremor, vertigo; *Respiratory:* dyspnea, bronchitis, pharyngeal discomfort, epistaxis, rhinitis, respiratory congestion; *Skin:* alopecia, dermatitis, dry skin, ecchymosis, erythema, flushing, photosensitivity, pruritus, rash, sweating, urticaria; *Special Senses:* blurred vision, burning/stinging in the eye, conjunctivitis, taste perversion, tinnitus, decrease in visual acuity; *Urogenital:* impotence, nocturia, urinary frequency, urinary tract infection.

Persistent dry cough (with an incidence of a few percent) has been associated with ACE inhibitor use and in practice can be a cause of discontinuation of ACE inhibitor therapy. Two prospective, parallel-group, double-blind, randomized, controlled trials were conducted to assess the effects of losartan on the incidence of cough in hypertensive patients who had experienced cough while receiving ACE inhibitor therapy. Patients who had typical ACE inhibitor cough when challenged with lisinopril, whose cough disappeared on placebo, were randomized to losartan 50 mg, lisinopril 20 mg, or either placebo (one study, n=97) or 25 mg hydrochlorothiazide (n=135). The double-blind treatment period lasted up to 8 weeks. The incidence of cough is shown below.

Study 1†	HCTZ	Losartan	Lisinopril
Cough	25%	17%	69%

Study 2††	Placebo	Losartan	Lisinopril
Cough	35%	29%	62%

† Demographics = (89% caucasian, 64% female)
†† Demographics = (90% caucasian, 51% female)

These studies demonstrate that the incidence of cough associated with losartan therapy, in a population that all had cough associated with ACE inhibitor therapy, is similar to that associated with hydrochlorothiazide or placebo therapy.

Cases of cough, including positive re-challenges, have been reported with the use of losartan in post-marketing experience.

Nephropathy in Type 2 Diabetic Patients

In the RENAAL study involving 1513 patients treated with COZAAR or placebo, the overall incidences of reported adverse experiences were similar for the two groups. COZAAR was generally well tolerated as evidenced by a similar incidence of discontinuations due to side effects compared to placebo (19% for COZAAR, 24% for placebo). The adverse experiences regardless of drug relationship, reported with an incidence of ≥4% of patients treated with COZAAR and occurring more commonly than placebo, on a background of conventional antihypertensive therapy are shown in the table below.

	Losartan and Conventional Antihypertensive Therapy Incidence % (n=751)	Placebo and Conventional Antihypertensive Therapy Incidence % (n=762)
Body as a Whole		
Asthenia/Fatigue	14	10
Chest Pain	12	8
Fever	4	3
Infection	5	4
Influenza-like disease	10	9
Trauma	4	3
Cardiovascular		
Hypotension	7	3
Orthostatic hypotension	4	1
Digestive		
Diarrhea	15	10
Dyspepsia	4	3
Gastritis	5	4
Endocrine		
Diabetic neuropathy	4	3
Diabetic vascular disease	10	9
Eyes, Ears, Nose and Throat		
Cataract	7	5
Sinusitis	6	5
Hemic		
Anemia	14	11
Metabolic and Nutrition		
Hyperkalemia	7	3
Hypoglycemia	14	10
Weight gain	4	3
Musculoskeletal		
Back pain	12	10
Leg pain	5	4
Knee pain	5	4
Muscular weakness	7	4
Nervous System		
Hypesthesia	5	4
Respiratory		
Bronchitis	10	9
Cough	11	10
Skin		
Cellulitis	7	6
Urogenital		
Urinary tract infection	16	13

Post-Marketing Experience

The following additional adverse reactions have been reported in post-marketing experience:

Hypersensitivity: Angioedema, including swelling of the larynx and glottis, causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue has been reported rarely in patients treated with losartan; some of these patients previously experienced angioedema with other drugs including ACE inhibitors. Vasculitis, including Henoch-Schönlein purpura, has been reported. Anaphylactic reactions have been reported.

Digestive: Hepatitis (reported rarely).

Respiratory: Dry cough (see above).

Hyperkalemia and hyponatremia have been reported.

Laboratory Test Findings

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of COZAAR.

Creatinine, Blood Urea Nitrogen: Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in less than 0.1 percent of patients with essential hypertension treated with COZAAR alone (see PRECAUTIONS, *Impaired Renal Function*).

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.11 grams percent and 0.09 volume percent, respectively) occurred frequently

in patients treated with COZAAR alone, but were rarely of clinical importance. No patients were discontinued due to anemia.

Liver Function Tests: Occasional elevations of liver enzymes and/or serum bilirubin have occurred. In patients with essential hypertension treated with COZAAR alone, one patient (<0.1%) was discontinued due to these laboratory adverse experiences.

OVERDOSAGE

Significant lethality was observed in mice and rats after oral administration of 1000 mg/kg and 2000 mg/kg, respectively, about 44 and 170 times the maximum recommended human dose on a mg/m^2 basis.

