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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-386/S-032

Medical Review(s)

**Division of Cardio-Renal Drug Products
Medical Officer Review**

Name of Drug: Cozaar® Losartan potassium Tablets

Sponsor: Merck Research Laboratory

Date of Review: January 23, 2003

Type of Submission: Financial statement for the LIFE study

Reviewer: Abraham M. Karkowsky, M.D., Ph.D.

Summary:

The Financial disclosure information is unlikely to impact on the conclusions for the LIFE study.

Body:

The sponsor submits form #3455, which covers investigators in the LIFE study. There were a total of 4,637 investigators involved in the study. Of these 1166 did not submit financial disclosure forms.

| Category | Number | |
|-------------------------------------------------------------------------------------------------------------------------------------|--------|--|
| • Total number of investigators, sub-investigators per protocol and per site | 4,637 | |
| • Number of investigators, sub-investigators who are certified regarding an absence of financial arrangements per protocol and site | 3,380 | |
| • Total number of investigators not providing information and not certified per protocol and site | 1166 | |
| • Investigator no longer at site, unable to obtain information | 1015 | |
| • Not returning requested information | 151 | |
| • Investigators not certified due to significant payment of other sorts or equity interest per protocol and site | 91 | |

The large number of investigators and sub-investigators with lacking information is not surprising given the large number of sites and the long duration of the study. I've asked Merck to submit information on the financial disclosure information on primary investigators who enrolled more than 20 subjects. Of the 97 sites that enrolled > 20 subjects all but 2 of the primary investigators submitted financial disclosure forms. In the two sites where the primary investigator did not submit forms there were a total of 3 events.

There were an additional 4 sites among these primary investigators that did have some financial information to disclose. There were 300 subjects enrolled in these four sites equally distributed between the losartan and atenolol cohorts. There were 20

primary events in the atenolol subjects and 17 in the losartan subjects, approximating the outcome from the overall study.

There is consequently no reason to suspect that any financial interactions altered the outcome of these studies.

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/s/

Abraham Karkowsky
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MEDICAL OFFICER

**Amended Clinical Review Cover
Sheet
Supplemental NDA Submission**

**NDA 20-386
Cozaar™ Tablets
Merck & Co., Inc**

**Thomas A. Marciniak, MD
Medical Officer
Division of Cardiorenal Drug Products**

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Amended Clinical Review for Supplemental NDA 20-386

NOTE: This document is an amended version of the Clinical Review for this supplemental NDA. The review has been amended to correct some typographical errors, to include some re-analyses and additional analyses based on data not available at the time of submission of the original review to the Division external advisory committee, and to incorporate labeling recommendations. A more detailed description of the changes from the original are given in Section V.A.

Executive Summary

I. Recommendations

A. Recommendation on Approvability

With this supplemental NDA the sponsor is seeking approval for a new indication for losartan, a drug approved for the treatment of hypertension. The sponsor proposes the new indication as “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 sponsor submitted the data from a single study to support this indication. The study is the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study, a large international study.

The reviewer believes that the LIFE study demonstrates adequately that antihypertensive regimens including losartan and hydrochlorothiazide are superior to ones including atenolol and hydrochlorothiazide for reducing the primary composite endpoint of death, myocardial infarction, and stroke in hypertensive patients with left ventricular hypertrophy. The endpoint is a vital one and the magnitude of the treatment effect is reasonable (about a 10% risk reduction) such that a single trial is acceptable for supporting a new indication. However, the advantage of the losartan/hydrochlorothiazide regimen over the atenolol/hydrochlorothiazide regiment appears to be predominantly a 25% reduction in stroke rates in older, non-black patients. The reviewer recommends that the new indication be approved as “an antihypertensive regimen including losartan and hydrochlorothiazide is superior to one including atenolol and hydrochlorothiazide in reducing the incidence of stroke in non-black hypertensive patients 55 years of age or older with left ventricular hypertrophy.”

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B. Recommendation on Phase 4 Studies and/or Risk Management Steps

The LIFE study raises a question regarding whether the beneficial effect of the losartan regimen is reversed in blacks. Other data sources should be sought to help address this issue.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Cozaar[®] (losartan potassium) is an oral angiotensin II receptor (type AT₁) antagonist approved for the treatment of hypertension. The sponsor is seeking an indication to reduce the risk of cardiovascular morbidity and mortality in hypertensive patients with left ventricular hypertrophy based on one trial comparing regimens including losartan or atenolol in these patients. The trial is called the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) Trial. The LIFE study involved 9,193 patients (4,588 atenolol and 4,605 losartan). Mean length of follow-up was 4.8 years. In addition to the primary study drugs, hydrochlorothiazide was specified to be added if the target blood pressure of < 140/90 was not reached, and the majority of patients also received hydrochlorothiazide. Investigators could also add additional antihypertensives to control blood pressure.

B. Efficacy

The LIFE study had a sponsor pre-specified primary endpoint of combined cardiovascular deaths, myocardial infarctions, and strokes. By the sponsor's pre-specified analysis, a Cox regression with baseline measures of left ventricular hypertrophy and Framingham risk score as covariates, the losartan regimen produced a 13% reduction in risk relative to the atenolol regimen, $p=0.021$. The effects upon the components of the primary endpoint were heterogeneous. The benefit from losartan was primary related to a reduction in strokes, a 25% risk reduction ($p=0.001$).

The LIFE study is the only study supporting the proposed new indication. However, because the magnitude of the treatment effect (a 13% risk reduction in the primary endpoint, a 25% reduction in strokes) is reasonable and the endpoint is vital, the reviewer believes that a description of the beneficial effect of the losartan regimen in the LIFE study should be included in the losartan label.

Some analyses of the LIFE study suggest a qualitative interaction, i.e., a reversal of the beneficial effect of the losartan regimen, in blacks. However, blacks were a subgroup with different baseline characteristics and different responses than the rest of the study population. The results of the LIFE study suggest that the losartan regimen is not

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superior to the atenolol regimen in blacks. The evidence from the LIFE study is not conclusive for establishing that the losartan regimen is inferior to the atenolol regimen in blacks.

Other subgroup analyses also generated interesting differences. Because they are subgroup analyses they must be interpreted with caution.

- The losartan regimen appears to be more effective in the elderly. The losartan regimen may be less effective in males younger than 65.
- The losartan regimen appears to be more effective in patients with isolated systolic hypertension at baseline. Isolated systolic hypertension is more frequent in the elderly.
- The losartan regimen appears to be more effective in patients with diabetes at baseline. The losartan regimen was also associated with a lower rate of onset of new diabetes.

One finding that is surprising is that atenolol use appeared to be associated with more atrial fibrillation and more strokes associated with atrial fibrillation. These associations need verification from other data.

C. Safety

Both regimens were tolerated reasonably well in this long-term study in high risk patients. The majority of adverse effects, such as bradycardia with atenolol, were expected ones. Losartan appeared to be better tolerated than atenolol based on a higher rate of primary drug discontinuations due to adverse effects with atenolol. Besides the question of greater rates of atrial fibrillation with atenolol, atenolol also was associated with slightly greater increases in blood uric acid and glucose and higher rates of gout and diabetes. Losartan was associated with greater decreases in blood hemoglobin and higher rates of anemia. All of these latter adverse effects were still uncommon.

D. Dosing

The LIFE study used standard approved dosages and once daily dosing regimens for both atenolol and losartan.

E. Special Populations

Possible differences in efficacy by race, age, and gender are mentioned under Efficacy above. Adverse effects were more frequent with increasing age and slightly more frequent in females but differential patterns of toxicity were not identified.

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Clinical Review Section

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Cozaar[®] (losartan potassium) is an angiotensin II receptor (type AT₁) antagonist approved for the treatment of hypertension. The sponsor is seeking an indication to reduce the risk of cardiovascular morbidity and mortality in hypertensive patients with left ventricular hypertrophy based on one trial comparing regimens including losartan or atenolol in these patients. The trial is called the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) Trial. In this trial once daily losartan was titrated from 50 to 100 mg to control blood pressure. The protocol for the trial specified the addition of hydrochlorothiazide 12.5 mg daily before raising the dose of losartan and also specified increasing the dose of hydrochlorothiazide and adding other antihypertensives to control blood pressure. The protocol restricted the patient population to ages 55 to 80.

B. State of Armamentarium for Indication(s)

Many classes of drugs are approved for the treatment of hypertension. Reducing blood pressure with drugs decreases cardiovascular morbidity and mortality as demonstrated in a large number of clinical trials in various countries regardless of sex, age, race, blood pressure level, or socioeconomic status. (JNC 1997) A recent meta-analysis did not find that different drugs have differential impacts upon overall cardiovascular morbidity and mortality beyond blood pressure control. (Staessen, Wang et al. 2001) A meta-analysis of antihypertensive trials in the elderly did not identify differential treatment effects based on patient risk factors, pre-existing cardiovascular disease, or competing co-morbidities. (Mulrow, Lau et al. 2000) Guidelines do recommend selecting agents based on co-morbidities, particularly type 1 diabetes with proteinuria, heart failure, isolated systolic hypertension, and myocardial infarction. (JNC 1997) Left ventricular hypertrophy (LVH) is a recognized risk factor for cardiovascular events, but no controlled studies demonstrate that reversal of LVH offers additional benefits beyond that offered by reduction of blood pressure. (JNC 1997; Devereux, Okin et al. 1999) Demonstration of a beneficial effect upon cardiovascular morbidity and mortality of a losartan-based regimen compared to acceptable alternative therapy would be valuable clinical information.

C. Important Milestones in Product Development

The sponsor submitted the LIFE Trial protocol to IND [redacted] on June 29, 1995 (Serial No. 496). The summary of the trial in the Efficacy section below includes a brief history of the regulatory background of the protocol and the trial.

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D. Other Relevant Information

1. Approvals in the United States and Other Countries

The FDA approved Cozaar for the treatment of hypertension on April 14, 1995. This supplement proposes to expand the indication to reducing the risk of cardiovascular morbidity and mortality in hypertensive patients with left ventricular hypertrophy.

As of May 23, 2002, the sponsor reports that 94 countries have approved the use of losartan 50 mg tablets and 25 countries have approved the use of losartan 100 mg tablets. Applications are pending in 14 countries for the 100 mg tablet. No marketing applications have been rejected or withdrawn and marketing approval has not been suspended, revoked, or withdrawn in any country.

2. Determination of Left Ventricular Hypertrophy

The sponsor conducted the LIFE study in patients with left ventricular hypertrophy (LVH) because LVH is a major risk factor for cardiovascular disease and antihypertensive agents have differing impacts upon it. The Framingham study data show that left ventricular mass assessed by echocardiography provides prognostic information beyond other risk factors. (Levy, Garrison et al. 1990) A recent review of 20 studies examining cardiovascular risk relative to baseline LVH, determined either by echocardiography or electrocardiography (ECG), found that all but one of the studies showed higher risk with baseline LVH. (Vakili, Okin et al. 2001) More recent epidemiological data have associated ECG-determined LVH with increased risk of stroke. (Bots, Nikitin et al. 2002)

The LIFE study used two standard ECG criteria for determining LVH:

- Sokolow-Lyon voltage criterion (Sokolow and Lyon 1949)
- Cornell voltage-duration product criterion (Casale, Devereux et al. 1985; Casale, Devereux et al. 1987)

ECG criteria are highly specific but not sensitive for detecting echocardiographically documented increases in left ventricular mass. The LIFE steering committee adjusted the ECG criteria used in LIFE to achieve reasonable sensitivity while maintaining high specificity for detection of increased left ventricular mass (see the review of the study in the Efficacy section below.)

E. Important Issues with Pharmacologically Related Agents

The LIFE study was not a simple drug vs. placebo controlled trial. It was a trial of regimens including hydrochlorothiazide plus other investigator-selected antihypertensives and either losartan or atenolol. The unique controlled comparator was atenolol. Hence

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the most relevant issues regarding pharmacologically related agents are regarding the characteristics and effects of atenolol and other beta blockers in hypertension.

1. Appropriateness of Atenolol as a Comparator

The sponsor gives the following rationale for its selection of comparator: "A β -blocker, atenolol, was chosen as the comparator agent since it is among the class of drugs with proven morbidity and mortality benefits in hypertensive patients and has also been established as an effective agent in secondary prevention in high-risk patients, when administered alone or in combination with diuretics." The sponsor justified its dose selection as follows: "The doses selected for both marketed agents were based on label-recommended prescribing information for the treatment of hypertension."

In its "FDA Advisory Committee Background Information" document for the January 6, 2003, meeting of the Cardiovascular and Renal Drugs Advisory Committee the sponsor provides excellent reviews of trials of beta-blockers in hypertensive patients with cardiovascular event endpoints and trials of diuretic-based regimens including beta-blockers. Please see that document for the details. The following is the reviewer's interpretation of the background trials.

Beta-blockers, along with diuretics, are the most extensively studied antihypertensives with the most trial results supporting their effectiveness in reducing cardiovascular morbidity and mortality. (Collins, Peto et al. 1990) The Joint National Committee (JNC) VI guidelines suggest starting with a beta-blocker or a diuretic for uncomplicated hypertension. However, the JNC guidelines recommend diuretics as preferred for patients with isolated systolic hypertension (older persons). They also suggest that a long-acting dihydropyridine calcium antagonist may be useful for these patients based on the results of the Systolic Hypertension-Europe Trial of a drug (nitrendipine) not available in the United States. (Staessen, Fagard et al. 1997) The relevance of the isolated systolic hypertension (ISH) studies to the LIFE Trial is that ISH is common in older patients with left ventricular hypertrophy, the population of the LIFE Trial.

Beta blockers have clearly been effective in combination with diuretics in treating hypertension in the elderly. The Systolic Hypertension in the Elderly Program (SHEP) used a diuretic (chlorthalidone) as the first step with atenolol 25-50 mg as additional steps. SHEP showed that this regimen reduced the incidence of stroke by 36%. (SHEP 1991) The Swedish Trial in Old Patients with Hypertension (STOP-Hypertension) randomized elderly (age 70-84) hypertensives without isolated systolic hypertension to one of three beta blockers (including atenolol 50 mg) daily plus hydrochlorothiazide 25 mg/amiloride 2.5 mg vs. placebo. (Dahlof, Lindholm et al. 1991). The active treatment groups had better results for a composite primary endpoint similar to that used in the LIFE trial, including improved stroke morbidity and mortality. One meta-analysis suggests that beta blockers are less effective than diuretics as monotherapy in the elderly, but even this meta-analysis concludes that beta blockers reduce the risk of stroke but not myocardial infarctions or cardiovascular deaths. (Messerli, Grossman et al. 1998) A

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more recent meta-analysis of hypertensive trials in the elderly concludes that both diuretics and beta blockers are effective. (Mulrow, Lau et al. 2000)

COMMENT: These studies and meta-analyses support atenolol, combined with a diuretic, as a reasonable comparator for the LIFE study. The reviewer believes that there is ample evidence that reducing blood pressure, as is demonstrated in the LIFE study, reduces cardiovascular event rates and that regimens including a beta blocker reduce event rates in a wide range of hypertensive populations. Actually, for a favorable interpretation of the LIFE study results, it is not necessary that the atenolol regimen have efficacy; it is sufficient that the atenolol regimen do no overall harm with regard to cardiovascular outcomes. The difficult and critical question to answer is not whether an atenolol regimen beats placebo. The difficult and critical questions are whether the LIFE study provides sufficient evidence that the losartan regimen is robustly superior to the atenolol regimen in reducing cardiovascular events and whether the regimens were realistic enough and the conduct appropriate enough to support translation of the results into routine clinical practice.

