

**Clinical Review Cover Sheet  
Supplemental NDA Submission**

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

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# Clinical Review for Supplemental NDA 20-386

## 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, long term international study.

The reviewer believes that the LIFE study demonstrates adequately that antihypertensive regimens including losartan are superior to ones including atenolol for reducing the 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 the new indication. The reviewer recommends that the new indication be approved as “to reduce the risk of death and cardiovascular morbidity as measured by the combined incidence of death, stroke, and myocardial infarction in hypertensive patients with left ventricular hypertrophy.”

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

The LIFE study raises a question regarding whether the beneficial effect of losartan 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<sup>®</sup> (losartan potassium) is an oral angiotensin II receptor (type AT<sub>1</sub>) 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.

### B. Efficacy

The LIFE study had a sponsor pre-specified primary endpoint of combined cardiovascular deaths, myocardial infarctions, and strokes. By the 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,  $p=0.023$ . For the FDA-recommended primary endpoint including total mortality the losartan regimen produced a 10% risk reduction,  $p=0.039$ . The effects upon the components of the primary endpoint were heterogeneous. The benefit from losartan was primarily related to a reduction in strokes, a 25% risk reduction ( $p=0.009$ ).

The LIFE study is the only study supporting the proposed new indication. However, because the magnitude of the treatment effect (a 10% risk reduction) is reasonable and the endpoint is vital, the reviewer believes that a description of the beneficial effect of losartan 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. 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 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.

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

- Losartan appears to be more effective in the elderly. Losartan may be less effective in males younger than 65.

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- Losartan appears to be more effective in patients with isolated systolic hypertension at baseline. Isolated systolic hypertension is more frequent in the elderly.
- Losartan appears to be more effective in patients with diabetes at baseline. Losartan 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 losartan and atenolol were tolerated 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 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. 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

#### I. Introduction and Background

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

Cozaar<sup>®</sup> (losartan potassium) is an angiotensin II receptor (type AT<sub>1</sub>) 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 33,383 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 patient 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  $\beta$ -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 <sub>max</sub>	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)  $\beta$  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.”

### 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 <sup>14</sup>C-labeled losartan, about 35% of radioactivity is recovered in the urine and about 60% in the feces. Following an intravenous dose of <sup>14</sup>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<sub>1</sub> receptor found in many tissues, (e.g., vascular smooth muscle, adrenal gland). There is also an AT<sub>2</sub> 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<sub>1</sub> receptor and have much greater affinity (about 1000-fold) for the AT<sub>1</sub> receptor than for the AT<sub>2</sub> receptor. In vitro binding studies indicate that losartan is a reversible, competitive inhibitor of the AT<sub>1</sub> 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<sub>1</sub> 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 AT<sub>1</sub>-receptor subtype. In contrast, there appear to be beneficial effects of stimulation of the AII AT<sub>2</sub> 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 this review.

The sponsor originally submitted the protocol and the data analysis plan for the LIFE study to IND 33,383. 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.

#### 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 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.

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### 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**

<b>Investigator Category</b>	<b>Total Number</b>
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

### **VI. Integrated Review of Efficacy**

#### **A. Brief Statement of Conclusions**

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

#### **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

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“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 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

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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.

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### 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

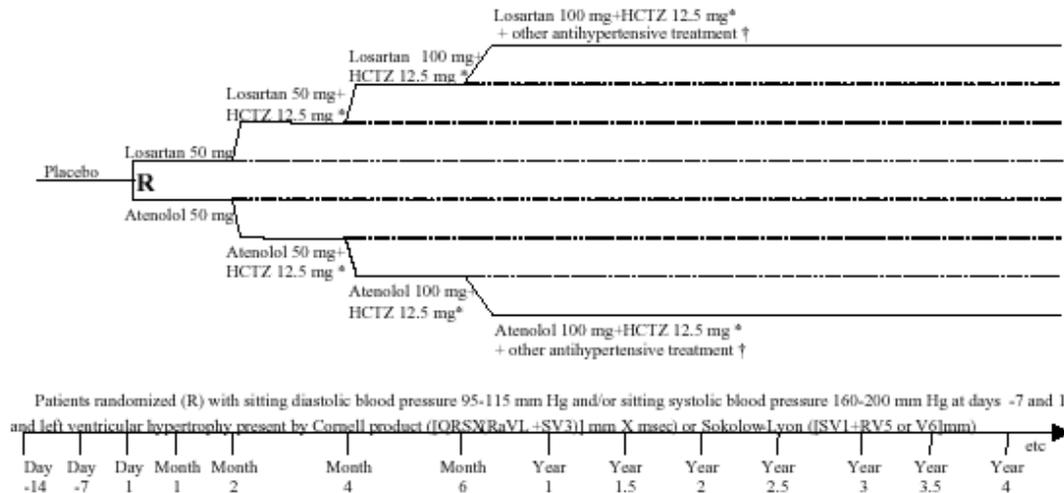
LIFE was a randomized, double blind, double dummy, active controlled, parallel group study. The study drug was losartan and the active control was atenolol. The sponsor refers to the study as triple-blind because of blinding of patients, investigators, and evaluators (Endpoint Classification Committee).