Limited data are available in regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

Neither losartan nor its active metabolite can be removed by hemodialysis.

DOSAGE AND ADMINISTRATION

COZAAR may be administered with other antihypertensive agents, and with or without food.

Hypertension

Dosing must be individualized. The usual starting dose of COZAAR is 50 mg once daily, with 25 mg used in patients with possible depletion of intravascular volume (e.g., patients treated with diuretics) (see WARNINGS, *Hypotension — Volume-Depleted Patients*) and patients with a history of hepatic impairment (see PRECAUTIONS, *General*). COZAAR can be administered once or twice daily with total daily doses ranging from 25 mg to 100 mg.

If the antihypertensive effect measured at trough using once-a-day dosing is inadequate, a twice-a-day regimen at the same total daily dose or an increase in dose may give a more satisfactory response. The effect of losartan is substantially present within one week but in some studies the maximal effect occurred in 3-6 weeks (see CLINICAL PHARMACOLOGY, *Pharmacodynamics and Clinical Effects)*.

If blood pressure is not controlled by COZAAR alone, a low dose of a diuretic may be added. Hydrochlorothiazide has been shown to have an additive effect (see CLINICAL PHARMACOLOGY, *Pharmacodynamics and Clinical Effects*).

No initial dosage adjustment is necessary for elderly patients or for patients with renal impairment, including patients on dialysis.

Nephropathy in Type 2 Diabetic Patients

The usual starting dose is 50 mg once daily. The dose should be increased to 100 mg once daily based on blood pressure response (see CLINICAL PHARMACOLOGY, *Pharmacodynamics and Clinical Effects*). COZAAR may be administered with insulin and other commonly used hypoglycemic agents (e.g., sulfonylureas, glitazones and glucosidase inhibitors).

HOW SUPPLIED

No. 3612 — Tablets COZAAR, 25 mg, are light green, teardrop-shaped, film-coated tablets with code MRK on one side and 951 on the other. They are supplied as follows:

NDC 0006-0951-54 unit of use bottles of 90

NDC 0006-0951-58 unit of use bottles of 100

NDC 0006-0951-28 unit dose packages of 100.

No. 3613 — Tablets COZAAR, 50 mg, are green, teardrop-shaped, film-coated tablets with code MRK 952 on one side and COZAAR on the other. They are supplied as follows:

NDC 0006-0952-31 unit of use bottles of 30

NDC 0006-0952-54 unit of use bottles of 90

NDC 0006-0952-58 unit of use bottles of 100

NDC 0006-0952-28 unit dose packages of 100
NDC 0006-0952-82 bottles of 1,000.

No. 6536 — Tablets COZAAR, 100 mg, are dark green, teardrop-shaped, film-coated tablets with code 960 on one side and MRK on the other. They are supplied as follows:

NDC 0006-0960-31 unit of use bottles of 30
NDC 0006-0960-58 unit of use bottles of 100
NDC 0006-0960-28 unit dose packages of 100.

Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Keep container tightly closed. Protect from light.

Dist. by:
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

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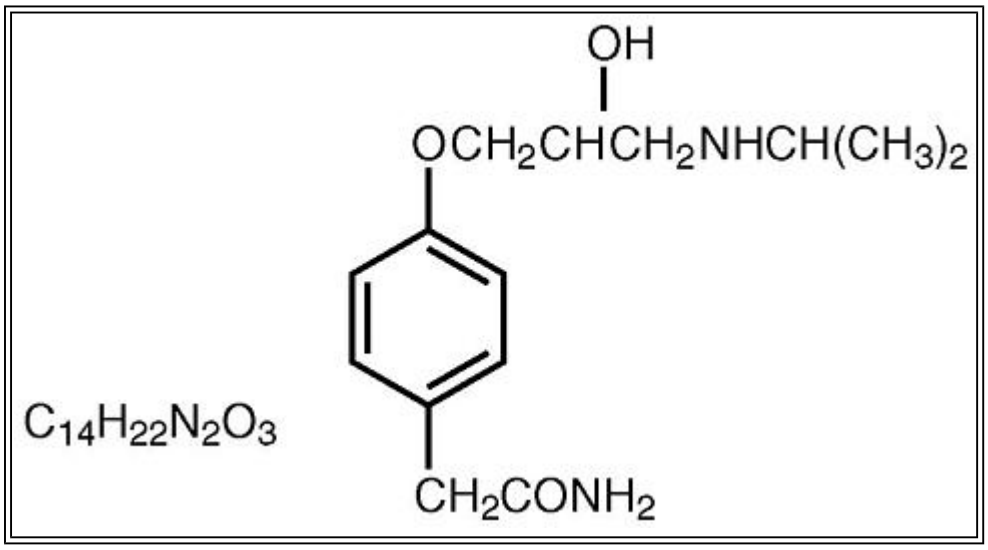
TENORMIN® Tablets (AstraZeneca)
TENORMIN® I.V. Injection
(atenolol)