2. Relevant Characteristics of Atenolol

Three characteristics of atenolol and other beta blockers are relevant to the LIFE Trial:

- Beta blockers are reported to be less effective in blacks. (JNC 1997) Combining a beta blocker with a diuretic is reported to increase antihypertensive efficacy in blacks. While this limitation is not described in the atenolol label, lower efficacy of losartan in blacks is described in the Cozaar label.
- Beta blockers may not control the early morning rise in blood pressure as well as other drugs. (Raftery and Carrageta 1985) The elimination half-life of atenolol is 6-7 hours, but the antihypertensive effect does not appear to be related to plasma level. Raftery suggests that the early morning rise is due to alpha adrenergic receptors that are unaffected by pure beta blockade. Lack of control in the early morning hours may also be a problem with hydrochlorothiazide (Lacourciere, Poirier et al. 2000)
- Beta blockers are used for rate control in patients with atrial fibrillation. One study has documented that asymptomatic paroxysmal atrial fibrillation occurs during treatment of atrial fibrillation with propranolol. (Wolk, Kulakowski et al. 1996)

COMMENT: The relevance of these observations is discussed in the Efficacy section.

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F. Abbreviations Used in this Review

The following are abbreviations, other than standard measurement units, used in this review:

| | |
|---------------------------|--------------------------------------------------------------|
| ABPM | ambulatory blood pressure monitoring |
| ACE | angiotensin converting enzyme |
| ACEI | angiotensin converting enzyme inhibitor |
| AE | adverse event |
| Afib | atrial fibrillation |
| Ang II | angiotensin II |
| Ang II Antagonist (= ARB) | angiotensin II antagonist (= ARB) |
| ALT | alanine transaminase (SGPT) |
| ARB | angiotensin receptor blocker (= Ang II Antagonist) |
| ASA | aspirin |
| AUC | area under the curve |
| BB | beta blocker |
| BMI | body mass index |
| BP | blood pressure |
| C _{max} | maximum concentration |
| CRF | case report form |
| CV | cardiovascular |
| DSMB | Data Safety and Monitoring Board |
| DBP | diastolic blood pressure |
| DSI | Division of Scientific Investigations (FDA) |
| ECC | Endpoint Classification Committee |
| ECG | electrocardiogram |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| HCTZ | hydrochlorothiazide |
| HDL | high density lipoprotein |
| HR | heart rate |
| ICH | International Conference on Harmonization |
| IND | Investigational New Drug |
| IRB | Investigational Review Board |
| ISH | isolated systolic hypertension |
| LIFE | Losartan Intervention for Endpoint Reduction in Hypertension |
| LVH | left ventricular hypertrophy |
| LVM | left ventricular mass |
| LVMi | left ventricular mass index (LVM/body surface area) |
| MI | myocardial infarction |
| NDA | New Drug Application |
| PEY | patient exposure years |
| PP | pulse pressure |

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| | |
|------|----------------------------------------------|
| S-L | Sokolow-Lyon (LVH ECG voltage criterion) |
| SAE | serious adverse event |
| SBP | systolic blood pressure |
| SHEP | Systolic Hypertension in the Elderly Program |
| Si | Sitting |
| sNDA | Supplemental New Drug Application |
| TIA | transient ischemic attack |
| UK | United Kingdom |
| US | United States |

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II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

The relevant statistical review is regarding the LIFE Trial. The Efficacy section incorporates relevant findings from the FDA statistician's review.

This supplemental NDA does not provide any new data regarding chemistry (except an environmental assessment), animal pharmacology and toxicology, microbiology, or biopharmaceutics. It does provide a review of published nonclinical pharmacologic effects of losartan in animal models of left ventricular hypertrophy, injury or dysfunction from 1993 to the present. The reviewer did not critique this review or its references. The sponsor's conclusions regarding these studies is the following:

"1. Nonclinical pharmacologic studies, in particular those utilizing chronic dosing regimens in a variety of rat models of myocardial infarction, genetic, surgical and pharmacologically-induced myocardial hypertrophy and injury, overwhelmingly demonstrate losartan to significantly reduce cardiac hypertrophy.

"2. Nonclinical studies also report losartan to reduce left ventricular wall thickness and/or dilation, and to improve hemodynamic status when administered either chronically or acutely.

"3. Studies in a variety of models and species report losartan to reduce ventricular collagen content and interstitial and perivascular fibrosis, in concert with reductions in the expression or activities of growth factors, neurohormones and enzymes implicated in the development of cardiac hypertrophy, collagen synthesis and/or degradation and fibrosis, including transforming growth factor (TGF) β 1 and Smad signaling proteins, matrix metalloproteinases, atrial natriuretic peptide (ANP) and aldosterone.

"4. Of particular note, losartan administration to stroke-prone spontaneously hypertensive rats (SHR-SPs), an experimental model of malignant hypertension in which animals develop severe cerebrovascular, cardiac and renal lesions and exhibit high mortality primarily from stroke, is reported in numerous studies to prevent stroke, significantly reduce mortality, and to reduce the incidence and severity of histologically-defined cerebrovascular, cardiac and renal lesions. The benefits of losartan on survival and prevention of stroke in SHR-SPs have been demonstrated with early vs late treatment initiation (relative to appearance of cerebral edema) and persist after discontinuation of treatment. Several studies in SHR-SPs report a significant survival benefit and the prevention of stroke and cerebrovascular lesions by losartan in the absence of significant lowering of blood pressure. These findings suggest that in SHR-SPs, angiotensin II through AT1 receptor stimulation, plays a major role in cerebrovascular pathology and the occurrence of stroke, and that losartan, apparently independently of its effect on blood pressure, affords significant and prolonged protection against cerebrovascular histopathologic changes, stroke and mortality."

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III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

This supplemental NDA does not provide any new data regarding pharmacokinetics. The following pharmacokinetic summary is extracted from the Cozaar label for ease of reference:

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.

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

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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.

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.

B. Pharmacodynamics

1. Pharmacodynamics from Label

The following pharmacodynamic summary is extracted from the Cozaar label for ease of reference:

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 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.

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.

The four studies of losartan monotherapy [for hypertension] 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

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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).

2. Pharmacodynamic Effects Related to Left Ventricular Hypertrophy

The sponsor chose the population of hypertensives with LVH for the LIFE study because of evidence that different antihypertensives have differing impacts upon LVH. The following is the reviewer's summary of the NDA discussion of possible pharmacodynamic effects related to LVH.

A recent review summarized the non-hemodynamic actions of angiotensin II (AII). (Williams 2001) AII may induce cell growth leading to LVH and vascular remodeling. AII induces fibrosis in both the cardiovascular and renal systems. AII predisposes to endothelial dysfunction and atherosclerosis and contributes to the formation and instability of atherosclerotic plaques. These effects appear to be mediated via the AII AT₁-receptor subtype. In contrast, there appear to be beneficial effects of stimulation of the AII AT₂ receptor to offset these pathologic effects, such as vasodilation and inhibition of fibrosis.

Although lowering of blood pressure produces a beneficial effect on LVH, meta-analyses of clinical trials have indicated that ACE inhibitors decrease LVH to a greater extent than other agents. (Dahlof, Pennert et al. 1992; Schmieder, Martus et al. 1996) A recent review suggests that angiotensin II antagonists, with the major one studied being losartan, have a similar effect upon LVH. (Dahlof 2001) A recent study compared losartan to atenolol for effects upon LVH. (Dahlof, Zanchetti et al. 2002) In this study 225 hypertensive patients with increased echocardiographically determined LVH at baseline found a significant reduction in LVH after 36 weeks in the losartan group, which was numerically greater than and significantly non-inferior to the atenolol group.

COMMENT: While speculations about a possible mechanism of action are interesting, LIFE is not designed to differentiate whether event rates related to reduction in LVH are independent of other effects of the two drugs.

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IV. Description of Clinical Data and Sources

A. Overall Data

The reviewer relied predominantly upon the data sets and case report forms from the LIFE study provided with this supplemental submission for NDA 20-386, Serial 032, dated July 25, 2002. In response to questions from this reviewer and other FDA reviewers the sponsor provided additional information in submissions dated October 22 and 28 and November 8, 13, 14, 18, 21, and 22, 2002. The reviewer incorporated the data from all of these submissions into the original review. For the amended review, the reviewer also incorporated data from submissions dated December 20, 2002.

The sponsor originally submitted the protocol and the data analysis plan for the LIFE study to IND [redacted]. The sponsor provided copies of these submissions in this NDA supplement. The reviewer did not consult the original submissions for these documents or for other information in the original IND or NDA. For background information the reviewer relied upon the information provided in the approved labeling for losartan and for atenolol and the literature reviews described below.

B. Tables Listing the Clinical Trials

The LIFE study is the only trial submitted to support the new indication.

C. Postmarketing Experience

The sponsor provided a report from its Worldwide Adverse Experience System database on spontaneous reports of adverse events of patients on Cozaar \geq 55 years of age with cardiac or left ventricular hypertrophy. From September 2, 1994, through March 31, 2002, 56 reports were identified. The reports cover a wide range of conditions without any evident pattern.

D. Literature Review

The sponsor provided a literature review of published nonclinical pharmacologic effects of losartan in animal models of left ventricular hypertrophy, injury or dysfunction from 1993 to the present and background references for the rationale for the study, including the selection of the comparator. The reviewer performed Medline searches focusing on the efficacy of atenolol and other beta blockers in hypertension, left ventricular hypertrophy as a cardiovascular risk factor, and the electrocardiographic determination of LVH. The reviewer incorporated the results of these Medline searches into the appropriate sections of this review.

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V. Clinical Review Methods

A. How the Review was Conducted

The reviewer relied predominantly upon the data sets and case report forms from the LIFE study provided with this NDA submission. The reviewer analyzed the raw data for this study provided in the NDA's electronic case tabulations. The reviewer duplicated the sponsor's primary analyses from the raw data as well as performed other pertinent analyses not presented by the sponsor. The reviewer confirmed that the sponsor's analyses corresponded to the data in the electronic case tabulations.

The reviewer prepared the original version of this Clinical Review on December 6, 2002, for distribution to the Cardio-Renal Drugs Advisory Committee for use at its meeting on January 6, 2003. After the original version was submitted the sponsor provided some additional data on December 20, 2002, and the sponsor also helped identify some typographical errors and data inconsistencies in the original review. The reviewer prepared this Amended Clinical Review to correct the identified typographical errors, to include some re-analyses and additional analyses based on data not available at the time of submission of the original review to the advisory committee, and to incorporate labeling recommendations. The reviewer specifically amended the review as follows:

- Corrected typographical errors.
- Replaced seven figures and four tables that did not reproduce well in the original version. The data in these figures and tables remain unchanged. These revised figures and tables were also distributed to the members of the advisory committee.
- Added analyses regarding the following data submitted too late to be incorporated into the original review:
 - robustness of the primary endpoint to reclassification by the reviewer based on the endpoint narratives in addition to the case report forms
 - atrial fibrillation and flutter rates based on ECGs
 - blood pressure data from a small Danish ambulatory blood pressure monitoring (ABPM) substudy
 - patients with incomplete follow-upThe atrial fibrillation and flutter rates on ECGs and the ABPM substudy data were presented to the advisory committee by the sponsor at the meeting on January 6, 2002.
- Re-analyzed the following data to provide more appropriate analyses:
 - incorporated six strokes reported only as deaths into the analyses of stroke rates
 - refined the analysis of the primary endpoint components to classify cardiovascular deaths by cause

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- corrected analyses of dose changes preceding strokes
The addition of the six strokes reported only as deaths changes the original review tables minimally, but all applicable tables have been updated in this amendment. The corrected analyses of dose changes preceding strokes replace the corresponding tables in the original submission.
- Revised the wording of the group references, particularly those in the Executive Summary, to be more consistent in referencing them as the “losartan regimen” and “atenolol regimen” rather than “losartan” and “atenolol”.
- Added recommendations on labeling.

The new and amended analyses in this amended review did not change the reviewer’s conclusions regarding the results of the LIFE study. However, the insight regarding these results provided by the advisory committee did affect the reviewer’s opinion regarding how the indication should be worded.

B. Overview of Materials Consulted in Review

As stated above, the reviewer relied predominantly upon the electronic data sets and case report forms provided with this NDA submission.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

The Division of Scientific Investigations did not perform any field audits for this supplemental NDA. One reason for not performing audits is that this study involved a large number of sites with the contribution of any one site being small.

To evaluate data quality the reviewer checked all case report forms for endpoints for which the Endpoint Classification Committee disagreed with the investigator (with an endpoint date difference of more than 30 days) and random samples of other case report forms. The reviewer verified that the data in the electronic data sets correspond to the data on the case report forms. The reviewer also re-analyzed the results based on his reclassification of endpoints. (The results for these reviewer reclassifications are presented in the Efficacy section.) The reviewer confirmed that the sponsor’s analyses corresponded to the data in the electronic case tabulations and case report forms.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The LIFE study appears to have been conducted in accordance with accepted ethical standards. Institutional review boards (for US sites) or independent ethics committees reviewed and approved the protocol. Investigators obtained informed consent from the

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participants and were bound by the Declaration of Helsinki. The overall design of the study, comparing two active drugs without proved advantages and including a diuretic and other investigator-selected antihypertensives to facilitate blood pressure control, is an ethically acceptable design. Monitoring for patient safety, with an unblinded Data Safety and Monitoring Board, was good.

E. Evaluation of Financial Disclosure

This study involved a large number of investigators and subinvestigators. The sponsor's tabulation of their financial interest disclosures is shown in the table below. Please see the secondary medical review for an analysis of these disclosures. The large number of investigators and the use of a blinded Endpoint Classification Committee help protect the study results from prejudicial influence by any one investigator.

Table 1: Sponsor's Tabulation of Financial Interest Disclosures for Investigators

| Investigator Category | Total Number |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|
| Grand Total Number of Investigators/ Subinvestigators per Protocol and Site | 4637 |
| Total Number of Investigators/ Subinvestigators Who Are Certified Regarding an Absence of Financial Arrangements per Protocol and Site | 3380 |
| Total Number of Investigators/ Subinvestigators Not Providing Information and Not Certified per Protocol and Site | 1166 |
| Total Number of Investigators/ Subinvestigators Not Certified Due to "Significant Payments of Other Sorts" or Equity Interest (Table D-1) per Protocol and Site | 91 |
| Total Number of Investigators/ Subinvestigators Receiving Payments Based on the Outcome of the Study per Protocol and Site | 0 |
| Total Number of Investigators/ Subinvestigators with Proprietary Interest in the Test Product or Company per Protocol and Site | 0 |

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VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

The reviewer concludes that the LIFE study shows that antihypertensive regimens including losartan and hydrochlorothiazide are superior to ones including atenolol and hydrochlorothiazide for reducing a composite endpoint of deaths, strokes, and myocardial infarctions in hypertensive patients with left ventricular hypertrophy. The predominant benefit is a reduction in strokes. The reviewer does not conclude that this finding is robust. However, because the magnitude of the treatment effect (a 10% risk reduction in the primary endpoint, a 25% reduction in stroke rates) is reasonable and the endpoint is vital, the reviewer believes that a description of the beneficial effect of the losartan-based regimen in the LIFE study should be included in the losartan label.

Some analyses of the LIFE study suggest a qualitative interaction, i.e., a reversal of the beneficial effect of losartan, in blacks. The reviewer concludes that blacks were a subgroup with different baseline characteristics and different responses than the rest of the study population. The results of the LIFE study suggest that losartan is not superior to atenolol in blacks. The evidence from the LIFE study is not conclusive for establishing that losartan is inferior to atenolol in blacks.

The reviewer also notes the following findings not described by the sponsor in its summaries of the LIFE study:

- Atenolol uses appears to be associated with increased rates of atrial fibrillation and strokes.
- Losartan appears to be more effective in the elderly. Losartan may be less effective in males younger than 65.

B. General Approach to Review of the Efficacy of the Drug

Support for the proposed new indication is provided by the LIFE study alone. Hence the review of the efficacy depends upon the review of the LIFE study. There is one major question and several related minor questions that are of prime interest. The major question is whether the LIFE study alone is robust enough to support a new indication. The minor questions are whether the indication should be qualified for various subgroups. The sponsor has discussed qualifying the indication for blacks. The reviewer also notes possible differential impacts in patients with or at risk for atrial fibrillation and in patients with isolated systolic hypertension.

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C. Detailed Review of the LIFE Study

The protocol for the LIFE study was entitled "A Triple-Blind, Parallel Study to Investigate the Effect of Losartan Versus Atenolol on the Reduction of Morbidity and Mortality in Hypertensive Patients With Left Ventricular Hypertrophy" and numbered "133/COZ368/925." The protocol number was 133 in the US and 925 in Europe and Iceland. The primary objective was to evaluate the long-term effects (4 years) of losartan compared to atenolol in hypertensive patients with documented left ventricular hypertrophy (LVH) on the combined endpoint of cardiovascular mortality, myocardial infarction, and stroke.