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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\* Titration upward if sitting diastolic blood pressure  $\geq$  90 mm Hg or sitting systolic blood pressure  $\geq$  140 mm Hg.  
 † Titration encouraged if sitting diastolic blood pressure  $\geq$  90 mm Hg or sitting systolic blood pressure  $\geq$  140 mm Hg but mandatory if sitting blood pressure  $\geq$  160/95 mm Hg. Addition of angiotensin-converting enzyme inhibitors, angiotensin II Type 1-receptor antagonists or  $\beta$ -blockers prohibited.

**Figure 1: Sponsor’s Study Design**

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 <sup>a</sup>
Medical history	X	X							X		X		X		X
Complete physical examination		X							X		X		X		X
Obtain informed consent	X <sup>b</sup>	X													
Sitting blood pressure and heart rate	(X)	X	X	X <sup>c</sup>	X	X	X	X	X	X	X	X	X	X	X
Standing blood pressure and heart rate				X	X	X <sup>d</sup>	X <sup>d</sup>	X <sup>d</sup>	X <sup>d</sup>	X <sup>d</sup>	X <sup>d</sup>	X <sup>d</sup>	X <sup>d</sup>	X <sup>d</sup>	X <sup>d</sup>
Laboratory safety tests <sup>e</sup>		X <sup>f</sup>		X	X <sup>g</sup>				X		X		X		X
Electrocardiogram (ECG) (12-lead)	X <sup>h</sup>	X <sup>i</sup>		X	X	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 <sup>j</sup>													
Dispense triple-blind medication				X <sup>k</sup>	X	X	X	X	X	X	X	X	X	X	X
Add additional antihypertensives to treatment regimen if appropriate						X <sup>l</sup>	X <sup>l</sup>	X <sup>l</sup>	X <sup>l</sup>	X <sup>l</sup>	X <sup>l</sup>	X <sup>l</sup>	X <sup>l</sup>	X <sup>l</sup>	X <sup>l</sup>
Healthcare resource utilization assessment <sup>m</sup>				X				X	X	X	X	X	X	X	X

<sup>a</sup> Note: Patients continued in the study until Year 4, and if necessary until 1040 patients reached a primary cardiovascular event, whichever was last. For patients who continued beyond Year 4, procedures were performed outlined for Year 1.5 and Year 2 for biannual and annual visits, respectively. All procedures listed for Year 4 were also performed at the final visit.  
<sup>b</sup> If ECG or other study tests were performed or medication discontinued with the intent to participate in the study.  
<sup>c</sup> Mean sitting diastolic blood pressure (SiDBP) was 95 to 115 and/or sitting systolic blood pressure (SiSBP) 160 to 200 mm Hg at 2 consecutive visits separated by at least 1 week for patient to be eligible to continue in study.  
<sup>d</sup> Standing blood pressure and heart rate measurement only necessary if patient required upward titration of study drug.  
<sup>e</sup> Glucose retesting may have been necessary for the evaluation of new-onset diabetes mellitus. See Appendix II in [3.3.2].  
<sup>f</sup> Abbreviated. Serum glucose and creatinine only.  
<sup>g</sup> Abbreviated. Serum sodium, potassium, and creatinine only.  
<sup>h</sup> May have been an old ECG (<12 months).  
<sup>i</sup> Sent to ECG Core Center for evaluation of left ventricular hypertrophy inclusion criteria. Taken up to 30 days prior to Visit 1.  
<sup>j</sup> Patients who did not qualify after 14 days on placebo could have remained on placebo for up to 14 additional days. They must have had 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 randomization.  
<sup>k</sup> The last placebo tablet should have been taken the previous morning, i.e., ~24 hours prior to this visit.  
<sup>l</sup> Additional antihypertensives were added to treatment regimen if mean SiDBP was  $\geq$ 90 and/or SiSBP  $\geq$ 140 mm Hg. Titration regimen was test agent 50 mg alone—test agent 50 mg plus HCTZ 12.5 mg—2x dose of test agent plus HCTZ 12.5 mg—other antihypertensive agents (excluding ACEIs, ARBs antagonists, or beta-blockers) plus 2 x dose of test agent plus HCTZ 12.5 mg or more.  
<sup>m</sup> As specified in Standard Operating Procedures and worksheets.