DESCRIPTION

TENORMIN (atenolol), a synthetic, beta $_1$ -selective (cardioselective) adrenoreceptor blocking agent, may be chemically described as benzeneacetamide, 4-[2'-hydroxy-3'-[(1-methylethyl)amino]propoxy]-. The molecular and structural formulas are:



Atenolol (free base) has a molecular weight of 266. It is a relatively polar hydrophilic compound with a water solubility of 26.5 mg/mL at 37°C and a log partition coefficient (octanol/ water) of 0.23. It is freely soluble in 1N HCl (300 mg/mL at 25°C) and less soluble in chloroform (3 mg/mL at 25°C).

TENORMIN is available as 25, 50 and 100 mg tablets for oral administration. TENORMIN for parenteral administration is available as TENORMIN I.V. Injection containing 5 mg atenolol in 10 mL sterile, isotonic, citrate-buffered, aqueous solution. The pH of the solution is 5.5-6.5.

Inactive Ingredients: TENORMIN Tablets: Magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate. TENORMIN I.V. Injection: Sodium chloride for isotonicity and citric acid and sodium hydroxide to adjust pH.

CLINICAL PHARMACOLOGY

TENORMIN is a beta $_1$ -selective (cardioselective) beta-adrenergic receptor blocking agent without membrane stabilizing or intrinsic sympathomimetic (partial agonist) activities. This preferential effect is not absolute, however, and at higher doses, TENORMIN inhibits beta $_2$ -adrenoreceptors, chiefly located in the bronchial and vascular musculature.

Pharmacokinetics and Metabolism: In man, absorption of an oral dose is rapid and consistent but incomplete. Approximately 50% of an oral dose is absorbed from the gastrointestinal tract, the remainder being excreted unchanged in the feces. Peak blood levels are reached between two (2) and four (4) hours after ingestion. Unlike propranolol or metoprolol, but like nadolol, TENORMIN undergoes little or no metabolism by the liver, and the absorbed portion is eliminated primarily by renal excretion. Over 85% of an intravenous dose is excreted in urine within 24 hours compared with approximately 50% for an oral dose. TENORMIN also differs from propranolol in that only a small amount (6%-16%) is bound to proteins in the plasma. This

kinetic profile results in relatively consistent plasma drug levels with about a fourfold interpatient variation.

The elimination half-life of oral TENORMIN is approximately 6 to 7 hours, and there is no alteration of the kinetic profile of the drug by chronic administration. Following intravenous administration, peak plasma levels are reached within 5 minutes. Declines from peak levels are rapid (5- to 10-fold) during the first 7 hours; thereafter, plasma levels decay with a half-life similar to that of orally administered drug. Following oral doses of 50 mg or 100 mg, both beta-blocking and antihypertensive effects persist for at least 24 hours. When renal function is impaired, elimination of TENORMIN is closely related to the glomerular filtration rate; significant accumulation occurs when the creatinine clearance falls below 35 mL/min/1.73m ^{2} . (See DOSAGE AND ADMINISTRATION).

Pharmacodynamics: In standard animal or human pharmacological tests, beta-adrenoreceptor blocking activity of TENORMIN has been demonstrated by: (1) reduction in resting and exercise heart rate and cardiac output, (2) reduction of systolic and diastolic blood pressure at rest and on exercise, (3) inhibition of isoproterenol induced tachycardia, and (4) reduction in reflex orthostatic tachycardia.

A significant beta-blocking effect of TENORMIN, as measured by reduction of exercise tachycardia, is apparent within one hour following oral administration of a single dose. This effect is maximal at about 2 to 4 hours, and persists for at least 24 hours. Maximum reduction in exercise tachycardia occurs within 5 minutes of an intravenous dose. For both orally and intravenously administered drug, the duration of action is dose related and also bears a linear relationship to the logarithm of plasma TENORMIN concentration. The effect on exercise tachycardia of a single 10 mg intravenous dose is largely dissipated by 12 hours, whereas beta-blocking activity of single oral doses of 50 mg and 100 mg is still evident beyond 24 hours following administration. However, as has been shown for all beta-blocking agents, the antihypertensive effect does not appear to be related to plasma level.

In normal subjects, the beta $_1$ -selectivity of TENORMIN has been shown by its reduced ability to reverse the beta $_2$ -mediated vasodilating effect of isoproterenol as compared to equivalent beta-blocking doses of propranolol. In asthmatic patients, a dose of TENORMIN producing a greater effect on resting heart rate than propranolol resulted in much less increase in airway resistance. In a placebo controlled comparison of approximately equipotent oral doses of several beta blockers, TENORMIN produced a significantly smaller decrease of FEV $_1$ than nonselective beta blockers such as propranolol and, unlike those agents, did not inhibit bronchodilation in response to isoproterenol.