1. Sites and Investigators

Nine hundred forty-five sites randomized 9,193 patients (4,605 losartan, 4,588 atenolol) in Denmark, Finland, Iceland, Norway, Sweden, the United Kingdom (UK), and the United States (US). One site (925-964) contributing 29 patients was disqualified by the sponsor in September 1997 because of issues concerning Good Clinical Practice (GCP) noncompliance. Its data are excluded. Another site was closed in December 2001 based on the suspension of the primary investigator's licenses. For this latter site there was no issue regarding data reliability, so the two patients from it are included in the analyses. The distributions of patients by country are shown in the table below.

Table 2: Reviewer's Patients by Country

| Country | Atenolol | Losartan | N | % | Sites |
|---------|----------|----------|------|------|-------|
| Denmark | 699 | 692 | 1391 | 15.1 | 89 |
| Finland | 737 | 748 | 1485 | 16.2 | 106 |
| Iceland | 68 | 65 | 133 | 1.5 | 8 |
| Norway | 701 | 714 | 1415 | 15.4 | 142 |
| Sweden | 1133 | 1112 | 2245 | 24.4 | 199 |
| US | 838 | 869 | 1707 | 18.6 | 294 |
| UK | 412 | 405 | 817 | 8.9 | 107 |
| All | 4588 | 4605 | 9193 | 100 | 945 |

The average site contributed only a small number of patients to the study (median 7, interquartile range 3 to 11). Treatment groups were very well balanced at sites. The Scandinavian sites contributed more patients on the average than the US and UK sites. The ten largest sites (n = 62 to 148) were all in Scandinavia except for one UK site with 85 patients.

2. Background

2.1. Initial Protocol

The initial protocol under which the study was conducted in the US was Protocol Number 133-00/COZ 368, dated June 9, 1995. The earliest version provided in the NDA of

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Protocol 925, the protocol used in Europe, is Protocol 925-0A, dated March 19, 1995. In a letter dated November 13, 2002, the sponsor gives the following description of the differences in the protocols: "The variations between the two sets of documents were the result of the two authoring groups having different writing styles. There were multiple amendments for each protocol, but summarily the studies were similar. Although, the regulatory requirements regarding clinical subjects and investigational supplies vary as they are based on local regulations, the Study Designs both in table form and text are identical in content. The Hypothesis, Objectives, Inclusion and Exclusion Criteria were similar for each study, with one exception. Protocol 133 included 'Pregnancy' as an exclusion criteria; it was not noted on Protocol 925 as it may have been regarded as self-event with the lower age of entry at 55 years of age. The Efficacy and Safety sections of the studies were also similar." The reviewer did not identify any significant differences between the two protocols.

2.2. Protocol Amendments

The following are the amendments to Protocol 133 included in the NDA:

- Protocol Amendment 133-01, dated March 29, 1996, changed the LVH criteria to include a Sokolow-Lyon >38 mm LVH criterion and modified the female adjustment for the Cornell Product LVH criterion from +8 to +6, specified that hydrochlorothiazide could be titrated to 25 mg or more, allowed the addition of other open-label antihypertensive for down titrations due to AEs, removed endpoint classification procedures from the protocol, and made miscellaneous other administrative changes.
- Protocol Amendment 133-02, dated May 23, 1996, added an echocardiogram substudy of left ventricular mass for 30 selected centers.
- Protocol Amendment 133-05, dated July 2, 1996, added an African-American echocardiogram substudy of left ventricular mass, oversampling Blacks in the echo substudy and adding three additional centers.
- Protocol Amendment 133-0A, dated May 5, 1998, provided for a 25 mg dose of study drug to investigators who request it on a patient-by-patient basis.
- Protocol Amendment 133-0C, dated December 15, 2000, provided for echo acquisition yearly after year 4, if applicable, and for termination of the echo substudy prior to the termination of the overall LIFE study.
- Protocol Amendment 133-0D, dated December 15, 2000, provided for echo acquisition yearly after year 4 in the African-American substudy, if applicable, and for termination of the echo substudy prior to the termination of the overall LIFE study.

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The following are the amendments to Protocol 925 included in the NDA:

- Protocol 925-0A, dated March 19, 1995 and the earliest version provided in the NDA, did not include Lyon criteria for LVH and described two primary endpoints (the combined stroke, myocardial infarction, and cardiovascular mortality composite and cardiovascular mortality alone.)
- Protocol 925-0B, dated May 22, 1995, specified the primary composite endpoint alone.
- Protocol 925-0B, dated June 19, 1995 (the protocol version in effect for the first randomized patients) made miscellaneous wording changes to the version dated May 22, 1995.
- Protocol 925-0C, dated June 9, 1995 (in error), made additional miscellaneous wording changes to the version dated June 19, 1995.
- Protocol 925-0C, dated March 29, 1996, amended the protocol like the Protocol Amendment 133-01 above.
- Protocol amendment 925-0D, dated May 5, 1998, provided for a 25 mg dose of study drug to investigators who request it on a patient-by-patient basis.
- Protocol Amendment 925-0F, dated December 15, 2000, provided for echo acquisition yearly after year 4, if applicable, and for termination of the echo substudy prior to the termination of the overall LIFE study.

The final data analysis plan was not specified in the original protocol. A Data Analysis Plan (DAP) was finalized in November 2001 and submitted on November 16, 2001 (Serial 971) prior to unblinding of study data but after completion of the interim analyses.

2.3. Study Dates

Patients were started on treatment between June 25, 1995 (August 10, 1995 in the US), and May 2, 1997, with follow-up continuing to November 15, 2001. The endpoint cutoff date is September 16, 2001.

3. Study Design

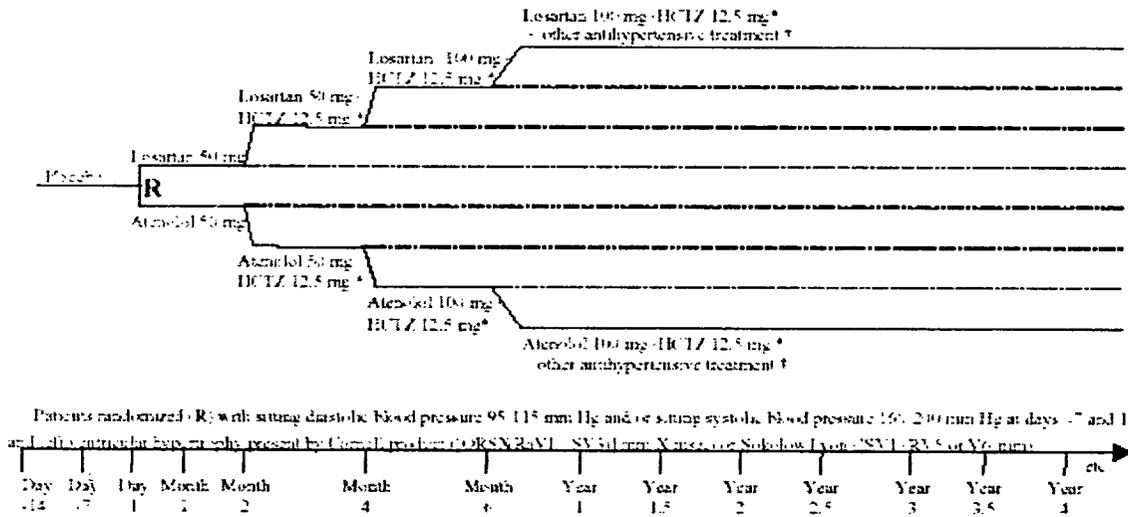
LIFE was a randomized, double blind, double dummy, active controlled, parallel group study. The study drug was losartan and the active control was atenolol. The sponsor refers to the study as triple-blind because of blinding of patients, investigators, and evaluators (Endpoint Classification Committee).

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After a 2-week placebo-run-in period (10 to 28 days were allowed), there was a minimum 4-year period of active triple-blind treatment. Treatment for the first enrollees continued beyond year four until 1040 patients experienced a primary cardiovascular event. Clinic visits were made each week during the placebo baseline period. Patients who were eligible were randomized in a 1:1 ratio to either losartan or atenolol. During the triple-blind treatment period, patients were seen at the clinic at the end of months 1, 2, 4, and 6, and at year 1, and thereafter at 6-month intervals. At each visit, trough sitting blood pressure and heart rate were measured and the occurrences of adverse experiences and endpoints were assessed.

The study design is diagrammed in the figure below. Following it is a table listing the schedule of observations. The screening and safety laboratory tests were hemoglobin, creatinine, ALT, glucose, uric acid, sodium, potassium, cholesterol, HDL cholesterol, urine microalbuminuria, and urine creatinine. The schedule of observations table below indicates when these tests or a subset of them were done. One central lab was used for US patients and a second one in Sweden for Scandinavian and UK patients. Östra University Hospital ECG Core Center, Göteborg, Sweden, analyzed all screening and protocol-required ECGs.



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| Procedure | Screening | Placebo Baseline Period | | | Triple-Blind Period | | | | | | | | | | |
|----------------------------------------------------------------------|-----------------------|-------------------------|-------------------|------------------|---------------------|--------------------|--------------------|--------------------|-------------------|---------------------|--------------------|----------------------|--------------------|----------------------|---------------------------------|
| | Prestudy -365 days | Visit 1 Day -14 | Visit 2 Day -7 | Visit 3 Day 1 | Visit 4 Month 1 | Visit 5 Month 2 | Visit 6 Month 4 | Visit 7 Month 6 | Visit 8 Year 1 | Visit 9 Year 1.5 | Visit 10 Year 2 | Visit 11 Year 2.5 | Visit 12 Year 3 | Visit 13 Year 3.5 | Visit 14 Year 4 ^a |
| Medical history | | X | | | | | | | | | | | | | |
| Complete physical examination | | X | | | | | | | X | | X | | X | | X |
| Obtain informed consent | X ^b | X | | | | | | | | | | | | | |
| Sitting blood pressure and heart rate | (X) | X | X | X ^c | X | X | X | X | X | X | X | X | X | X | X |
| Standing blood pressure and heart rate | | | | X | | X ^d | X ^d | X ^d | X ^d | X ^d | X ^d | X ^d | X ^d | X ^d | |
| Laboratory safety tests ^e | | X ^f | | X | X ^g | | | | X | | X | | X | | X |
| Electrocardiogram (ECG) (12-lead) | X ^h | X ⁱ | | X | X | | | X | X | X | X | X | X | X | X |
| Adverse experience evaluation | | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Discontinue all antihypertensive medication | X | | | | | | | | | | | | | | |
| Dispense placebo baseline medication | | X ^j | | | | | | | | | | | | | |
| Dispense triple-blind medication | | | | X ^k | X | X | X | X | X | X | X | X | X | X | X |
| Add additional antihypertensives to treatment regimen if appropriate | | | | | | X ^l | X ^l | X ^l | X ^l | X ^l | X ^l | X ^l | X ^l | X ^l | X ^l |
| Healthcare resource utilization assessment ^m | | | | X | | | | X | X | X | X | X | X | X | X |

Figure 2: Sponsor's Schedule of Clinical Observations and Laboratory Measurements

- a) Year 4 or final visit.
- b) If tests performed or medication discontinued with the intent to participate in the study.
- c) DBP 95-115 or SBP 160-200 at 2 consecutive visits separated by at least 1 week for continued eligibility.
- d) Standing BP and heart rate if study drug upward titrated.
- e) Glucose retesting for evaluation of new-onset diabetes mellitus.
- f) Glucose and creatinine only.
- g) Sodium, potassium, and creatinine only.
- h) ECG within past year.
- i) Within 30 days prior to Visit 1 and sent to ECG Core Center for evaluation of LVH.
- j) Patients could remain on placebo for up to 28 days to qualify for elevated BP as in c).
- k) The last placebo tablet should have been taken the previous morning.
- l) BP control was titrated as described under Duration and Adjustment of Treatment below.
- m) As specified in Standard Operating Procedures and worksheets.

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3.1. Objectives

The primary objective was to evaluate the long-term effects (≥ 4 years) of losartan compared to atenolol in hypertensive patients with documented LVH on the combination of cardiovascular mortality and morbidity. Cardiovascular mortality was defined as death due to fatal MI, fatal stroke, sudden death, progressive heart failure, other cardiovascular deaths. Cardiovascular morbidity was defined as nonfatal MI, excluding silent MI, and nonfatal stroke.

Secondary objectives were to compare the long-term effects of losartan with atenolol on

- cardiovascular mortality
- total mortality
- fatal and nonfatal myocardial infarction
- fatal and nonfatal stroke
- angina pectoris requiring hospitalization
- regression of LVH, as measured by ECG
- the relationship between regression of LVH (ECG-LVH) and cardiovascular mortality and morbidity (defined as primary endpoint)
- the incidence of coronary or peripheral revascularization procedures
- the incidence of silent myocardial infarction as evaluated from serial readings of annual ECGs
- safety and tolerability based upon adverse experience profile and incidence of discontinuations due to adverse events

Tertiary objectives were

- to evaluate the relationship between blood pressure control and cardiovascular morbidity and mortality
- to assess the influence of various risk factors on cardiovascular event rate, including microalbuminuria, smoking, age, gender, level of systolic and diastolic blood pressure at randomization, total serum cholesterol, HDL cholesterol, and diabetes mellitus
- to evaluate the long-term effects of losartan versus atenolol on new-onset diabetes mellitus (WHO criteria)

COMMENT: While the sponsor typically describes the comparison as losartan vs. atenolol, the LIFE study really compares antihypertensive regimens including losartan and hydrochlorothiazide to ones including atenolol and hydrochlorothiazide. Also, the Division had suggested to the sponsor to use total mortality rather than cardiovascular mortality in the composite endpoint in a meeting on September 21, 1995, but the trial's Steering Committee rejected the suggestion. The primary endpoint from the original protocol is used for the primary efficacy analysis of the NDA. Note that the effects of losartan vs. atenolol on new-onset diabetes by WHO criteria was a tertiary endpoint in the original protocol.

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3.2. Number of Subjects, Randomization, and Blinding

The study was sized to attain 1,040 primary endpoints. To achieve this number of endpoints the sponsor estimated that 8,300 patients were needed. The investigators ultimately assessed 10,779 patients and randomized 9,222. The sponsor excluded from all analyses 29 patients belonging to one site due to serious GCP compliance issues at that site in September 1997. The sponsor used the data from the remaining 9,193 patients for efficacy and safety analyses.

The sponsor's statisticians created computerized allocation schedules separately for each participating country, with a statistical block size of four. The sponsor's agents packaged study drug and matching placebo in a blinded fashion and identified by allocation number. The agents shipped blocks of study drug (in multiples of four) to each site. Investigators assigned eligible patients the next available allocation number. There was no patient stratification at the sites.

The sponsor provided study drug in a double-dummy format to maintain blinding of patients and investigators. The Endpoint Classification Committee was blinded but the Data Safety and Monitoring Board (DSMB) was not. The only individual of the sponsor's organization who was unblinded was the statistician designated to perform interim analyses for the DSMB. The statistician was instructed not to release unblinded information to the sponsor.

3.3. Inclusion and Exclusion Criteria

The inclusion criteria were the following:

1. male or female aged 55 to 80 years
2. previously untreated or treated hypertension
3. a qualifying ECG (taken up to 30 days prior to Visit 1) with interpretation of LVH confirmed by the ECG Core Center before randomization
4. trough sitting blood pressure measurement requirements per the table below

| Study Day | Visit Number | Trough Sitting Blood Pressure (BP) Mean Reading |
|----------------------------------|--------------|-------------------------------------------------|
| Day -7 (after 1 week on placebo) | 2 | SiDBP 95 to 115 and/or SiSBP 160 to 200 mm Hg |
| Day 1 (after 2 weeks on placebo) | 3 | SiDBP 95 to 115 and/or SiSBP 160 to 200 mm Hg |

Sitting BP Mean Reading was the calculated average of 2 consecutive readings at 1-minute intervals.
Patients who did not qualify after 2 weeks on placebo could remain on placebo for up to 2 additional weeks in order to qualify for randomization (2 consecutive blood pressures separated by at least 1 week equal to SiDBP 95 to 115 and/or SiSBP 160 to 200 mm Hg for inclusion).