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

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#### 3.1. Objectives

The primary objective was to evaluate the long-term effects ( $\geq 4$  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: 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 <sup>†</sup>
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) <sup>‡</sup>	3	SiDBP 95 to 115 and/or SiSBP 160 to 200 mm Hg

<sup>†</sup> Sitting BP Mean Reading was the calculated average of 2 consecutive readings at 1-minute intervals.  
<sup>‡</sup> 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  $125 \text{ g/m}^2$  in men and  $110 \text{ g/m}^2$  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  $1.8 \text{ mg/dL}$ ) or patient with solitary kidney or renal transplant
7. significant known aortic stenosis (known mean antegrade Doppler gradient  $\geq 20$  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<sup>†</sup> ≥90 mm Hg and/or SiSBP<sup>‡</sup> ≥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.
<sup>†</sup> SiDBP: sitting diastolic blood pressure. <sup>‡</sup> 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  $\alpha$  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 <sup>†</sup>	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) <sup>‡</sup>	4557 (99.0%)	4546 (99.1%)	9103 (99.0%)
DISCONTINUED FOLLOW-UP:	48 (1.0%)	42 (0.9%)	90 (1.0%)
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 <sup>§</sup> : Total	1024 (22.2%)**	1220 (26.6%)**	2244 (24.4%)
Endpoint other than death	150 (3.3%)*	114 (2.5%)*	264 ((2.9%)
Required other therapy	143 (3.1%)	168 (3.7%)	311 (3.4%)
Adverse experience	500 (10.9%)**	702 (15.3%)**	1202 (13.1%)
Patient withdrew consent	30 (0.7%)	27 (0.6%)	57 (0.6%)
Lost to follow-up	2 (0.0%)	1 (0.0%)	3 (0.0%)
Other administrative reason	199 (4.3%)	208 (4.5%)	407 (4.4%)

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

<sup>†</sup> Excludes 29 patients randomized from disqualified site 925-964.

<sup>‡</sup> 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.

<sup>§</sup> 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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COMMENT: The rate of completed follow-up (99%) is good. The number of patients lost to follow-up (12, or about 0.1%) is excellent, but the number of patients without vital status information due to withdrawal of consent (78, or about 0.8%) is problematic.