Consistent with its negative chronotropic effect due to beta blockade of the SA node, TENORMIN increases sinus cycle length and sinus node recovery time. Conduction in the AV node is also prolonged. TENORMIN is devoid of membrane stabilizing activity, and increasing the dose well beyond that producing beta blockade does not further depress myocardial contractility. Several studies have demonstrated a moderate (approximately 10%) increase in stroke volume at rest and during exercise.

In controlled clinical trials, TENORMIN, given as a single daily oral dose, was an effective antihypertensive agent providing 24-hour reduction of blood pressure. TENORMIN has been studied in combination with thiazide-type diuretics, and the blood pressure effects of the combination are approximately additive. TENORMIN is also compatible with methyldopa, hydralazine, and prazosin, each combination resulting in a larger fall in blood pressure than with the single agents. The dose range of TENORMIN is narrow and increasing the dose beyond 100 mg once daily is not associated with increased antihypertensive effect. The mechanisms of the antihypertensive effects of beta-blocking agents have not been established. Several possible mechanisms have been proposed and include: (1) competitive antagonism of catecholamines at peripheral (especially cardiac) adrenergic neuron sites, leading to decreased cardiac output, (2) a central effect leading to reduced sympathetic outflow to the periphery, and (3) suppression of renin activity. The results from long-term studies have not shown any diminution of the antihypertensive efficacy of TENORMIN with prolonged use.

By blocking the positive chronotropic and inotropic effects of catecholamines and by decreasing blood

pressure, atenolol generally reduces the oxygen requirements of the heart at any given level of effort, making it useful for many patients in the long-term management of angina pectoris. On the other hand, atenolol can increase oxygen requirements by increasing left ventricular fiber length and end diastolic pressure, particularly in patients with heart failure.

In a multicenter clinical trial (ISIS-1) conducted in 16,027 patients with suspected myocardial infarction, patients presenting within 12 hours (mean = 5 hours) after the onset of pain were randomized to either conventional therapy plus TENORMIN (n = 8,037), or conventional therapy alone (n = 7,990). Patients with a heart rate of <50 bpm or systolic blood pressure <100 mm Hg, or with other contraindications to beta blockade, were excluded. Thirty-eight percent of each group were treated within 4 hours of onset of pain. The mean time from onset of pain to entry was 5.0 ± 2.7 hours in both groups. Patients in the TENORMIN group were to receive TENORMIN I.V. Injection 5-10 mg given over 5 minutes plus TENORMIN Tablets 50 mg every 12 hours orally on the first study day (the first oral dose administered about 15 minutes after the IV dose) followed by either TENORMIN Tablets 100 mg once daily or TENORMIN Tablets 50 mg twice daily on days 2-7. The groups were similar in demographic and medical history characteristics and in electrocardiographic evidence of myocardial infarction, bundle branch block, and first degree atrioventricular block at entry.

During the treatment period (days 0-7), the vascular mortality rates were 3.89% in the TENORMIN group (313 deaths) and 4.57% in the control group (365 deaths). This absolute difference in rates, 0.68%, is statistically significant at the P <0.05 level. The absolute difference translates into a proportional reduction of 15% (3.89-4.57/4.57 = -0.15). The 95% confidence limits are 1%-27%. Most of the difference was attributed to mortality in days 0-1 (TENORMIN--121 deaths; control--171 deaths).

Despite the large size of the ISIS-1 trial, it is not possible to identify clearly subgroups of patients most likely or least likely to benefit from early treatment with atenolol. Good clinical judgment suggests, however, that patients who are dependent on sympathetic stimulation for maintenance of adequate cardiac output and blood pressure are not good candidates for beta blockade. Indeed, the trial protocol reflected that judgment by excluding patients with blood pressure consistently below 100 mm Hg systolic. The overall results of the study are compatible with the possibility that patients with borderline blood pressure (less than 120 mm Hg systolic), especially if over 60 years of age, are less likely to benefit.

The mechanism through which atenolol improves survival in patients with definite or suspected acute myocardial infarction is unknown, as is the case for other beta blockers in the postinfarction setting. Atenolol, in addition to its effects on survival, has shown other clinical benefits including reduced frequency of ventricular premature beats, reduced chest pain, and reduced enzyme elevation.

INDICATIONS AND USAGE

Hypertension: TENORMIN is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

Angina Pectoris Due to Coronary Atherosclerosis: TENORMIN is indicated for the long-term management of patients with angina pectoris.

Acute Myocardial Infarction: TENORMIN is indicated in the management of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment can be initiated as soon as the patient's clinical condition allows. (See DOSAGE AND ADMINISTRATION , CONTRAINDICATIONS , AND WARNINGS .) In general, there is no basis for treating patients like those who were excluded from the ISIS-1 trial (blood pressure less than 100 mm Hg systolic, heart rate less than 50 bpm) or have other reasons to avoid beta blockade. As noted above, some subgroups (eg, elderly patients with systolic blood pressure below 120 mm Hg) seemed less likely to benefit.