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LVH was confirmed by ECG interpreted at the core lab before randomization. The Cornell voltage-duration product was calculated as the QRS duration in msec times the sum of R_{aVL} and S_{V3} in mm plus 8 mm in women and was interpreted as LVH if $> 2,440$ mm*msec. An amendment date March 29, 1996, changed the adjustment in women to 6 mm and added a Sokolow-Lyon criterion of $S_{V1} + R_{V5 \text{ or } V6} > 38$ mm (36 mm is usual, but 38 mm was used to achieve greater specificity.) The partition value has approximately 45% sensitivity in men and 25% sensitivity in women compared to echocardiographic LV mass using partition values of 125 g/m^2 in men and 110 g/m^2 in women.

Patients were excluded from entering the study if they had any of the following conditions or histories:

1. known secondary hypertension of any etiology (e.g., uncorrected renal artery stenosis), malignant hypertension, or hypertensive encephalopathy
2. increased diastolic BP >115 or systolic BP >200 mm Hg during the placebo period
3. a history of stroke or myocardial infarction within 6 months prior to study start
4. angina pectoris requiring treatment with a beta-blocker or a calcium antagonist
5. presence of heart failure or known left ventricular ejection fraction $\leq 40\%$
6. a history of renal or hepatic disorders with severe impairment of function (serum creatinine $>160 \text{ } \mu\text{mol/L}$ or 1.8 mg/dL) or patient with solitary kidney or renal transplant
7. significant known aortic stenosis (known mean antegrade Doppler gradient ≥ 20 mm Hg)
8. known hypersensitivity or contraindication to losartan, atenolol, or hydrochlorothiazide
9. a condition that, in the treating physician's opinion, required treatment with atenolol or another beta-blocker, hydrochlorothiazide or another diuretic, losartan or another angiotensin II-receptor antagonist, or angiotensin-converting enzyme inhibitors (e.g., patient requiring beta-blockers for angina)
10. other serious disease expected to cause a substantial deterioration of the patient's health during the next 4-6 years
11. patient currently abusing or having a recent history of alcohol or other drug substance abuse
12. mentally or legally incapacitated patient

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- 13. patient participating, or has been participating during the last 30 days, in another investigational drug or device trial using a non-approved drug or device (A patient may participate in a study using marketed drugs or devices provided they do not interfere with the study or are otherwise excluded by the study protocol.)
- 14. patients with a low compliance at the end of the placebo period, as judged by the investigator
- 15. patient unwilling to participate
- 16. pregnancy

3.4. Dosage and Administration

Starting dosages were 50 mg for both losartan and atenolol. Medication was given in a double dummy fashion, i.e., losartan with atenolol placebo or atenolol with losartan placebo. Study medication was to be taken once daily orally at the same time each day, preferably in the morning. It was not to be taken on the morning of any clinic visit.

3.5. Duration and Adjustment of Therapy

Study medication was taken for the duration of the study, up to six years for the first enrollees. The mean duration of follow-up from randomization through death or September 16, 2001, was 4.8 years.

Dosages and additional open-label antihypertensives were adjusted as follows: Blood pressure was measured at trough, i.e., 22-26 hours after the last dose (and time since last dose was recorded.) Target BP was defined as sitting trough BP <140/90 mm Hg. If the patient's BP was not within target, additional anti-hypertensives were added or dosage was increased to 100 mg according to the table below. The types of additional anti-hypertensives were left to the discretion of the investigators other than ACEIs, ARBs, and beta-blockers were not permitted.

Upward Titration Steps if SiDBP[†] ≥90 mm Hg and/or SiSBP[‡] ≥140 mm Hg

| End of Month | Treatment |
|---------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1 | Losartan 50 mg or atenolol 50 mg |
| 2 | Losartan 50 mg or atenolol 50 mg <i>plus</i> HCTZ 12.5 mg |
| 4 | Losartan 100 mg or atenolol 100 mg and HCTZ 12.5 mg |
| 6 | Losartan 100 mg or atenolol 100 mg and HCTZ 12.5 mg <i>plus other antihypertensive therapy (excluding ACEIs, AIIAs, or beta-blockers)</i> The dosage of HCTZ could be increased. The choice of additional antihypertensive therapy was left to the discretion of the investigator. |
| [†] SiDBP: sitting diastolic blood pressure. [‡] SiSBP: sitting systolic blood pressure. | |

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At month 6 and later throughout the study, HCTZ could be increased to 25 mg or more or other antihypertensive therapy could be added to study drug at the discretion of the investigator. If the blood pressure was $\geq 160/95$ mm Hg, it was mandatory to try additional medication.

When necessary, back-titration was performed in reverse order of the initial titration of the study test medication. However, if the back-titration was due to adverse experiences thought to be related to losartan 100 mg or atenolol 100 mg, the dosage of HCTZ could be increased or other additional antihypertensive medication added to losartan 50 mg or atenolol 50 mg in order to reach the target blood pressure. Open-label ACEIs, ARBs, or beta-blockers were not allowed as chronic therapy. In May 1998 a protocol amendment provided for the usage of a 25-mg dose of losartan or atenolol. This dosage was intended for use by patients who otherwise would have been discontinued from blinded study drug therapy by the investigator. Investigators were required to contact the Medical Monitor for approval to use this study drug dose, prior to prescribing.

The selection of an appropriate post study antihypertensive regimen was at the discretion of the investigator. Since there was a 50% chance that the blinded study medication was atenolol, a beta-blocker, and sudden termination of long-term treatment with this medication could possibly induce a rebound phenomenon in some patients, consisting of an uncontrolled rise in blood pressure and/or heart rate, the Steering Committee made an allowance for the tapering or down-titration of study drug therapy over a 1- to 2-week period after the investigator performed and recorded final protocol-required measurements.

3.6. Safety and Efficacy Endpoints

The primary endpoint was the composite of cardiovascular mortality, myocardial infarction (MI), and stroke. The main section of the protocol does not describe how the investigators were to monitor for these three endpoint events. It defines briefly each event as follows:

- myocardial infarction – acute, recognized MI or recent MI by autopsy
- stroke – non-hemorrhagic, hemorrhagic, embolic, or stroke of uncertain etiology
- death from coronary heart disease – sudden death within 1 hour or 24 hours, non-sudden death due to coronary heart disease, or death resulting from coronary revascularization
- other cardiovascular death – death due to stroke, aortic aneurysm, peripheral vascular disease or revascularization procedure, or heart failure

Appendix III of the protocol expands the definitions as follows:

- acute, recognized MI – two out of three of serial ECG changes, consistent chest pain or discomfort, and elevated cardiac enzymes

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- stroke – a neurologic deficit lasting 24 hours or more with one or more of depression of state of consciousness, disturbance of vision, paresis or paralysis of one or more extremities, sensory impairment, speech impairment, cranial nerve dysfunction, memory defect, ataxia, or movement disorder

An amendment dated March 29, 1996, clarified the definition of MI for the primary endpoint to include MIs interrupted by cardiac revascularization and to exclude probable MIs and MIs associated with a non-cardiac procedure.

A blinded Endpoint Classification Committee (ECC) adjudicated primary endpoints using an Endpoint Classification Committee Manual. This manual was submitted to the FDA on August 12, 1996 (Serial 578) and a revised version was submitted on May 6, 1999 (Serial 807). The Division had suggested to the sponsor to use total mortality rather than cardiovascular mortality in the composite endpoint in a meeting on September 21, 1995, but the trial's Steering Committee rejected the suggestion.

The ECC consisted of two experienced clinicians. Each evaluated the endpoints initially working from endpoint worksheets, endpoint narratives, and reports of electrocardiograms (ECG) coded to the Minnesota code by the central ECG lab. They requested additional information if they believed it was needed to classify an endpoint. They resolved differences in their initial readings at face-to-face meetings.

The ECC classified other secondary endpoints including total mortality, angina pectoris requiring hospitalization, heart failure requiring hospitalization, coronary or peripheral arterial revascularization procedures, and resuscitated cardiac arrest. They did not evaluate silent MI, regression of LVH as assessed by ECG, relationship between regression of LVH and cardiovascular morbidity and mortality, relationship between blood pressure control and cardiovascular morbidity and mortality, relationship between risk factors and cardiovascular event rate, and incidence of new-onset diabetes mellitus.

Safety endpoints included adverse experiences, vital signs (other than blood pressure), and laboratory values. These were reported while the patient was on study drug or within 14 days of the last dose of study therapy. Exclusions for safety were applied after permanent study drug discontinuation as well as during gaps in study therapy > 14 days.

Two major articles regarding this study (the main results and a subgroup analysis of diabetics) were published in *The Lancet* in March 2002. The data, other than classified endpoints, included in the NDA are from the final CRF data set that was finalized after the submission of these publications. There are slight differences in the NDA reports of non-endpoint data from those in the published manuscripts (i.e., disease history counts, the number of patients with new-onset diabetes mellitus, and counts of prespecified adverse experiences of special interest).

COMMENT: One weakness of this study is that there is no protocol requiring tests to be done to verify the occurrence of any of the components of the primary endpoint. This

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weakness is difficult and expensive to correct. The endpoints can occur at home or at hospitals other than the ones frequented by the investigators. The investigators do not have control over these environments. Hence all of the data needed for the primary endpoint determinations were not collected in a standardized fashion and even limited data may have been difficult to obtain or unobtainable in some cases.

The sponsor attempted to provide standardization of the endpoints by using a blinded Endpoint Classification Committee. The process used for this committee was reasonable and should help to avoid bias and reduce variation. However, it cannot compensate for the unavailability of data. The components of the primary endpoint cannot be completely objectively determined. The reviewer's analyses in the Efficacy section explore the variability in the components from the investigator's, committee's, and reviewer's perspectives and the effects of different endpoint classifications upon the results.

Another weakness of the study, now obvious in retrospect, is that the case report forms did not specify a rating of the severity of stroke. The one factor collected related to the severity of a stroke was whether the duration of the neurologic deficit was more than 24 hours or until death. Because differences in stroke rates are the major differences encountered between the two treatment arms, it would be illuminating to know whether there were differences in stroke severity between the two arms.

3.7. Statistical Considerations

3.7.1. Sample Size Calculations

The sample size calculation for this trial was based on the combined incidence of cardiovascular morbidity and mortality. It assumed that the 5-year event rate in the atenolol group would be 15%, and that this rate would be reduced by 15%, to 12.75%, in the losartan group. The predicted event rate in the atenolol group was based on Framingham data, which show that the 5-year cardiovascular event rate in 65-year-old patients with systolic hypertension and left ventricular hypertrophy, but no other significant evidence of heart disease, is ~17% among men and 12% among women. The patient population in this trial was expected to be 2/3 male and have a mean age of 65 years, resulting in an estimated cardiovascular event rate of ~15%.

Based on these assumptions, in order to have 80% power at the 5% (two-sided) significance level, the trial should proceed until a total of 1,040 patients experience one or more primary cardiovascular events. The study's sample size of 8,300 patients was chosen in an attempt to achieve the required 1,040 patients with an event at approximately the same time that the final patient reached four years of follow-up. The method used to calculate sample size was based on the log-rank test.

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3.7.2. Analysis Cohorts and Missing Data

The efficacy analysis was based on the intention-to-treat principle. That is, all randomized patients were to be included in all analyses, regardless of any protocol violations or discontinuation of study medication. The one appropriate exception to this strict principle was the exclusion in September 1997 of 29 patients from a site with GCP noncompliance. All randomized patients (N = 9,193) were included in the efficacy and safety analyses.

A goal for this study was to obtain complete endpoint follow-up on all randomized patients. However, as expected, some follow-up was unavailable. Two approaches were used for different types of missing endpoint data: (1) If the patient's survival status was known, but other endpoint data were unknown beginning at some date prior to death or final study termination, then the patient was counted as if full follow-up were available through death or study termination and no nonfatal endpoints had occurred. For endpoints other than mortality (all-cause or cause-specific) or the primary composite, the patient was censored at the date of the last known follow-up. (2) If the patients' survival status and other endpoint data were both unknown beginning at some date prior to final study termination, then the patient was counted as censored at the last known follow-up date for all endpoint analyses.

Missing data for baseline covariates (Cornell voltage duration product and S-L voltage as measured at the Visit 3 ECG and baseline data used to calculate the patient's Framingham risk score) were interpolated by using the median value among all patients with non-missing data. These values were calculated from the pooled treatment groups. Missing data for other variables, such as blood pressure, pulse, weight, and laboratory measurements, were not interpolated, and patients with missing data were excluded from all relevant analyses.

3.7.3. Pre-specified Analyses

The primary efficacy analysis proposed was a Cox regression survival analysis comparing the two treatment groups with respect to the time to the first clinical endpoint. The analysis pre-specified covariates for degree of LVH (Cornell voltage duration product and Sokolow-Lyon voltage on the baseline ECG) and a Framingham risk score.

The two interim analyses for the DSMB used O'Brien-Fleming boundaries with critical p-values of 0.0004 and 0.013. To maintain the overall significance level at 0.05, the significance level for the primary analysis was adjusted to a two-sided α of 0.046.

The same Cox regression approach was proposed for all secondary and tertiary time-to-event endpoints. Safety analyses were to be tabulations of adverse experiences, reasons for discontinuing study follow-up and reasons for study drug discontinuation, mean

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changes in laboratory variables, changes outside predefined limits for selected laboratory variables, and tabulation of concomitant medications.

4. Results

4.1. Study Implementation

4.1.1. Disposition of Subjects

A total of 10,779 patients were assessed for eligibility for the LIFE study and 9,222 were randomized. Twenty-nine patients belonging to one center were excluded from all analyses due to serious GCP compliance issues at the treatment center in September 1997. Therefore, data from the remaining 9,193 patients were used for efficacy and safety analyses. The dispositions of these patients are listed in the table below.

Table 3: Sponsor's Disposition of Patients

| | Losartan | Atenolol | Total |
|---------------------------------------------------------------------|-----------------|-----------------|-----------------|
| ENTERED: Total ¹ | 4605 | 4588 | 9193 |
| Male (age range—years) | 2118 (45 to 82) | 2112 (48 to 80) | 4230 (45 to 82) |
| Female (age range—years) | 2487 (49 to 83) | 2476 (47 to 83) | 4963 (47 to 83) |
| COMPLETED FOLLOW-UP: (Through death or 16-Sep-2001) ² | 4557 (99.0%) | 4546 (99.1%) | 9103 (99.0%) |
| DISCONTINUED FOLLOW-UP: | | | |
| Lost To Follow-up | 4 (0.1%) | 8 (0.2%) | 12 (0.1%) |
| Patient Withdrew Consent | 44 (1.0%) | 34 (0.7%) | 78 (0.8%) |
| DISCONTINUED Study Drug ³ : 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%) |

¹ p-Values <0.05 and <0.01, respectively, for comparison between losartan and atenolol.

² Excludes 29 patients randomized from disqualified site 925-964.

³ For 107 patients, 57 in the losartan group and 50 in the atenolol group, only vital status was known at time of death or as of 16-Sep-2001.

⁴ Includes reasons for discontinuing study medication prior to death, nonfatal myocardial infarction or stroke, or stopping study follow-up.

Overall, significantly more patients discontinued study drug in the atenolol group than in the losartan group. More patients in the atenolol group discontinued study therapy due to an adverse experience.

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Table 3 above does not account for all patients with incomplete follow-up. For some patients the last contact was a phone contact one or more years after the last visit. For these patients the determination of endpoint event occurrences since the last visit is problematic. The sponsor provided a SAS data set of 197 patients (92 atenolol and 105 losartan) with incomplete or partial follow-up on December 20, 2002. In addition, the reviewer found that 11 patients who withdrew consent and discontinued treatment at a median time of 82 days were not included among these 197 patients. These 11 patients are counted as living with a median follow-up of 1,669 days. A review of the case report forms suggests that follow-up for these patients is also incomplete. Hence follow-up is incomplete in at least 208 patients (2.3%, 99 atenolol and 109 losartan). Of these 208 patients, 39 (19%) were counted as having primary endpoints as compared to 12% of patients with complete follow-up.