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**

	Losartan (N=4605)	Atenolol (N=4588)	Total (N=9193)
	n (%)	n (%)	n (%)
<b>Age (Years)</b>			
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
<b>Gender</b>			
Female	2487 (54.0)	2476 (54.0)	4963 (54.0)
Male	2118 (46.0)	2112 (46.0)	4230 (46.0)
<b>Ethnic Group</b>			
White	4258 (92.5)	4245 (92.5)	8503 (92.5)
Black	270 (5.9)	263 (5.7)	533 (5.8)
Hispanic	47 (1.0)	53 (1.2)	100 (1.1)
Asian	25 (0.5)	18 (0.4)	43 (0.5)
Other	5 (0.1)	9 (0.2)	14 (0.2)
<b>Alcoholic Drinks</b>			
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)
<b>Tobacco Use</b>			
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)
<b>Exercise</b>			
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	122.0	165.0	173.0	185.0	220.0
	Atenolol	4588	174.5	120.0	165.0	174.0	185.0	222.5
SiSBP (mm Hg) (SiDBP<95)	Losartan	1290	173.8	130.0	165.0	171.5	181.0	211.0
	Atenolol	1294	174.3	129.0	165.0	172.0	182.5	205.0
SiDBP (mm Hg) all patients	Losartan	4605	97.9	60.0	93.0	98.0	104.0	130.0
	Atenolol	4588	97.7	48.0	93.0	98.0	103.0	126.5
SiDBP (mm Hg) (SiSBP<160)	Losartan	516	99.1	67.0	96.0	99.0	101.0	116.5
	Atenolol	516	98.7	70.5	96.0	98.0	101.0	113.0
StSBP (mm Hg)	Losartan	4341	171.8	100.0	160.0	170.0	182.0	221.0
	Atenolol	4333	172.2	107.0	160.0	170.0	184.0	230.0
StDBP (mm Hg)	Losartan	4341	100.2	58.0	94.0	100.0	108.0	140.0
	Atenolol	4333	100.2	50.0	95.0	100.0	108.0	130.0
Sitting pulse pressure (mm Hg)	Losartan	4605	76.4	23.5	67.0	76.5	87.0	134.0
	Atenolol	4588	76.9	24.0	67.0	77.0	87.5	135.0
Standing pulse pressure (mm Hg)	Losartan	4341	71.6	10.0	60.0	70.0	82.0	144.0
	Atenolol	4333	72.0	7.0	60.0	70.0	84.0	160.0
Pulse rate (beats/min)	Losartan	4603	73.9	44.0	66.0	72.0	80.0	159.0
	Atenolol	4587	73.7	42.0	66.0	72.0	80.0	150.0
Height (cm)	Losartan	4570	167.6	121.9	160.0	167.0	175.0	200.7
	Atenolol	4534	167.5	123.5	160.0	167.0	175.0	195.6
Weight (kg)	Losartan	4568	78.6	33.1	68.0	78.0	87.5	179.6
	Atenolol	4545	78.6	31.0	68.6	77.6	87.0	178.5
BMI (kg/cm <sup>2</sup> )	Losartan	4554	28.0	11.7	24.8	27.5	30.5	76.0
	Atenolol	4525	28.0	13.8	24.9	27.3	30.5	64.1

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

Note: Missing values for baseline LV Mass 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)	4101	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%
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.

#### 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 <sup>†</sup>	844	(18.0)	930	(20.0)
100 mg with or without additional drugs <sup>†</sup>	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)
<sup>†</sup> 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	(%)
<b>Cardiovascular System</b>	<b>2996</b>	<b>(65.1)</b>	<b>2976</b>	<b>(64.9)</b>
<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

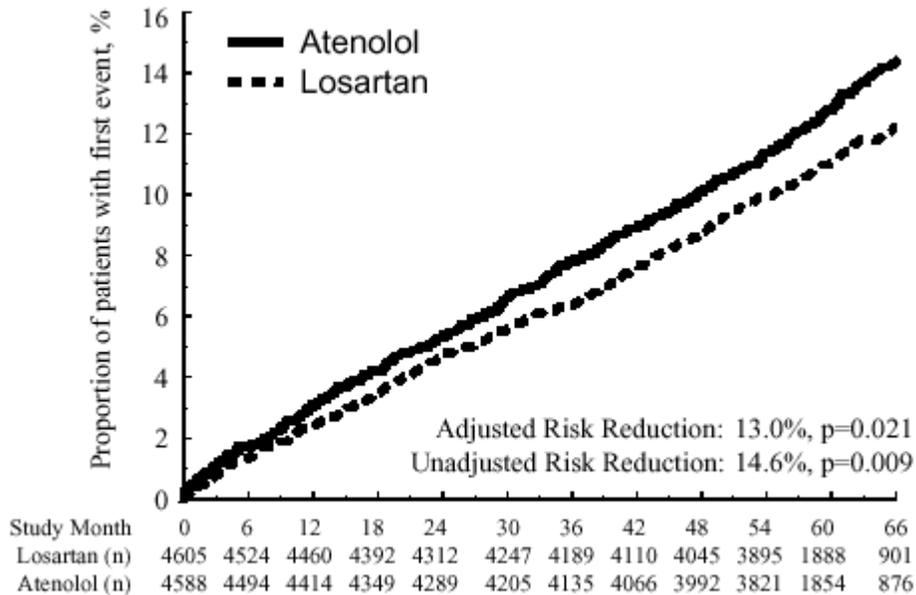
##### 4.2.1. Sponsor's Primary Endpoint

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)