CONTRAINDICATIONS

TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure. (See WARNINGS .)

TENORMIN is contraindicated in those patients with a history of hypersensitivity to the atenolol or any of the drug product's components.

WARNINGS

Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In patients who have congestive heart failure controlled by digitalis and/or diuretics, TENORMIN should be administered cautiously. Both digitalis and atenolol slow AV conduction.

In patients with acute myocardial infarction, cardiac failure which is not promptly and effectively controlled by 80 mg of intravenous furosemide or equivalent therapy is a contraindication to beta-blocker treatment.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be treated appropriately according to currently recommended guidelines, and the response observed closely. If cardiac failure continues despite adequate treatment, TENORMIN should be withdrawn. (See DOSAGE AND ADMINISTRATION .)

Cessation of Therapy with TENORMIN: Patients with coronary artery disease, who are being treated with TENORMIN, should be advised against abrupt discontinuation of therapy. Severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias have been reported in angina patients following the abrupt discontinuation of therapy with beta blockers. The last two complications may occur with or without preceding exacerbation of the angina pectoris. As with other beta blockers, when discontinuation of TENORMIN is planned, the patients should be carefully observed and advised to limit physical activity to a minimum. If the angina worsens or acute coronary insufficiency develops, it is recommenced that TENORMIN be promptly reinstituted, at least temporarily. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue TENORMIN therapy abruptly even in patients treated only for hypertension. (See DOSAGE AND ADMINISTRATION .)

Concomitant Use of Calcium Channel Blockers: Bradycardia and heart block can occur and the left ventricular end diastolic pressure can rise when beta blockers are administered with verapamil or diltiazem. Patients with pre-existing conduction abnormalities or left ventricular dysfunction are particularly susceptible. (See **PRECAUTIONS** .)

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta $_1$ selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta $_1$ selectivity is not absolute, the lowest possible dose of TENORMIN should be used with therapy initiated at 50 mg and a beta $_2$ -stimulating agent (bronchodilator) should be made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

Anesthesia and Major Surgery: It is not advisable to withdraw beta-adrenoreceptor blocking drugs prior to surgery in the majority of patients. However, care should be taken when using anesthetic agents such as those which may depress the myocardium. Vagal dominance, if it occurs, may be corrected with atropine (1-2 mg

IV).

Additionally, caution should be used when TENORMIN I.V. Injection is administered concomitantly with such agents.

TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents: eg, dobutamine or isoproterenol with caution (see section on OVERDOSAGE).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. At recommended doses TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Patients suspected of having thyroid disease should be monitored closely when adminstering TENORMIN I.V. Injection. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely. (See DOSAGE AND ADMINISTRATION .)

Untreated Pheochromocytoma: TENORMIN and TENORMIN I.V. should not be given to patients with untreated pheochromocytoma.

Pregnancy and Fetal Injury: Atenolol can cause fetal harm when administered to a pregnant woman. Atenolol crosses the placental barrier and appears in cord blood. Administration of atenolol, starting in the second trimester of pregnancy, has been associated with the birth of infants that are small for gestational age. No studies have been performed on the use of atenolol in the first trimester and the possibility of fetal injury cannot be excluded. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg/day or 25 or more times the maximum recommended human antihypertensive dose*. Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg/day or 12.5 times the maximum recommended human antihypertensive dose*.

*Based on the maximum dose of 100 mg/day in a 50 kg patient.

PRECAUTIONS

General: Patients already on a beta blocker must be evaluated carefully before TENORMIN is administered. Initial and subsequent TENORMIN dosages can be adjusted downward depending on clinical observations including pulse and blood pressure. TENORMIN may aggravate peripheral arterial circulatory disorders.

Impaired Renal Function: The drug should be used with caution in patients with impaired renal function. (See DOSAGE AND ADMINISTRATION .)

Drug Interactions: Catecholamine-depleting drugs (eg, reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope or postural hypotension.

Calcium channel blockers may also have an additive effect when given with TENORMIN (See WARNINGS .).

Beta blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two drugs are coadministered, the beta blocker should be withdrawn several days before the gradual withdrawal of clonidine. If replacing clonidine by beta-blocker therapy, the introduction of beta blockers should be delayed for several days after clonidine administration has stopped.

Caution should be exercised with TENORMIN I.V. Injection when given in close proximity with drugs that may also have a depressant effect on myocardial contractility. On rare occasions, concomitant use of intravenous beta blockers and intravenous verapamil has resulted in serious adverse reactions, especially in patients with severe cardiomyopathy, congestive heart failure, or recent myocardial infarction.

Concomitant use of prostaglandin synthase inhibiting drugs, e.g., indomethacin, may decrease the hypotensive effects of beta-blockers.