COMMENT: The rate of completed follow-up (97.7%) is good but not excellent. The number of patients lost to follow-up (12, or about 0.1%) is excellent. How incomplete follow-up could affect the results is explored in the Efficacy section.

One category in the figure above that needs further explanation is the category "Other administrative reason". The reviewer examined the text fields in the NDA data files provided by the investigators explaining the reasons for discontinuation. The category "Other administrative reasons" includes patient unwilling to continue therapy (common) or unable to continue therapy because of residence moves or other reasons. Note that this category is fairly evenly distributed between the two groups.

Accounting for patients who discontinued study medication also requires some explanation. Patients may have discontinued and restarted study medication more than one time. The investigators may also have reported more than one reason for discontinuing study medication, i.e., both an adverse event and an endpoint. The timing of discontinuation may also be close, i.e., within days, of death or other endpoint. For some statistics the sponsor did not count discontinuations occurring within 14 days of death or other endpoint as discontinuations. Depending upon how these various circumstances are counted the statistics for discontinuations of study medications vary moderately.

4.1.2. Subject Demographics and Baseline Characteristics

4.1.2.1. Overall Baseline Comparisons

The sponsor's summary of baseline demographics is shown in the following table.

COMMENT: The reviewer confirmed that the summary demographic statistics in the table above matched the data in the NDA data files. The baseline demographic characteristics are very evenly distributed between the two treatment groups. Basic demographics are virtually identical in the two groups: the mean ages were 66.9 and the median age 67, 54% were female, and 92.5% were white.

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Table 4: Sponsor's Baseline Demographics

| | (N=4605) | (N=4588) | (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 |
| Male | 45 to 82 | 48 to 80 | 45 to 82 |
| Female | 49 to 83 | 47 to 83 | 47 to 83 |
| 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) | 4248 (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) |
| 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) |

The baseline vital signs were also very similar in the two groups, as shown in the following table:

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Table 5: Sponsor's Baseline Vital Signs

| Event | Treatment | N | Mean | Percentiles of Distribution | | | | |
|---------------------------------|-----------|------|-------|-----------------------------|-------|--------|-------|---------|
| | | | | Minimum | 25% | Median | 75% | Maximum |
| SiSBP (mm Hg) all patients | Losartan | 4605 | 174.3 | | 165.0 | 173.0 | 185.0 | |
| | Atenolol | 4588 | 174.5 | | 165.0 | 174.0 | 185.0 | |
| SiSBP (mm Hg) (SiDBP<95) | Losartan | 1290 | 173.8 | | 165.0 | 171.5 | 181.0 | |
| | Atenolol | 1294 | 174.3 | | 165.0 | 172.0 | 182.5 | |
| SiDBP (mm Hg) all patients | Losartan | 4605 | 97.9 | | 93.0 | 98.0 | 104.0 | |
| | Atenolol | 4588 | 97.7 | | 93.0 | 98.0 | 103.0 | |
| SiDBP (mm Hg) (SiSBP<160) | Losartan | 516 | 99.1 | | 96.0 | 99.0 | 101.0 | |
| | Atenolol | 516 | 98.7 | | 96.0 | 98.0 | 101.0 | |
| StSBP (mm Hg) | Losartan | 4341 | 171.8 | | 160.0 | 170.0 | 182.0 | |
| | Atenolol | 4333 | 172.2 | | 160.0 | 170.0 | 184.0 | |
| StDBP (mm Hg) | Losartan | 4341 | 100.2 | | 94.0 | 100.0 | 108.0 | |
| | Atenolol | 4333 | 100.2 | | 95.0 | 100.0 | 108.0 | |
| Sitting pulse pressure (mm Hg) | Losartan | 4605 | 76.4 | | 67.0 | 76.5 | 87.0 | |
| | Atenolol | 4588 | 76.9 | | 67.0 | 77.0 | 87.5 | |
| Standing pulse pressure (mm Hg) | Losartan | 4341 | 71.6 | | 60.0 | 70.0 | 82.0 | |
| | Atenolol | 4333 | 72.0 | | 60.0 | 70.0 | 84.0 | |
| Pulse rate (beats/min) | Losartan | 4605 | 73.9 | | 66.0 | 72.0 | 80.0 | |
| | Atenolol | 4587 | 73.7 | | 66.0 | 72.0 | 80.0 | |
| Height (cm) | Losartan | 4570 | 167.6 | | 160.0 | 167.0 | 175.0 | |
| | Atenolol | 4534 | 167.5 | | 160.0 | 167.0 | 175.0 | |
| Weight (kg) | Losartan | 4568 | 78.6 | | 68.0 | 78.0 | 87.5 | |
| | Atenolol | 4545 | 78.6 | | 68.6 | 77.6 | 87.0 | |
| BMI (kg·cm ⁻²) | Losartan | 4554 | 28.0 | | 24.8 | 27.5 | 30.5 | |
| | Atenolol | 4525 | 28.0 | | 24.9 | 27.3 | 30.5 | |

Note: Missing values for sitting baseline blood pressures are imputed by corresponding means.

The baseline ECG indices for left ventricular hypertrophy, Framingham risk scores, and lab test results were fairly evenly distributed between the two treatment groups, as shown in the following two tables.

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Table 6: Sponsor's Baseline ECG Measurements 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 | 2828.6 | | 2303.0 | 2668.0 | 3150.0 | |
| | Atenolol | 4588 | 2818.9 | | 2304.0 | 2668.0 | 3150.0 | |
| Cornell product mm x msec (men only) | Losartan | 2118 | 2714.0 | | 2204.0 | 2650.0 | 3120.0 | |
| | Atenolol | 2112 | 2713.9 | | 2205.0 | 2662.5 | 3120.0 | |
| Cornell product mm x msec (women only) | Losartan | 2487 | 2925.1 | | 2376.0 | 2695.0 | 3192.0 | |
| | Atenolol | 2476 | 2908.5 | | 2365.0 | 2668.0 | 3192.0 | |
| Sokolow-Lyon (S-L) voltage mm (all patients) | Losartan | 4605 | 30.0 | | 22.5 | 29.0 | 37.0 | |
| | Atenolol | 4588 | 30.0 | | 22.5 | 29.0 | 36.5 | |
| S-L voltage mm (men only) | Losartan | 2118 | 32.0 | | 24.0 | 31.0 | 39.0 | |
| | Atenolol | 2112 | 32.2 | | 25.0 | 31.0 | 39.5 | |
| S-L voltage mm (women only) | Losartan | 2487 | 28.2 | | 21.5 | 27.0 | 34.5 | |
| | Atenolol | 2476 | 28.2 | | 21.5 | 27.0 | 34.0 | |
| Framingham risk score | Losartan | 4605 | 22.271 | | 14.880 | 20.983 | 28.639 | |
| | Atenolol | 4588 | 22.509 | | 15.041 | 21.075 | 28.778 | |

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

Table 7: Sponsor's Baseline Lab Test Results

| | Losartan (N=4605) | | | Atenolol (N=4588) | | |
|--------------------------------------------|-------------------|--------|--------|-------------------|--------|--------|
| | n | Mean | SD | n | Mean | SD |
| Hemoglobin (gm/dL) | 4191 | 14.24 | 1.23 | 4093 | 14.25 | 1.18 |
| Creatinine (mg/dL) | 4394 | 0.99 | 0.23 | 4384 | 0.98 | 0.23 |
| SGPT (ALAT) (µkat/L) | 3491 | 0.50 | 0.29 | 3502 | 0.51 | 0.34 |
| SGPT (ALAT) -US (mU/mL) | 830 | 16.46 | 41.80 | 786 | 15.69 | 13.41 |
| Glucose (mg/dL) | 4354 | 108.42 | 39.12 | 4334 | 108.62 | 39.87 |
| Uric acid (mg/dL) | 4321 | 5.54 | 1.31 | 4289 | 5.55 | 1.31 |
| Sodium (mEq(Na)/L) | 4324 | 140.32 | 2.56 | 4286 | 140.32 | 2.53 |
| Potassium (mEq(K)/L) | 4309 | 4.17 | 0.38 | 4277 | 4.17 | 0.41 |
| Total cholesterol (mg/dL) | 4321 | 233.45 | 43.26 | 4290 | 233.77 | 43.59 |
| HDL cholesterol (mg/dL) | 4317 | 57.87 | 16.87 | 4289 | 57.64 | 16.92 |
| Urine microalbumin (mg/dL) | 4126 | 6.46 | 23.81 | 4081 | 6.28 | 22.12 |
| Urine creatinine (mg/dL) | 4126 | 111.58 | 63.18 | 4080 | 110.45 | 67.63 |
| Urine microalbumin/urine creatinine (mg/g) | 4126 | 69.33 | 322.73 | 4080 | 65.13 | 275.80 |

n = Number of patients with laboratory test.
 SGPT (ALAT) = Alanine transaminase.
 HDL = High density lipoprotein.

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In addition to the baseline demographics, vital signs, ECG measurement, Framingham risk scores, and lab test result compared in the figures above, the sponsor also analyzed baseline disease histories, time since most recent MI or stroke, and prior therapies. Pertinent results from these analyses are shown in the following table.

Table 8: Reviewer's Selected Other Baseline Comparisons

| | Losartan | Atenolol |
|--------------------------------|----------|----------|
| No tobacco | 50.8% | 50.5% |
| No alcohol | 45.8% | 46.0% |
| No exercise | 22.2% | 21.7% |
| Angina | 10.7% | 9.3% |
| Prior MI | 6.7% | 5.7% |
| Months since MI | 84 | 90 |
| Prior stroke | 4.1% | 4.6% |
| Months since stroke | 44 | 40 |
| Diabetes | 12.7% | 13.3% |
| History of atrial fibrillation | 3.5% | 4.0% |
| Hypercholesterolemia | 16.1% | 17.2% |
| Prior ACEI | 20.2% | 20.4% |
| Prior BB | 26.4% | 25.5% |
| Prior aspirin | 34.2% | 34.1% |
| Prior statin | 6.2% | 6.2% |

MI = myocardial infarction; BB = beta blocker;
ACEI = ACE inhibitor

COMMENT: All baseline characteristics appear to be very well balanced between the two treatment groups. The baseline characteristics reported are comprehensive. There do not appear to be any observed baseline imbalances that would explain the observed differences in outcomes. The contributions of any of the slight differences in observed baseline factors to the outcome differences should be small. Note, however, the small difference in history of atrial fibrillation between the two groups. The significance of this difference is explored in the Efficacy section.

4.1.2.2. Baseline Comparisons by Country

LIFE was a multinational study. The FDA is most interested in the applicability of the results to the US population. In other studies of cardiovascular treatments differences in results by country have been observed. Hence differences in the patient populations and in the results by country are pertinent.

Baseline demographic and behavioral characteristics are shown by country in the following table. Note the US patients include a slightly higher percentage of males and lower alcohol use and exercise rates.

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Table 9: Reviewer's Baseline Demographic Characteristics by Country

| Country | Group | N | Median Age | Male | Smoker | Alcohol | Exercise |
|---------|----------|------|------------|-------|--------|---------|----------|
| Denmark | Atenolol | 699 | 67 | 46.1% | 29.8% | 73.5% | 72.4% |
| | Losartan | 692 | 67 | 47.7% | 26.4% | 75.0% | 74.4% |
| Finland | Atenolol | 737 | 64 | 47.8% | 11.1% | 57.8% | 91.2% |
| | Losartan | 748 | 64 | 44.9% | 9.6% | 56.7% | 91.6% |
| Iceland | Atenolol | 68 | 70 | 55.9% | 8.8% | 58.8% | 77.9% |
| | Losartan | 65 | 69 | 63.1% | 16.9% | 56.9% | 72.3% |
| Norway | Atenolol | 701 | 69 | 42.5% | 16.7% | 46.5% | 75.0% |
| | Losartan | 714 | 69 | 43.6% | 20.3% | 47.5% | 72.0% |
| Sweden | Atenolol | 1133 | 69 | 45.3% | 12.5% | 53.0% | 85.8% |
| | Losartan | 1112 | 69 | 44.5% | 10.3% | 52.7% | 86.3% |
| US | Atenolol | 838 | 66 | 48.4% | 17.8% | 34.0% | 66.9% |
| | Losartan | 869 | 67 | 50.7% | 15.9% | 37.2% | 66.1% |
| UK | Atenolol | 412 | 67 | 44.4% | 16.7% | 69.7% | 73.3% |
| | Losartan | 405 | 67 | 40.5% | 16.5% | 66.7% | 70.6% |
| All | | 9193 | 67 | 46.0% | 16.4% | 54.1% | 78.0% |

Selected baseline risk factors by country are shown in the following table. Note that the US median BMI is slightly greater than the overall median and the US median SBP is slightly less. Otherwise these risk factors are very similar in all countries except for lower age and Framingham risk score in Finland. In particular the Cornell voltage duration products, the Sokolow-Lyon voltages, and Framingham risk scores, the three risk factors pre-specified as covariates for the primary efficacy analysis, are very similar in all countries (except for Framingham risk score in Finland) despite the differences in outcome rates.

Table 10: Reviewer's Selected Baseline Risk Factor Medians by Country

| Country | Group | BMI | SBP | DBP | Cornell | S-L | Cholesterol | Risk Score |
|---------|----------|------|-------|------|---------|------|-------------|------------|
| Denmark | Atenolol | 27.0 | 178 | 100 | 26.5 | 29.0 | 6.1 | 20.9 |
| | Losartan | 27.5 | 177 | 100 | 26.0 | 29.0 | 6.1 | 20.9 |
| Finland | Atenolol | 27.2 | 173 | 99 | 26.5 | 30.5 | 5.9 | 18.1 |
| | Losartan | 27.7 | 171 | 98 | 26.4 | 30.0 | 6.0 | 18.0 |
| Iceland | Atenolol | 27.3 | 169.5 | 98.5 | 26.9 | 25.0 | 5.9 | 25.3 |
| | Losartan | 27.8 | 170 | 100 | 26.7 | 25.5 | 6.1 | 26.6 |
| Norway | Atenolol | 26.5 | 174 | 98 | 26.7 | 29.0 | 6.4 | 22.0 |
| | Losartan | 26.5 | 173 | 98 | 26.7 | 29.0 | 6.4 | 21.6 |
| Sweden | Atenolol | 27.6 | 175 | 98 | 27.1 | 28.5 | 6.0 | 22.2 |
| | Losartan | 27.4 | 174 | 98 | 27.6 | 28.3 | 6.0 | 21.4 |
| US | Atenolol | 28.3 | 170 | 97 | 26.5 | 29.5 | 5.4 | 22.1 |
| | Losartan | 28.2 | 170 | 97 | 26.7 | 29.5 | 5.5 | 22.4 |
| UK | Atenolol | 27.4 | 176 | 99 | 26.7 | 26.0 | 5.9 | 21.9 |
| | Losartan | 27.4 | 178 | 100 | 26.7 | 27.0 | 5.9 | 20.4 |
| All | | 27.4 | 174 | 98 | 26.7 | 29.0 | 6.0 | 21.0 |

BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure
 Cornell = Cornell voltage duration product; S-L = Sokolow-Lyon voltage;
 Risk Score = Framingham risk score

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Selected baseline disease histories by country are shown in the following table. Note that the US patients have higher rates for all diseases.