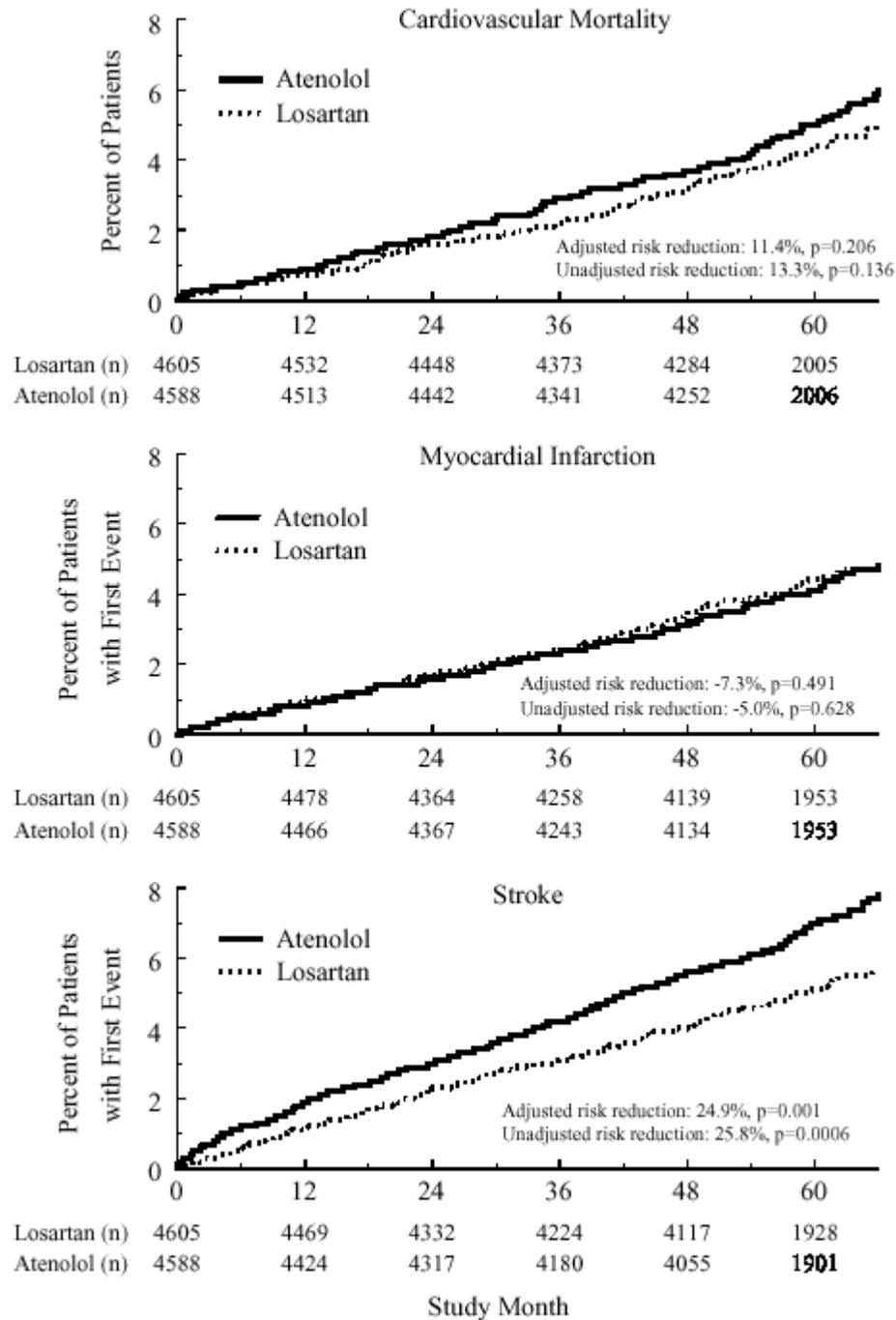
MI = myocardial infarction; CV = cardiovascular  
% = percent of number of patients in treatment group

As can be seen in the table, myocardial infarction (MI) and cardiovascular (CV) death primary endpoints were similar in the two groups, with slightly more CV deaths in the atenolol group and scarcely more MIs in the losartan group. The dominant factor in the composite endpoint is the substantially greater stroke rate in the atenolol group compared to the losartan group.

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.