Information on concurrent usage of atenolol and aspirin is limited. Data from several studies, ie, TIMI-II, ISIS-2, currently do not suggest any clinical interaction between aspirin and beta blockers in the acute myocardial infarction setting.

While taking beta blockers, patients with a history of anaphylactic reaction to a variety of allergens may have a more severe reaction on repeated challenge, either accidental, diagnostic or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat the allergic reaction.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human antihypertensive dose,* did not indicate a carcinogenic potential of atenolol. A third (24 month) rat study, employing doses of 500 and 1,500 mg/kg/day (250 and 750 times the maximum recommended human antihypertensive dose*) resulted in increased incidences of benign adrenal medullary tumors in males and females, mammary fibroadenomas in females, and anterior pituitary adenomas and thyroid parafollicular cell carcinomas in males. No evidence of a mutagenic potential of atenolol was uncovered in the dominant lethal test (mouse), in vivo cytogenetics test (Chinese hamster) or Ames test (*S typhimurium*).

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose*) was unaffected by atenolol administration.

Animal Toxicology: Chronic studies employing oral atenolol performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human antihypertensive dose*) and increased incidence of atrial degeneration of hearts of male rats at 300 but not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human antihypertensive dose,* respectively).

*Based on the maximum dose of 100 mg/day in a 50 kg patient.

Usage in Pregnancy: Pregnancy Category D: See WARNINGS --Pregnancy and Fetal Injury.

Nursing Mothers: Atenolol is excreted in human breast milk at a ratio of 1.5 to 6.8 when compared to the concentration in plasma. Caution should be exercised when TENORMIN is administered to a nursing woman. Clinically significant bradycardia has been reported in breast fed infants. Premature infants, or infants with impaired renal function, may be more likely to develop adverse effects.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Most adverse effects have been mild and transient.

The frequency estimates in the following table were derived from controlled studies in hypertensive patients in which adverse reactions were either volunteered by the patient (US studies) or elicited, eg, by checklist (foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects of TENORMIN and placebo is similar, causal relationship to TENORMIN is uncertain.

	Volunteered (US Studies)		Total--Volunteered and Elicited (Foreign + US Studies)	
	Atenolol (n = 164) %	Placebo (n = 206) %	Atenolol (n = 399) %	Placebo (n = 407) %
CARDIOVASCULAR				
Bradycardia	3	0	3	0
Cold Extremities	0	0.5	12	5
Postural Hypotension	2	1	4	5
Leg Pain	0	0.5	3	1
CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR				
Dizziness	4	1	13	6
Vertigo	2	0.5	2	0.2
Light-headedness	1	0	3	0.7
Tiredness	0.6	0.5	26	13
Fatigue	3	1	6	5
Lethargy	1	0	3	0.7
Drowsiness	0.6	0	2	0.5
Depression	0.6	0.5	12	9
Dreaming	0	0	3	1
GASTROINTESTINAL				
Diarrhea	2	0	3	2
Nausea	4	1	3	1
RESPIRATORY (see WARNINGS)				
Wheeziness	0	0	3	3
Dyspnea	0.6	1	6	4

Acute Myocardial Infarction: In a series of investigations in the treatment of acute myocardial infarction, bradycardia and hypotension occurred more commonly, as expected for any beta blocker, in atenolol-treated patients than in control patients. However, these usually responded to atropine and/or to withholding further dosage of atenolol. The incidence of heart failure was not increased by atenolol. Inotropic agents were infrequently used. The reported frequency of these and other events occurring during these investigations is given in the following table.

In a study of 477 patients, the following adverse events were reported during either intravenous and/or oral atenolol administration:

	Conventional Therapy Plus Atenolol (n=244)		Conventional Therapy Alone (n=233)	
Bradycardia	43	(18%)	24	(10%)
Hypotension	60	(25%)	34	(15%)
Bronchospasm	3	(1.2%)	2	(0.9%)
Heart Failure	46	(19%)	56	(24%)
Heart Block	11	(4.5%)	10	(4.3%)
BBB + Major Axis Deviation	16	(6.6%)	28	(12%)
Supraventricular Tachycardia	28	(11.5%)	45	(19%)
Atrial Fibrillation	12	(5%)	29	(11%)
Atrial Flutter	4	(1.6%)	7	(3%)
Ventricular Tachycardia	39	(16%)	52	(22%)
Cardiac Reinfarction	0	(0%)	6	(2.6%)
Total Cardiac Arrests	4	(1.6%)	16	(6.9%)
Nonfatal Cardiac Arrests	4	(1.6%)	12	(5.1%)
Deaths	7	(2.9%)	16	(6.9%)
Cardiogenic Shock	1	(0.4%)	4	(1.7%)
Development of Ventricular Septal Defect	0	(0%)	2	(0.9%)
Development of Mitral Regurgitation	0	(0%)	2	(0.9%)
Renal Failure	1	(0.4%)	0	(0%)
Pulmonary Emboli	3	(1.2%)	0	(0%)