Table 11: Reviewer's Baseline Disease Histories by Country

| Country | Group | Angina | MI | Heart Failure | Stroke | Diabetes |
|---------|----------|--------|-------|---------------|--------|----------|
| Denmark | Atenolol | 7.2% | 4.3% | 1.7% | 5.6% | 8.2% |
| | Losartan | 7.9% | 6.6% | 1.2% | 5.5% | 10.8% |
| Finland | Atenolol | 4.6% | 1.5% | 0.4% | 3.7% | 10.4% |
| | Losartan | 4.3% | 1.9% | 1.1% | 1.9% | 9.6% |
| Iceland | Atenolol | 13.2% | 2.9% | 0.0% | 5.9% | 13.2% |
| | Losartan | 12.3% | 7.7% | 1.5% | 3.1% | 7.7% |
| Norway | Atenolol | 6.8% | 6.3% | 1.0% | 3.3% | 10.8% |
| | Losartan | 9.8% | 7.0% | 0.7% | 3.9% | 8.7% |
| Sweden | Atenolol | 11.9% | 4.6% | 1.1% | 4.3% | 14.2% |
| | Losartan | 12.5% | 6.1% | 1.1% | 3.2% | 15.6% |
| US | Atenolol | 14.6% | 12.3% | 5.1% | 7.2% | 23.0% |
| | Losartan | 18.3% | 11.7% | 5.3% | 6.2% | 19.8% |
| UK | Atenolol | 6.8% | 4.9% | 1.0% | 1.9% | 8.7% |
| | Losartan | 7.2% | 4.9% | 1.0% | 4.7% | 6.7% |
| All | | 10.0% | 6.2% | 1.8% | 4.4% | 13.0% |

MI = myocardial infarction

Selected prior drug therapies are shown in the following table. Note the greater use of ACEIs, aspirin, and statins in the US. Iceland also shows a different pattern of drug use, although the numbers in Iceland are relatively small. Finnish patients appear to have lower rates of prior cardiac disease.

Table 12: Reviewer's Selected Prior Drug Therapies by Country

| Country | Group | ACEI | ARB | BB | ASA | Statin |
|---------|----------|-------|------|-------|-------|--------|
| Denmark | Atenolol | 20.7% | 6.3% | 17.6% | 33.2% | 2.1% |
| | Losartan | 21.2% | 6.6% | 19.5% | 27.7% | 2.3% |
| Finland | Atenolol | 19.9% | 0.4% | 24.8% | 27.8% | 4.3% |
| | Losartan | 17.0% | 0.1% | 26.6% | 28.6% | 3.5% |
| Iceland | Atenolol | 35.3% | 1.5% | 44.1% | 7.4% | 1.5% |
| | Losartan | 35.4% | 0.0% | 35.4% | 16.9% | 1.5% |
| Norway | Atenolol | 21.7% | 6.6% | 21.4% | 18.4% | 6.8% |
| | Losartan | 21.0% | 6.7% | 22.7% | 16.9% | 7.1% |
| Sweden | Atenolol | 14.7% | 2.5% | 33.5% | 36.5% | 4.9% |
| | Losartan | 15.1% | 1.9% | 36.0% | 35.8% | 4.4% |
| US | Atenolol | 35.2% | 7.3% | 24.1% | 49.5% | 14.3% |
| | Losartan | 34.5% | 6.0% | 26.5% | 52.9% | 15.1% |
| UK | Atenolol | 17.0% | 1.5% | 37.4% | 39.3% | 3.4% |
| | Losartan | 20.2% | 1.2% | 32.3% | 40.0% | 2.7% |
| All | | 21.7% | 3.9% | 27.2% | 33.9% | 6.2% |

ACEI = ACE inhibitor; ARB = angiotensin receptor blocker;
BB = beta blocker; ASA = aspirin

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COMMENT: For the risk factors pre-specified by the sponsor for the primary analysis the US patients are very similar to the Scandinavian patients. However, for other risk factors (increased BMI and prior ischemic heart disease, stroke, and diabetes) the US patients are worse than the Scandinavian while baseline blood pressures were lower in the US patients. However, note that all risk factors and baseline characteristics are reasonably evenly distributed between the two treatment groups, overall and by country.

4.1.2.3. Baseline Comparisons by Race

The FDA requires that differences in efficacy and safety be examined by age, gender, and race. The outcomes in LIFE appear to vary by race, so it is instructive to examine whether baseline characteristics differ by race. In LIFE the races with substantial representations were whites and blacks. Because only 2% of blacks were non-US and because the US study population appears to differ overall from the Scandinavian, the following baseline comparisons of blacks and non-blacks include US cases compared to the non-US cases. The following four tables by race show the same baseline factors as the preceding four tables by country.

Table 13: Reviewer's Baseline Demographic and Behavioral Characteristics by Race

| | N | Median Age | Male | Smoker | Alcohol | Exercise |
|--------------|------|------------|------|--------|---------|----------|
| US non-black | 1184 | 68 | 48% | 13% | 37% | 70% |
| US black | 523 | 64 | 54% | 25% | 33% | 59% |
| Non-US | 7486 | 67 | 45% | 16% | 58% | 81% |

Table 14: Reviewer's Selected Baseline Risk Factor Medians by Race

| | BMI | SBP | DBP | Cornell | S-L | Cholesterol | Risk Score |
|--------------|------|-----|-----|---------|-----|-------------|------------|
| US non-black | 28.1 | 170 | 96 | 27 | 28 | 5.5 | 22.5 |
| US black | 28.5 | 171 | 98 | 25.5 | 35 | 5.4 | 21.7 |
| Non-US | 27.2 | 175 | 99 | 26.7 | 29 | 6.1 | 20.7 |

BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure
 Cornell = Cornell voltage duration product; S-L = Sokolow-Lyon voltage;
 Risk Score = Framingham risk score

Table 15: Reviewer's Baseline Disease Histories by Race

| | Angina | MI | Heart Failure | Stroke | Diabetes |
|--------------|--------|----|---------------|--------|----------|
| US non-black | 18% | 6% | 14% | 6% | 20% |
| US black | 12% | 4% | 8% | 9% | 25% |
| Non-US | 9% | 1% | 5% | 4% | 11% |

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Table 16: Reviewer's Selected Prior Drug Therapies by Race

| | ACEI | ARB | BB | ASA | Statin |
|--------------|------|-----|-----|-----|--------|
| US non-black | 36% | 7% | 27% | 54% | 17% |
| US black | 31% | 5% | 21% | 44% | 9% |
| Non-US | 19% | 3% | 28% | 30% | 4% |

ACEI = ACE inhibitor; ARB = angiotensin receptor blocker;
BB = beta blocker; ASA = aspirin

COMMENT: The preceding four tables confirm that there are significant differences among the three subgroups in baseline characteristics. Blacks are younger and heavier, more likely to be male and smokers, and less likely to use alcohol and to exercise. They have higher Sokolow-Lyon voltage but lower Cornell voltage duration products. They are intermediate between US non-blacks and non-US cases for heart disease and the selected CV drugs (except beta blockers, for which they have the lowest use) but have histories of more strokes and diabetes. US non-blacks are differentiated from non-US cases by lower blood pressures, lower smoking, alcohol use, and exercise rates, a slightly higher BMI, the highest rates of cardiac disease, higher use of ACEIs, ARBs, aspirin, and statins, and intermediate rates of stroke and diabetes.

The baseline differences among the three subgroups raises the question of whether the three subgroups are best lumped together for the efficacy and safety analyses. Differences in safety and efficacy in these subgroups are explored in the reviewer's analyses in Section 4.2.

4.1.3. Conduct

The sponsor's description of some features of the trial conduct is as follows: "Numerous procedures were undertaken to ensure the study was conducted according to Good Clinical Practices guidelines. All investigators received an instruction manual, 'Guide to LIFE'. 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." The sponsor also employed a blinded Endpoints Classification Committee to provide unbiased assessments of endpoints, two central labs (one in the US and one in Europe) to insure consistency and accuracy of lab results, and an unblinded Data Safety and Monitoring Board to insure patient safety.

COMMENT: All of these measures help to ensure study integrity.

4.1.3.1. Monitoring

The sponsor's description of the trial monitoring is as follows: "Regular site monitoring was conducted by the SPONSOR to verify protocol adherence and compare the accuracy

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of the study data against source documentation. 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 US and international investigative sites was audited by the SPONSOR for compliance to ICH/GCP guidelines and the SPONSOR's own internal standard operating procedures. All authors reviewed this Clinical Study Report for accuracy and scientific content."

Note that one site's data were dropped because of GCP noncompliance and another site was closed, but its two cases retained, because of loss of the investigator's medical license. The sponsor audited 48 sites at random and did not identify any problems.

4.1.3.2. Protocol Changes and Violations

Minor changes were made to the protocol during the course of the study:

- Protocol Amendment 133-01, dated March 29, 1996, altered the LVH criteria for entry into the study. It lowered the correction factor for the calculation of Cornell product in women to 6 mm based on data published after the start of the study and introduced a second acceptance criterion based on the Sokolow-Lyon voltage combination (SV1 + RV5 or V6) > 38 mm irrespective of gender, in order to increase the sensitivity of detecting ECG-LVH without loss of specificity. These changes took effect on May 1, 1996, at which time 2,375 patients (1,453 women) had been enrolled.
- Resuscitated cardiac arrest was added as a secondary endpoint proposed by the Endpoint Classification Committee and approved by the Steering Committee on March 29, 1996.
- Protocol Amendment 133-0A, dated May 5, 1998, provided for a 25 mg dose of study drug to investigators who request it on a patient-by-patient basis.

Protocol violations were infrequent: Thirty-two patients did not meet LVH criteria by screening ECG, 20 patients did not have a qualifying measurement, either SBP or DBP, at either of last 2 visits before study start, 2 patients experienced a MI or stroke within 4 months prior to study start, and 152 patients took prohibited medications during the baseline period. See the Dosing section below for statistics on patients taking prohibited medications during the study period.

Fifty-eight patients were unblinded prematurely. Ten patients (10065, 10591, 40463, 60717, 60841, 60028, 30169, 30355, 31470, and 30848) continued on study drug therapy after unblinding.

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4.1.3.3. Dosing

4.1.3.3.1. Study Drug

The mean dose for losartan was 74.4 mg and for atenolol was 71.4 mg. Losartan-treated patients received study drug for 84% of study follow-up compared to 79% for atenolol-treated patients. The study drug dosages at the final visit are shown in the following table.

Table 17: Sponsor's Study Drug Dosages at Final Visit

| | Losartan | | Atenolol | |
|------------------------------------------------------|----------|--------|----------|--------|
| | n | % | n | % |
| Drug Doses | | | | |
| 50 mg only | 434 | (9.0) | 436 | (10.0) |
| 50 mg plus additional drugs [†] | 844 | (18.0) | 930 | (20.0) |
| 100 mg with or without additional drugs [†] | 2284 | (50.0) | 1979 | (43.0) |
| Alone | 95 | (2.0) | 78 | (2.0) |
| With HCTZ only | 829 | (18.0) | 713 | (16.0) |
| With other drugs only | 162 | (4.0) | 172 | (4.0) |
| With HCTZ and other drugs | 1198 | (26.0) | 1016 | (22.0) |
| Off study drugs | 1043 | (23.0) | 1243 | (27.0) |

[†] Including hydrochlorothiazide (HCTZ).

At the final visit 2773 (60%) patients in the losartan treatment group and 2569 (56%) patients in the atenolol group received hydrochlorothiazide (HCTZ) as a study drug. The mean dose was ~20 mg in each treatment group and the distribution of doses was similar between the two treatment groups. These statistics on HCTZ use do not include other open-label, non-study drug use of HCTZ.

4.1.3.3.2. Concomitant Therapy

The sponsor tabulated concomitant therapy in the two groups by drug class. Use of noncardiovascular drugs was very similar between the two groups. Use of cardiovascular drugs is shown in the table below.

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Table 18: Sponsor's Concomitant Use of Cardiovascular Drugs

| | Losartan (N=4605) | | Atenolol (N=4588) | |
|-----------------------------------------------------------------|----------------------|---------------|----------------------|---------------|
| | n | (%) | n | (%) |
| Cardiovascular System | 2996 | (65.1) | 2976 | (64.9) |
| <i>Agent acting on the Renin-Angiotensin System</i> | 178 | (3.9) | 195 | (4.3) |
| Angiotensin II antagonists | 51 | (1.1) | 47 | (1.0) |
| Angiotensin-converting enzyme (ACE) inhibitors, plain | 119 | (2.6) | 147 | (3.2) |
| <i>Antihypertensive</i> | 574 | (12.5) | 573 | (12.5) |
| Antiadrenergic agents, centrally acting | 158 | (3.4) | 139 | (3.0) |
| Antiadrenergic agents, peripherally acting | 478 | (10.4) | 496 | (10.8) |
| <i>Beta-Blocking Agent</i> | 368 | (8.0) | 288 | (6.3) |
| Beta-blocking agents | 362 | (7.9) | 286 | (6.2) |
| <i>Calcium Channel Blocker</i> | 1819 | (39.5) | 1852 | (40.4) |
| Selective calcium channel blockers with direct cardiac effects | 256 | (5.6) | 201 | (4.4) |
| Selective calcium channel blockers with mainly vascular effects | 1688 | (36.7) | 1769 | (38.6) |
| <i>Cardiac Therapy</i> | 726 | (15.8) | 681 | (14.8) |
| Antiarrhythmics, class I and III | 54 | (1.2) | 46 | (1.0) |
| Cardiac glycosides | 262 | (5.7) | 252 | (5.5) |
| Vasodilators used in cardiac diseases | 478 | (10.4) | 453 | (9.9) |
| <i>Diuretic</i> | 543 | (11.8) | 612 | (13.3) |
| High-ceiling diuretics | 368 | (8.0) | 413 | (9.0) |
| Low-ceiling diuretics, thiazides | 84 | (1.8) | 96 | (2.1) |
| Potassium-sparing agents | 104 | (2.3) | 115 | (2.5) |
| <i>Serum Lipid-Reducing Agent</i> | 950 | (20.6) | 1013 | (22.1) |
| Cholesterol and triglyceride reducers | 950 | (20.6) | 1013 | (22.1) |

The reviewer also examined aspirin, other antiplatelet drug, and statin use. Aspirin and other antiplatelet drug use were similar in the two groups, e.g., for aspirin, 34.0% in the atenolol group and 33.8% in the losartan group. Statin use was slightly higher in the atenolol group (24.0% vs 21.9%).

COMMENT: Note that angiotensin II antagonists or ACE inhibitors were taken by 178 (3.9%) patients on study drug in the losartan group and 195 (4.3%) in the atenolol group. Beta blockers were taken by 368 (8.0%) and 288 (6.3%) patients in the losartan and atenolol groups, respectively. These differences are small, but they do suggest that blinding of the study therapies was not perfect. Blinding of two agents with well known and slightly different side effect profiles, e.g., reduction in heart rate with a beta blocker, is difficult.

4.1.3.4. Blinding

The study drug was dispensed in double dummy fashion to hide the identity of the active drug for each patient. For emergency use each site was given sealed envelopes with the

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drug identities by allocation number. If a site broke the blind, the sponsor monitor was to be notified as soon as possible or, if possible, prior to the unblinding. The rates and results of premature unblinding are discussed above under Protocol Changes and Violations.

The Endpoint Classification Committee was also blinded. The DSMB was unblinded as was the one sponsor statistician who performed the two interim analyses for the DSMB. The statistician was instructed not to reveal any study findings prematurely to other sponsor staff.

COMMENT: The methodology for blinding is as sophisticated as is practical for a trial of this size. There is slight evidence that the blinding may have been partially broken in the field, i.e., the differential use of open-label beta blockers noted in the previous section. There is no consistent evidence that endpoint determination was unblinded as discussed in the Efficacy section below.

4.2. Efficacy

4.2.1. Sponsor's Primary Endpoint

The sponsor's primary endpoint for the study is the composite of cardiovascular mortality, myocardial infarction, and stroke. All three components were adjudicated by the blinded Endpoint Classification Committee. The pre-specified analysis for this primary endpoint was a time-to-event analysis using a Cox proportional hazards regression with degree of left ventricular hypertrophy (Cornell voltage duration product and Sokolow-Lyon voltage on the baseline ECG) and Framingham risk score as covariates.

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 hazard ratio (HR) was 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 HR was 0.854 (95% CI 0.759 to 0.962, $p=0.009$). The Kaplan-Meier plot of the primary composite endpoint is shown in the following figure.