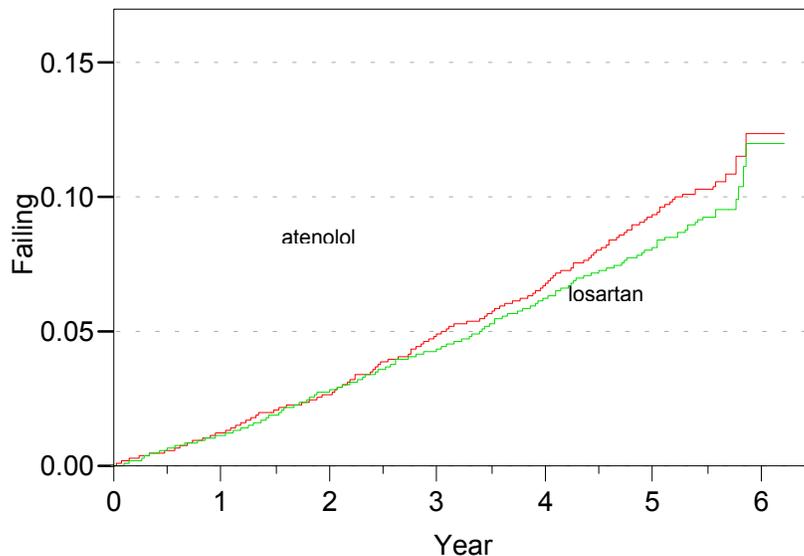


Figure 5: Reviewer's Kaplan-Maier Plot of Total Mortality by Group

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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 20: 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

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, whether by the reviewer or by the Endpoint Classification Committee, produces similar results for the sponsor's primary composite endpoint.

#### 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 21: 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

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Endpoint Event Classifier			
	Investigator	Reviewer	Committee
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 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 22: 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 23: 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

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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 24: Sponsor’s Per Protocol Primary Endpoint Results**

	Crude Rate						Kaplan-Meier Rates								Hazard <sup>‡</sup> Ratio	95% CI		p-Value <sup>§</sup>
	Losartan (N=4504)			Atenolol (N=4485)			Losartan				Atenolol					Lower	Upper	
	Rate <sup>†</sup>	n	(%)	Rate <sup>†</sup>	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	1.178	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	0.558	0.845	<0.001**

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

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.

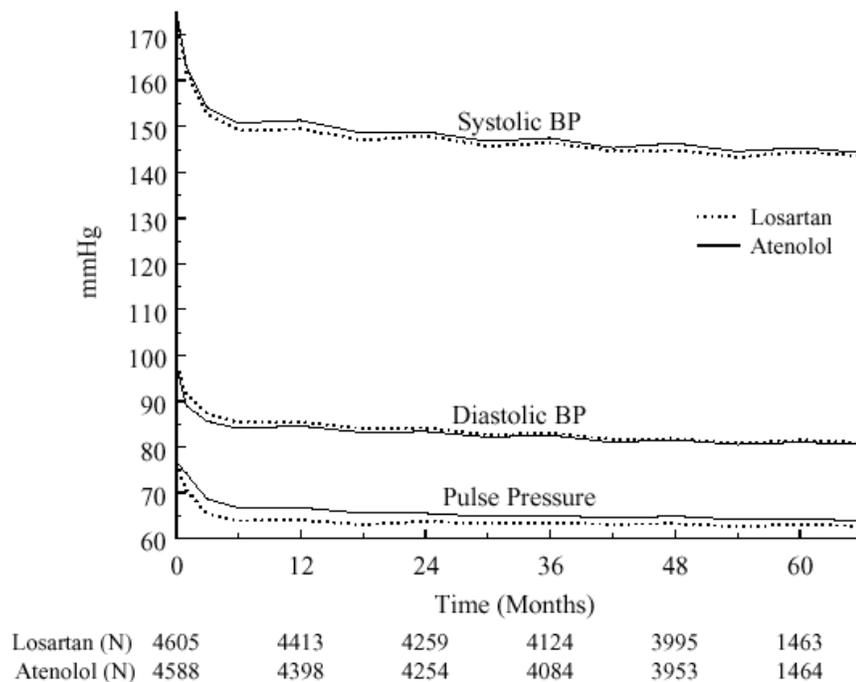
The intention-to-treat analysis is the preferred analysis. The interpretation of the on drug or per protocol analysis is difficult because of the potential for informative censoring. The ideal is to have no or minimal drug discontinuations or protocol violations such that all analyses are identical.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

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### 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.