In the subsequent International Study of Infarct Survival (ISIS-1) including over 16,000 patients of whom 8,037 were randomized to receive TENORMIN treatment, the dosage of intravenous and subsequent oral TENORMIN was either discontinued or reduced for the following reasons:

	Reasons for Reduced Dosage IV Atenolol Reduced Dose (<5 mg) *		Oral Partial Dose	
Hypotension/Bradycardia	105	(1.3%)	1168	(14.5%)
Cardiogenic Shock	4	(.04%)	35	(.44%)
Reinfarction	0	(0%)	5	(.06%)
Cardiac Arrest	5	(.06%)	28	(.34%)
Heart Block (> first degree)	5	(.06%)	143	(1.7%)
Cardiac Failure	1	(.01%)	233	(2.9%)
Arrhythmias	3	(.04%)	22	(.27%)

Bronchospasm	1	(.01%)	50	(.62%)

* Full dosage was 10 mg and some patients received less than 10 mg but more than 5 mg.

During postmarketing experience with TENORMIN, the following have been reported in temporal relationship to the use of the drug: elevated liver enzymes and/or bilirubin, hallucinations, headache, impotence, Peyronie's disease, postural hypotension which may be associated with syncope, psoriasiform rash or exacerbation of psoriasis, psychoses, purpura, reversible alopecia, thrombocytopenia, visual disturbances, sick sinus syndrome, and drymouth. TENORMIN, like other beta blockers, has been associated with the development of antinuclear antibodies (ANA), lupus syndrome, and Raynaud's phenomenon.

POTENTIAL ADVERSE EFFECTS

In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN.

Hematologic: Agranulocytosis.

Allergic: Fever, combined with aching and sore throat, laryngospasm, and respiratory distress.

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation of time and place; short-term memory loss; emotional lability with slightly clouded sensorium; and decreased performance on neuropsychometrics.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Other: Erythematous rash.

Miscellaneous: There have been reports of skin rashes and/ or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small, and in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy. (SEE DOSAGE AND ADMINISTRATION .)

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with TENORMIN. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

OVERDOSAGE

Overdosage with TENORMIN has been reported with patients surviving acute doses as high as 5 g. One death was reported in a man who may have taken as much as 10 g acutely.

The predominant symptoms reported following TENORMIN overdose are lethargy, disorder of respiratory drive, wheezing, sinus pause and bradycardia. Additionally, common effects associated with overdosage of any beta-adrenergic blocking agent and which might also be expected in TENORMIN overdose are congestive heart failure, hypotension, bronchospasm and/or hypoglycemia.

Treatment of overdose should be directed to the removal of any unabsorbed drug by induced emesis, gastric lavage, or administration of activated charcoal. TENORMIN can be removed from the general circulation by hemodialysis. Other treatment modalities should be employed at the physician's discretion and may include:

BRADYCARDIA: Atropine intravenously. If there is no response to vagal blockade, give isoproterenol cautiously. In refractory cases, a transvenous cardiac pacemaker may be indicated.

HEART BLOCK (SECOND OR THIRD DEGREE): Isoproterenol or transvenous cardiac pacemaker.

CARDIAC FAILURE: Digitalize the patient and administer a diuretic. Glucagon has been reported to be useful.

HYPOTENSION: Vasopressors such as dopamine or norepinephrine (levarterenol). Monitor blood pressure continuously.

BRONCHOSPASM: A beta $_2$ stimulant such as isoproterenol or terbutaline and/or aminophylline.

HYPOGLYCEMIA: Intravenous glucose.

Based on the severity of symptoms, management may require intensive support care and facilities for applying cardiac and respiratory support.

DOSAGE AND ADMINISTRATION

Hypertension: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to diuretic therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit.

TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa.

Angina Pectoris: The initial dose of TENORMIN is 50 mg given as one tablet a day. If an optimal response is not achieved within one week, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Some patients may require a dosage of 200 mg once a day for optimal effect.

Twenty-four hour control with once daily dosing is achieved by giving doses larger than necessary to achieve an immediate maximum effect. The maximum early effect on exercise tolerance occurs with doses of 50 to 100 mg, but at these doses the effect at 24 hours is attenuated, averaging about 50% to 75% of that observed with once a day oral doses of 200 mg.

Acute Myocardial Infarction: In patients with definite or suspected acute myocardial infarction, treatment with TENORMIN I.V. Injection should be initiated as soon as possible after the patient's arrival in the hospital and after eligibility is established. Such treatment should be initiated in a coronary care or similar unit immediately after the patient's hemodynamic condition has stabilized. Treatment should begin with the intravenous administration of 5 mg TENORMIN over 5 minutes followed by another 5 mg intravenous injection 10 minutes later. TENORMIN I.V. Injection should be administered under carefully controlled conditions including monitoring of blood pressure, heart rate, and electrocardiogram. Dilutions of TENORMIN I.V. Injection in Dextrose Injection USP, Sodium Chloride Injection USP, or Sodium Chloride and Dextrose Injection may be used. These admixtures are stable for 48 hours if they are not used immediately.