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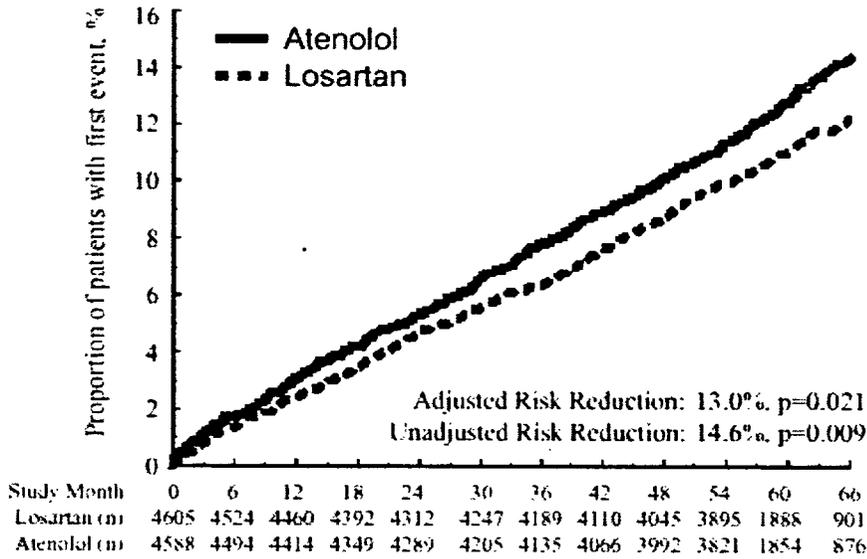


Figure 3: Sponsor's Kaplan-Meier Curves for Primary Composite Endpoint

The categorization of the event types of the primary composite endpoint is shown in the following table.

Table 19: Reviewer's Endpoint Types of Primary Composite Endpoint

| Type | Atenolol N (%) | Losartan N (%) |
|----------|-------------------|-------------------|
| CV death | 154 (3.4) | 137 (3.0) |
| MI | 168 (3.7) | 174 (3.8) |
| Stroke | 266 (5.8) | 197 (4.3) |

MI = myocardial infarction; CV = cardiovascular
% = percent of number of patients in treatment group

The FDA Statistical Review includes a Table 3 with a slightly different categorization of the components of the primary composite endpoint. The pertinent data from that table are reproduced in the table below.

Table 20: Statistical Reviewer's Endpoint Types of Primary Composite Endpoint (from Table 3 in the FDA Statistical Review)

| Type | Atenolol N (%) | Losartan N (%) |
|----------|-------------------|-------------------|
| CV death | 134 (2.9) | 125 (2.7) |
| MI | 168 (3.7) | 174 (3.8) |
| Stroke | 286 (6.2) | 209 (4.5) |

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Note that the stroke rates are slightly lower and the cardiovascular (CV) mortality rates are slightly higher in the clinical reviewer's table than in the statistical reviewer's table. The clinical reviewer generated the table based on a data set supplied by the sponsor that classified strokes followed by death within seven days as cardiovascular deaths rather than strokes. The statistical reviewer generated his table from a different data set supplied by the sponsor that did not include this re-classification.

COMMENT: The tables are useful for trying to understand what is the contribution of CV death relative to non-fatal endpoints to the primary composite endpoint. From that perspective the clinical reviewer's table is preferable. Another perspective is the relative contribution of stroke vs. MI in the composite endpoint. From this latter perspective neither table is ideal because CV mortality is a composite of deaths from MI and deaths from strokes and a few other miscellaneous CV causes. If one re-classifies CV deaths as to the specific CV cause, then one obtains the following tabulation.

Table 21: Reviewer's Cardiovascular Causes for Primary Endpoint

| Type | Atenolol N (%) | Losartan N (%) |
|------------------------|-------------------|-------------------|
| Stroke | 295 (6.4) | 218 (4.7) |
| Coronary heart disease | 255 (5.6) | 259 (5.6) |
| Peripheral vascular | 19 (0.4) | 12 (0.3) |
| Heart failure | 10 (0.2) | 15 (0.3) |
| Other cardiovascular | 9 (0.2) | 4 (0.1) |

Note that the difference in the primary endpoint rates is dominated by the difference in the stroke rates. Endpoints due to coronary heart disease are very evenly distributed between the two groups. There are low rates of other CV events with interesting differences in the rates

These differences are also seen in the Kaplan-Meier curves for the separate components of the composite endpoint shown in the following figure. Note that the figure differs from the previous table in that the figure includes all first events of the designated types while in the table includes only the first occurrence of any type of primary endpoint event.

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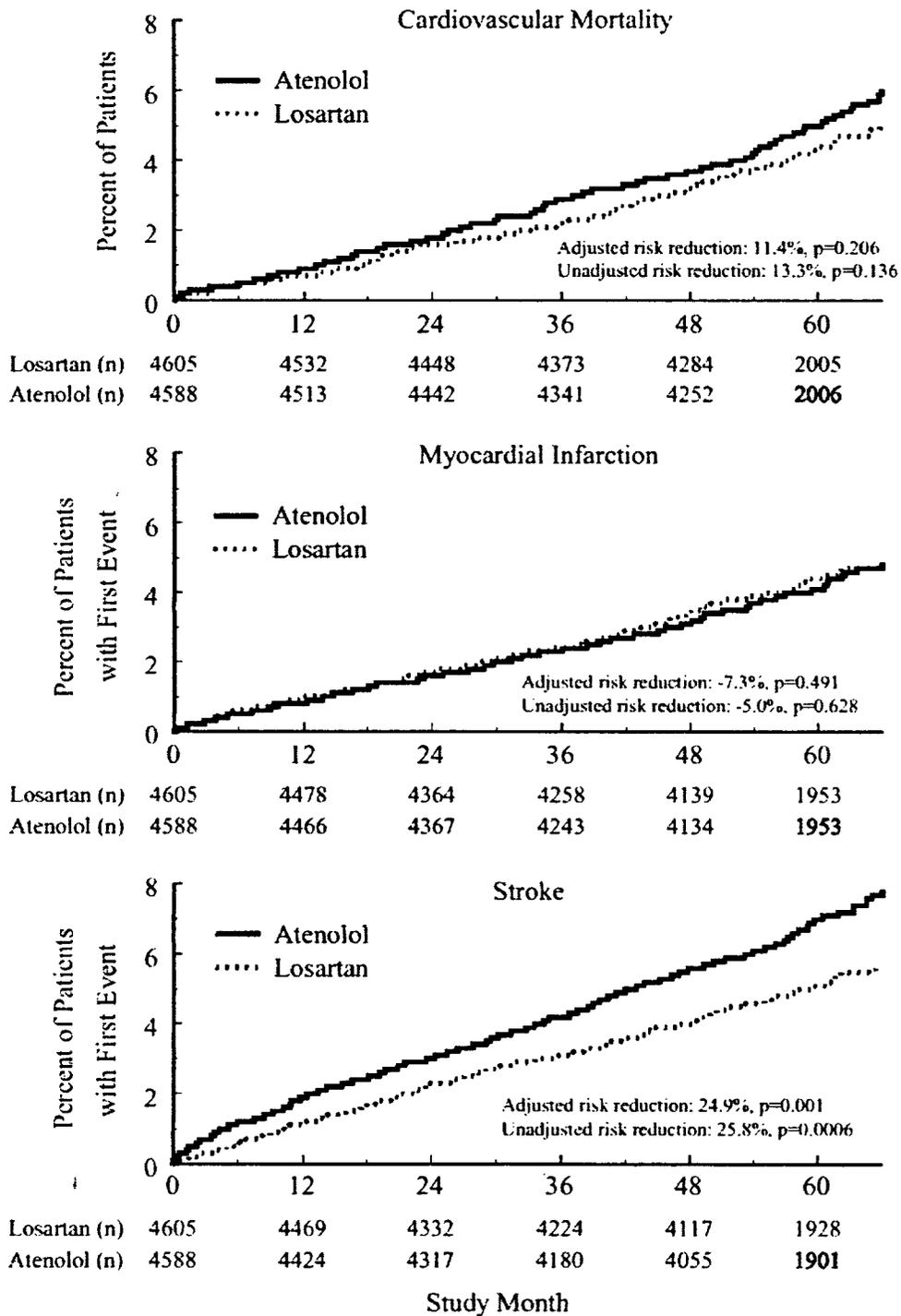


Figure 4: Sponsor's Kaplan-Meier Curves for Components of the Primary Composite Endpoint

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The reviewer's analyses of the data files in the NDA agree with the sponsor's Kaplan-Meier curves and p values given in the preceding figures. See the FDA statistician's review for additional comments on the statistical methodology.

COMMENT: For the sponsor's primary composite endpoint losartan shows a favorable effect with a relative risk reduction of about 13%. The statistical significance of this effect is not extreme, i.e., $p = 0.021$. Regarding the components of the primary composite endpoint the relative risk reduction in strokes is impressive, about 25%. The differences in the other two components are small and not statistically significant. There is a slight, statistically insignificant difference favoring atenolol in the rates of MIs while there is a trend towards lower cardiovascular mortality with losartan.

All three components of the sponsor's primary composite endpoint have a degree of softness or uncertainty in ascertainment. Because of this softness and also because of its overall importance, the Division had suggested to the sponsor that total mortality, rather than cardiovascular mortality, be used in the primary composite endpoint. The important issue of total mortality will be examined next. The other issue that will be examined is the robustness of the results, i.e., how much can a different interpretation of some of the endpoint events affect the results?

4.2.2. Total Mortality

Four hundred thirty one (9.4%) patients in the atenolol group died and 383 (8.3%) in the losartan group died. A Kaplan-Meier plot of the total mortality curves is shown in the figure below.

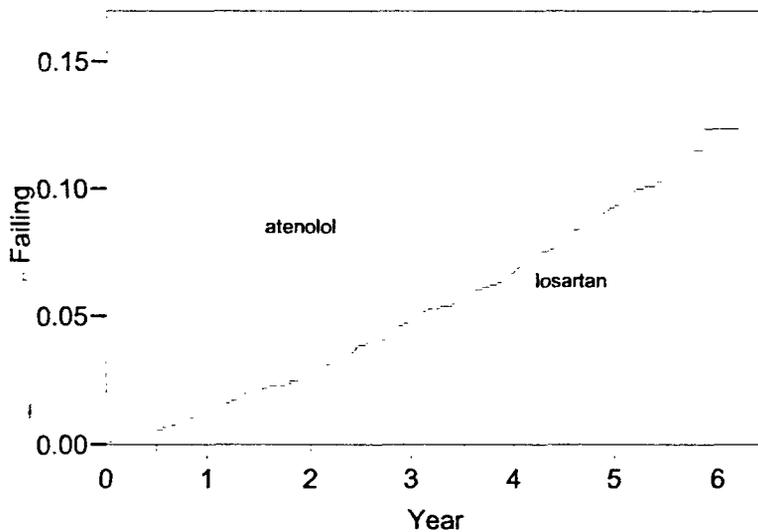


Figure 5: Reviewer's Kaplan-Meier Plot of Total Mortality by Group

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There appears to be a trend towards improved survival in the losartan group that does not quite achieve statistical significance by the log-rank test ($p = 0.076$). Using the sponsor's Cox proportional hazards model with baseline LVH and Framingham risk score as covariates the statistical significance is reduced ($p = 0.13$).

COMMENT: Total mortality does not differ significantly between the two groups. The effect of including total mortality rather than cardiovascular mortality in the primary composite endpoint, the Division's recommendation, is explored in a later section.

4.2.3. Robustness of Primary Endpoint to Event Reclassification

All three components of the primary composite endpoint are subject to interpretation. One example of differences in interpretation is the difference in initial assessments by the Endpoint Classification Committee (ECC). The ECC reviewed 4,365 cases. The two ECC members agreed on the initial assessment for 3,567 cases (82%).

Another example of differences in interpretation of the primary endpoint is the difference between the investigators' reporting of primary endpoint events and the ECC's adjudication of them. Investigators reported primary endpoints in 1,227 cases while the ECC classified 1,096 cases as meeting the pre-specified primary endpoint criteria, including 12 cases reported by investigators as angina that the ECC reclassified as definite myocardial infarctions (MIs). The investigators' and the ECC's classification of whether a primary endpoint occurred differ in 211 cases, the endpoint day differs in 244 cases, and either the day or the endpoint occurrence differ in 314 cases, or about 29% of the adjudicated endpoints. Of these 314 cases 55% were in the atenolol group and 45% were in the losartan group. These differences probably overestimate the variation in endpoint interpretation because investigators should have reported endpoints that they considered uncertain so that real endpoints were not missed.

To characterize better the variability of endpoint classification the reviewer checked endpoints against the case report forms (CRFs). For these checks the reviewer did not reference the cases' treatment groups. The reviewer's primary focus for these checks was upon the cases for which there are differences between the investigator's and the ECC's endpoint classifications. The reviewer also examined random samples of other cases.

For 20 randomly selected cases without an adjudicated primary endpoint the NDA included CRFs for nine. The reviewer confirmed that the CRFs lacked evidence of primary endpoints for all nine. Two cases had secondary angina endpoints that the reviewer confirmed did not meet the criteria for a MI.

For 40 randomly selected cases with an adjudicated primary endpoint but without an investigator-committee difference the NDA included CRFs for all 40. The reviewer confirmed that the CRFs contained acceptable evidence of the primary endpoints for all 40 cases.

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Of the 314 cases with investigator-committee endpoint differences, 73 cases represent endpoint day differences of 30 days or less. The reviewer did not check these 73 cases systematically because of the low impact of any changes. The reviewer checked CRFs for the other 241 cases.

Of the 211 cases for which the committee disagreed with the investigator regarding the occurrence of any primary endpoint event, 58 cases represent differences in classification of deaths as cardiovascular (CV) deaths, or about 18% of adjudicated CV deaths. The reviewer agreed with the committee for 28 cases, disagreed with the committee for 9 cases, and judged the decision to be difficult based on available data in 21 cases. The reviewer's best estimate agreed with the committee's assessment in 76% of cases.

Of the 12 cases for which the committee adjudicated a primary endpoint and the investigator did not report one, all were adjudicated as definite myocardial infarctions (MIs). The reviewer disagreed with the committee for 6 cases, agreed for 3 cases, and judged the decision to be difficult for 3 cases. The reviewer's best estimate agreed with the committee's assessment in 33% of cases. Ten of the 12 cases were in the atenolol group. The reviewer classified 6 of these cases as not definite MIs and both losartan cases as not definite MIs.

The committee did not adjudicate any primary endpoint strokes not reported by the investigators as strokes. The committee adjudicated five secondary stroke endpoints (four in atenolol patients and 1 in a losartan patient) not reported by the investigators as stroke endpoints. In all but one of the cases the CRFs had supporting data regarding the stroke (three on the death report and the other on a second CT scan during a hospitalization for an earlier stroke.)

Of the 141 cases other than deaths for which the investigator reported a primary endpoint but the committee did not confirm it, the reviewer agree with the committee in 53 cases, disagreed in 72 cases, and judged the decision to be difficult in 16. The reviewer's best estimate agreed with the committee's assessment in 47% of cases.

For the 26 cases in which the investigator's endpoint day was earlier than the adjudicated endpoint day, the reviewer's best estimate agreed with the committee's assessment in 31% of the cases. For the four cases in which the investigator's endpoint day was later than the adjudicated endpoint day, the reviewer's best estimate agreed with the committee's assessment in 75% of the cases.

The problematic events for classification had some similarities. For MIs, investigators not uncommonly reported chest pain events with enzyme rises less than twofold as MIs. For strokes, investigators not uncommonly reported cerebral ischemic events of less than 24 hours duration as strokes. For deaths, all classifiers had difficulty with classifying deaths of unknown cause with no information about the time course of events leading to death.

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Overall for these 241 cases checked the reviewer agreed with the committee's assessment in 48% of the cases. The direction of the Endpoint Classification Committee's changes for these cases was completely neutral, with 120 changes favoring atenolol and 121 changes favoring losartan.

The different classifications of endpoint events have small effects upon the primary endpoint results. The effects of the different endpoint analyses upon the sponsor's primary composite endpoint analyses are shown in the following table.

Table 22: Reviewer's Comparison of Different Primary Endpoint Event Classifications

| | Endpoint Event Classifier | | |
|-------------------|---------------------------|----------|-----------|
| | Investigator | Reviewer | Committee |
| Atenolol events | 651 | 619 | 588 |
| Losartan events | 576 | 538 | 508 |
| Log rank p | 0.02 | 0.01 | 0.009 |
| Cox regression* p | 0.039 | 0.023 | 0.021 |

* with baseline LVH and Framingham risk score

The reviewer's endpoint reclassifications above are based on the CRFs as originally submitted by the sponsor. The sponsor omitted including in the original supplemental NDA submission "endpoint narratives" that were submitted by the investigators and used by the ECC. The reviewer requested and obtained a sample of these endpoint narratives late in the review process. The reviewer requested endpoint narratives primarily on cases for which the data provided in the CRFs was incomplete.

The reviewer examined endpoint narratives for 129 events, for 118 of which there were disagreements among the investigators', the reviewer's, or the ECC's classifications. For 33 of these events (28%) the reviewer changed his classification to the ECC's classification based on the additional information in the endpoint narrative. For four (3%) the reviewer changed his classification from agreeing with the ECC to agreeing with the investigator. While the changes appear to be in the direction of greater agreement with the ECC, the effect of these reclassifications is to reduce slightly the significance of the primary composite endpoint analysis by Cox regression (p increased from .023 to 0.038).

How patients with incomplete follow-up are counted also affects the significance of the results. If the patients with incomplete follow-up and no events are censored at the time of last complete follow-up, then the statistical significance of the primary composite endpoint difference by the sponsor's usual Cox regression is reduced slightly (p= 0.025). If the worst case scenario is assumed, i.e., atenolol patients with incomplete follow-up are left unchanged and the losartan patients with incomplete follow-up and no events are

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assumed to have failed at the time of the last follow-up plus one day, then the hazard ratio is 0.96 and statistically insignificant ($p > 0.5$).

COMMENT: While each component of the sponsor's primary composite endpoint is subject to interpretation in some cases, the Endpoint Classification Committee's assessment of events appears to have been conducted in a unbiased manner. Reclassification of problematic events by the reviewer reduces slightly the statistical significance of the difference in the primary composite endpoint. Censoring cases with incomplete follow-up at the time of the last complete follow-up also reduces slightly the statistical significance of the difference in the primary composite endpoint. The primary endpoint does appear to be sensitive to the interpretation of primary endpoint events and to incomplete follow-up.

4.2.4. Primary Endpoint Including Total Mortality

The Division recommended that total mortality, rather than cardiovascular mortality, be incorporated into the primary composite endpoint. While the trial coordinating committee and the sponsor rejected this recommendation, it is informative to examine the results of including total mortality in the primary composite endpoint. There were 814 deaths during the study of which 376 were classified as non-cardiovascular deaths. The results of including total mortality in the primary composite endpoint are shown in the following table.

Table 23: Reviewer's Primary Composite Endpoint Results Incorporating Total Mortality

| | Endpoint Event Classifier | | |
|-------------------|---------------------------|----------|-----------|
| | Investigator | Reviewer | Committee |
| Atenolol events | 808 | 780 | 751 |
| Losartan events | 730 | 701 | 670 |
| Log rank p | 0.027 | 0.023 | 0.018 |
| Cox regression* p | 0.056 | 0.051 | 0.039 |

* with baseline LVH and Framingham risk score covariates

COMMENT: Not surprisingly incorporating total mortality reduces the statistical significance of the results. The results with endpoints adjudicated by the Endpoint Classification Committee retain statistical significance but the results with endpoints classified by the reviewer fail to achieve statistical significance for the Cox regression.

4.2.5. Composite Endpoints For Patients on Study Drug

The sponsor's pre-specified primary endpoint analysis and all of the analyses presented previously follow a strict, as randomized, intention-to-treat principle. For example, a

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stroke endpoint on day one for a patient randomized to atenolol but occurring before the patient received atenolol is included in the previous analyses. An alternative analysis is to censor patients who discontinue treatment for other than a primary endpoint occurrence. In all 3,484 patients (1,859 atenolol, 1,625 losartan) discontinued study drug at least once, and 440 patients discontinued study drug more than once. The analyses below censor patients at the times of their last study drug discontinuations if the discontinuations were not for primary endpoints. Because of variations in the reporting of dates and to capture events immediately following drug discontinuation, study drug discontinuations dated within 30 days prior to a primary endpoint event are not counted as discontinuations. The results for all of the primary endpoint variations presented previously are shown in the following two tables.

Table 24: Reviewer's Composite Endpoint Results on Study Drug

| | Endpoint Event Classifier | | |
|-------------------|---------------------------|----------|-----------|
| | Investigator | Reviewer | Committee |
| Atenolol events | 482 | 450 | 418 |
| Losartan events | 440 | 413 | 378 |
| Log rank p | 0.033 | 0.047 | 0.033 |
| Cox regression* p | 0.052 | 0.073 | 0.055 |

Table 25: Reviewer's Composite Endpoint with Total Mortality Results on Study Drug

| | Endpoint Event Classifier | | |
|-------------------|---------------------------|----------|-----------|
| | Investigator | Reviewer | Committee |
| Atenolol events | 546 | 519 | 492 |
| Losartan events | 512 | 489 | 453 |
| Log rank p | 0.063 | 0.080 | 0.039 |
| Cox regression* p | 0.097 | 0.12 | 0.064 |

The sponsor performed a per protocol analysis that excluded patients with important protocol violations and censored patients 14 days after permanently discontinuing study medications or 14 days after starting prohibited therapy. The results are similar to the above and are presented in the table below.

Table 26: Sponsor's Per Protocol Primary Endpoint Results

| | Crude Rate | | | | | | Kaplan-Meier Rates | | | | | | | | Hazard Ratio | 95% CI | | p-Value [†] |
|--------------------------|------------------------------------------|-----|-------|-------------------|-----|-------|---------------------|------|------|------|----------|------|------|------|--------------|--------|-------|----------------------|
| | Losartan (N=4504) | | | Atenolol (N=4485) | | | Losartan | | | | Atenolol | | | | | Lower | Upper | |
| | Rate | n | (%) | Rate | n | (%) | 1 Yr | 2 Yr | 3 Yr | 4 Yr | 1 Yr | 2 Yr | 3 Yr | 4 Yr | | | | |
| 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 |
| 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 | 1.176 | 0.927 | 1.496 | 0.180 |
| 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 | 0.556 | 0.845 | <0.001** |

** 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.

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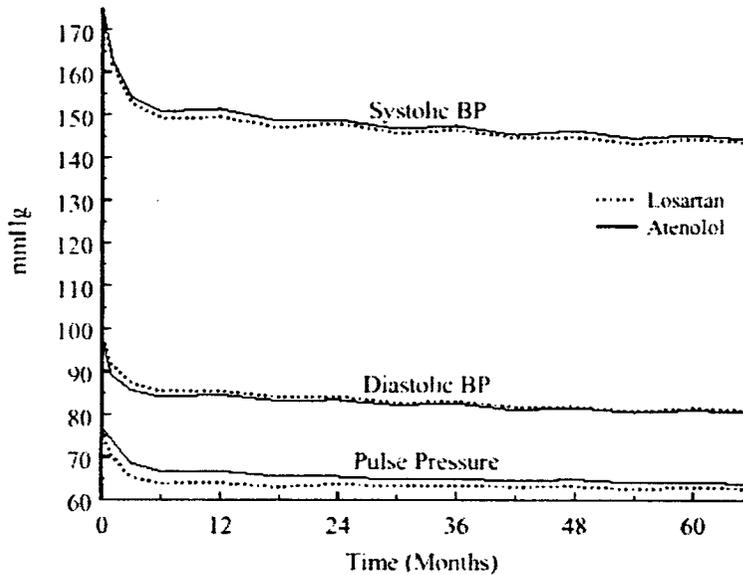
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COMMENT: Note that 170 (29%) atenolol and 130 losartan primary committee-adjudicated events occurred more than 30 days after discontinuation of study drug. The statistical significance of all results is reduced by this alternative analysis.

The intention-to-treat analysis is the preferred analysis. The interpretation of the on drug or per protocol analysis is difficult because of the potential for informative censoring. The ideal is to have no or minimal drug discontinuations or protocol violations such that all analyses are identical. For LIFE that ideal was not achieved.

4.2.6. Blood Pressure Reduction in Relationship to the Primary Endpoint

One potential confounder is difference in blood pressure control between the two treatment groups. The NDA summarizes well the differences in mean blood pressures (BP) between the two groups. The figure below graphs the BP over time and is followed by a table containing the values.



| | | | | | | |
|--------------|------|------|------|------|------|------|
| Losartan (N) | 4605 | 4413 | 4259 | 4124 | 3995 | 1463 |
| Atenolol (N) | 4588 | 4398 | 4254 | 4084 | 3953 | 1464 |

Figure 6: Sponsor's Blood Pressure Over Time

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Table 27: Sponsor's Table of Mean Blood Pressures

| | Losartan (N=4605) | | | | Atenolol (N=4588) | | | | p-Value ¹ |
|---------------------------------------|-------------------|----------|-----------|--------|-------------------|----------|-----------|--------|----------------------|
| | n | Mean | | | n | Mean | | | |
| | | Baseline | Follow-up | Change | | Baseline | Follow-up | Change | |
| Sitting SBP (mm Hg) | | | | | | | | | |
| Month 1 | 4545 | 174.3 | 162.0 | -12.3 | 4531 | 174.5 | 163.4 | -11.1 | <0.001** |
| Month 2 | 4513 | 174.3 | 157.3 | -17.0 | 4472 | 174.5 | 158.9 | -15.6 | <0.001** |
| Month 3 | 4458 | 174.3 | 152.6 | -21.7 | 4431 | 174.5 | 154.2 | -20.3 | <0.001** |
| Month 6 | 4448 | 174.3 | 149.2 | -25.1 | 4438 | 174.5 | 150.8 | -23.7 | <0.001** |
| Year 1 | 4413 | 174.2 | 149.5 | -24.8 | 4398 | 174.5 | 151.4 | -23.2 | <0.001** |
| Year 1.5 | 4348 | 174.2 | 147.0 | -27.2 | 4302 | 174.5 | 148.6 | -26.0 | 0.013* |
| Year 2 | 4259 | 174.1 | 148.0 | -26.2 | 4254 | 174.6 | 148.9 | -25.7 | 0.197 |
| Year 2.5 | 4180 | 174.2 | 145.8 | -28.3 | 4145 | 174.5 | 146.8 | -27.7 | 0.151 |
| Year 3 | 4124 | 174.2 | 146.5 | -27.7 | 4084 | 174.4 | 147.5 | -26.9 | 0.057 |
| Year 3.5 | 4041 | 174.1 | 144.7 | -29.4 | 4004 | 174.4 | 145.4 | -29.0 | 0.197 |
| Year 4 | 3995 | 174.1 | 144.9 | -29.2 | 3953 | 174.4 | 146.4 | -28.0 | 0.003** |
| Year 4.5 | 3239 | 174.3 | 143.3 | -30.9 | 3130 | 174.5 | 144.6 | -29.9 | 0.054 |
| Year 5 | 1463 | 174.5 | 144.5 | -30.0 | 1464 | 175.1 | 145.4 | -29.8 | 0.925 |
| Year 5.5 | 440 | 175.2 | 143.6 | -31.6 | 426 | 175.0 | 144.3 | -30.8 | 0.512 |
| Sitting DBP (mm Hg) | | | | | | | | | |
| Month 1 | 4545 | 97.9 | 91.5 | -6.4 | 4531 | 97.7 | 89.1 | -8.6 | <0.001** |
| Month 2 | 4513 | 97.9 | 89.4 | -8.5 | 4472 | 97.7 | 87.4 | -10.3 | <0.001** |
| Month 3 | 4458 | 97.9 | 87.2 | -10.7 | 4431 | 97.7 | 85.6 | -12.1 | <0.001** |
| Month 6 | 4447 | 97.9 | 85.3 | -12.6 | 4438 | 97.7 | 84.1 | -13.6 | <0.001** |
| Year 1 | 4412 | 98.0 | 85.5 | -12.5 | 4399 | 97.8 | 84.6 | -13.1 | <0.001** |
| Year 1.5 | 4348 | 98.0 | 84.0 | -13.9 | 4302 | 97.8 | 83.1 | -14.7 | <0.001** |
| Year 2 | 4258 | 98.0 | 84.2 | -13.7 | 4254 | 97.8 | 83.4 | -14.4 | <0.001** |
| Year 2.5 | 4180 | 98.0 | 82.6 | -15.3 | 4145 | 97.9 | 82.1 | -15.8 | 0.012* |
| Year 3 | 4124 | 98.0 | 83.1 | -14.9 | 4084 | 97.9 | 82.5 | -15.4 | 0.006** |
| Year 3.5 | 4041 | 98.0 | 81.6 | -16.4 | 4004 | 97.9 | 81.0 | -16.9 | 0.023* |
| Year 4 | 3995 | 98.0 | 81.8 | -16.3 | 3953 | 97.9 | 81.5 | -16.4 | 0.547 |
| Year 4.5 | 3239 | 98.1 | 80.7 | -17.4 | 3130 | 98.0 | 80.5 | -17.4 | 0.629 |
| Year 5 | 1463 | 98.5 | 81.5 | -17.0 | 1464 | 98.5 | 81.0 | -17.5 | 0.128 |
| Year 5.5 | 440 | 99.6 | 80.9 | -18.7 | 426 | 99.4 | 80.5 | -19.0 | 0.378 |
| Sitting Pulse Pressure (mm Hg) | | | | | | | | | |
| Month 1 | 4545 | 76.4 | 70.5 | -5.9 | 4531 | 76.8 | 74.3 | -2.5 | <0.001** |
| Month 2 | 4513 | 76.4 | 67.9 | -8.5 | 4472 | 76.8 | 71.5 | -5.3 | <0.001** |
| Month 3 | 4458 | 76.4 | 65.4 | -11.0 | 4431 | 76.8 | 68.6 | -8.2 | <0.001** |
| Month 6 | 4447 | 76.3 | 63.9 | -12.5 | 4438 | 76.8 | 66.7 | -10.0 | <0.001** |
| Year 1 | 4412 | 76.3 | 64.0 | -12.3 | 4398 | 76.8 | 66.7 | -10.0 | <0.001** |
| Year 1.5 | 4348 | 76.3 | 63.0 | -13.2 | 4302 | 76.7 | 65.5 | -11.2 | <0.001** |
| Year 2 | 4258 | 76.2 | 63.7 | -12.5 | 4254 | 76.7 | 65.5 | -11.3 | <0.001** |
| Year 2.5 | 4180 | 76.2 | 63.2 | -13.0 | 4145 | 76.6 | 64.7 | -11.9 | 0.001** |
| Year 3 | 4124 | 76.1 | 63.3 | -12.8 | 4084 | 76.5 | 65.1 | -11.4 | <0.001** |
| Year 3.5 | 4040 | 76.1 | 63.1 | -13.0 | 4004 | 76.5 | 64.4 | -12.1 | 0.004** |
| Year 4 | 3995 | 76.0 | 63.2 | -12.9 | 3953 | 76.4 | 64.9 | -11.6 | <0.001** |
| Year 4.5 | 3239 | 76.2 | 62.6 | -13.5 | 3130 | 76.5 | 64.1 | -12.5 | 0.003** |
| Year 5 | 1463 | 76.1 | 63.0 | -13.0 | 1464 | 76.6 | 64.3 | -12.2 | 0.289 |
| Year 5.5 | 440 | 75.6 | 62.7 | -13.0 | 426 | 75.6 | 63.8 | -11.8 | 0.274 |

^{*} p-Values <0.05.
^{**} p-Values <0.01.
¹ The p-values are based on Wilcoxon test.
n = Total number of patients with available data at each designated study time point.

The sponsor's summary of these mean changes is reasonable: "In general, systolic blood pressure tended to be slightly lower in the losartan group while diastolic pressure tended to be slightly lower in the atenolol group, resulting in consistently lower mean pulse pressure values in the losartan group. At Year 4, mean systolic blood pressure was 144.9 in the losartan group and 146.4 in the atenolol group (p=0.003), while mean diastolic