In patients who tolerate the full intravenous dose (10 mg), TENORMIN Tablets 50 mg should be initiated 10 minutes after the last intravenous dose followed by another 50 mg oral dose 12 hours later. Thereafter, TENORMIN can be given orally either 100 mg once daily or 50 mg twice a day for a further 6-9 days or until discharge from the hospital. If bradycardia or hypotension requiring treatment or any other untoward effects occur, TENORMIN should be discontinued. (See full prescribing information prior to initiating therapy with TENORMIN tablets.)

Data from other beta blocker trials suggest that if there is any question concerning the use of IV beta blocker or clinical estimate that there is a contraindication, the IV beta blocker may be eliminated and patients fulfilling the safety criteria may be given TENORMIN Tablets 50 mg twice daily or 100 mg once a day for at

least seven days (if the IV dosing is excluded).

Although the demonstration of efficacy of TENORMIN is based entirely on data from the first seven postinfarction days, data from other beta blocker trials suggest that treatment with beta blockers that are effective in the postinfarction setting may be continued for one to three years if there are no contraindications.

TENORMIN is an additional treatment to standard coronary care unit therapy.

Elderly Patients or Patients with Renal Impairment: TENORMIN is excreted by the kidneys; consequently dosage should be adjusted in cases of severe impairment of renal function. Some reduction in dosage may also be appropriate for the elderly, since decreased kidney function is a physiologic consequence of aging. Atenolol excretion would be expected to decrease with advancing age.

No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 mL/min/1.73 m^2. Accumulation of atenolol and prolongation of its half-life were studied in subjects with creatinine clearance between 5 and 105 mL/min. Peak plasma levels were significantly increased in subjects with creatinine clearances below 30 mL/min.

The following maximum oral dosages are recommended for elderly, renally-impaired patients and for patients with renal impairment due to other causes:

Creatinine Clearance (mL/min/1.73m^2)	Atenolol Elimination Half-Life (h)	Maximum Dosage (tablets)	Maximum Dosage (I.V.)
15-35	16-27	50 mg daily	50 mg daily
<15	>27	25 mg daily	50 mg daily

Some renally-impaired or elderly patients being treated for hypertension may require a lower starting dose of TENORMIN: 25 mg given as one tablet a day. If this 25 mg dose is used, assessment of efficacy must be made carefully. This should include measurement of blood pressure just prior to the next dose ("trough" blood pressure) to ensure that the treatment effect is present for a full 24 hours.

Although a similar dosage reduction may be considered for elderly and/or renally-impaired patients being treated for indications other than hypertension, data are not available for these patient populations.

Patients on hemodialysis should be given 25 mg or 50 mg after each dialysis; this should be done under hospital supervision as marked falls in blood pressure can occur.

Cessation of Therapy in Patients with Angina Pectoris: If withdrawal of TENORMIN therapy is planned, it should be achieved gradually and patients should be carefully observed and advised to limit physical activity to a minimum.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

TENORMIN Tablets: Tablets of 25 mg atenolol, NDC 0310-0107 (round, flat, uncoated white tablets identified with "T" debossed on one side and 107 debossed on the other side) are supplied in bottles of 100 tablets.

Tablets of 50 mg atenolol, NDC 0310-0105 (round, flat, uncoated white tablets identified with "TENORMIN"

debossed on one side and 105 debossed on the other side, bisected) are supplied in bottles of 100 tablets and 1000 tablets.

Tablets of 100 mg atenolol, NDC 0310-0101 (round, flat, uncoated white tablets identified with "TENORMIN" debossed on one side and 101 debossed on the other side) are supplied in bottles of 100 tablets.

Store at controlled room temperature, 20-25°C (68-77°F) [see USP]. Dispense in well-closed, light resistant containers.

TENORMIN I.V. Injection:*

TENORMIN I.V. Injection, NDC 0310-0108, is supplied as 5 mg atenolol in 10 mL ampules of isotonic citrate-buffered aqueous solution.

Protect from light. Keep ampules in outer packaging until time of use. Store at controlled room temperature 20-25°C (68-77°F) [see USP].

ZENECA

Manufactured for:

Zeneca Pharmaceuticals

A Business Unit of Zeneca Inc.

Wilmington, Delaware 19850-5437

By: IPR Pharmaceuticals, Inc.

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TENORMIN I.V. Injection

is manufactured by:

Marsam Pharmaceuticals Inc.

Cherry Hill, NJ 08034

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610100 Rev. 10/00

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