**Figure 6: Sponsor's Blood Pressure Over Time**

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**Table 25: Sponsor’s Table of Mean Blood Pressures**

	Losartan (N=4605)				Atenolol (N=4588)				p-Value <sup>†</sup>
	n	Mean			n	Mean			
		Baseline	Follow-up	Change		Baseline	Follow-up	Change	
<b>Sitting SBP (mm Hg)</b>									
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	0.935
Year 5.5	440	175.2	143.6	-31.6	426	175.0	144.3	-30.8	0.512
<b>Sitting DBP (mm Hg)</b>									
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
<b>Sitting Pulse Pressure (mm Hg)</b>									
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.									
† 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

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pressure was similar in the 2 groups (81.8 versus 81.5, NS). Year 4 mean pulse pressure was lower in the losartan group (63.2 versus 64.9,  $p < 0.001$ ).”

The mean changes in BP and heart rate (HR) at the primary endpoint or at the end of follow-up are shown in the following table.

**Table 26: Sponsor’s Last Vital Signs Using Primary Endpoint Censoring Rule**

	Atenolol	Losartan	Difference
<b>SBP</b>	145.4	144.1	1.3
<b>DBP</b>	80.9	81.3	-0.4
<b>PP</b>	64.5	62.8	1.7
<b>SBP change</b>	-29.1	-30.2	1.1
<b>DBP change</b>	-16.8	-16.6	-0.2
<b>PP change</b>	-12.4	-13.6	1.2
<b>SBP SD</b>	17.2	16.4	0.8
<b>DBP SD</b>	9.5	9.6	-0.1
<b>HR</b>	66	72.1	-6.1
<b>HR change</b>	-7.7	-1.8	-5.9

Source: NDA Appendix 4.5.21

HR = heart rate; PP = pulse pressure; SD = standard deviation

The difference in SBP is statistically significant ( $p = 0.015$ ). To explore the effects of the differences in BP upon the endpoints the sponsor incorporated SBP, DBP, and PP as time-varying covariates into separate Cox regression models. The results of these analyses are shown in the following tables.

**Table 27: Sponsor’s Primary Endpoints with SBP Time-Varying**

	Crude Rate				Covariates in the Model	Hazard Ratio	95% CI		p-Value
	Losartan (N=4605)		Atenolol (N=4588)				Lower	Upper	
	n	(%)	n	(%)					
Composite	508	(11.0)	588	(12.8)	Systolic BP Treatment	1.007 0.861	1.003 0.765	1.010 0.970	<0.001** 0.014*
Cardiovascular mortality	204	(4.4)	234	(5.1)	Systolic BP Treatment	0.999 0.866	0.994 0.718	1.005 1.045	0.775 0.133
MI (fatal/nonfatal)	198	(4.3)	188	(4.1)	Systolic BP Treatment	1.009 1.063	1.003 0.870	1.014 1.297	0.003** 0.551
Stroke (fatal/nonfatal)	232	(5.0)	309	(6.7)	Systolic BP Treatment	1.012 0.755	1.007 0.637	1.017 0.895	<0.001** 0.001**

\* P-values <0.05.  
 \*\* P-values <0.01.  
 Treatment is included in Cox proportional hazard model as covariate.

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**Table 28: Sponsor’s Primary Endpoints with DBP Time-Varying Covariate**

	Crude Rate				Covariates in the Model	Hazard Ratio	95% CI		p-Value
	Losartan (N=4605)		Atenolol (N=4588)				Lower	Upper	
	n	(%)	n	(%)					
Composite	508	(11.0)	588	(12.8)	Diastolic BP	0.994	0.988	1.001	0.087
					Treatment	0.858	0.762	0.966	0.012*
Cardiovascular mortality	204	(4.4)	234	(5.1)	Diastolic BP	0.982	0.972	0.992	<0.001**
					Treatment	0.879	0.728	1.060	0.177
MI (fatal/nonfatal)	198	(4.3)	188	(4.1)	Diastolic BP	0.986	0.976	0.997	0.013*
					Treatment	1.062	0.870	1.297	0.555
Stroke (fatal/nonfatal)	232	(5.0)	309	(6.7)	Diastolic BP	1.002	0.993	1.011	0.680
					Treatment	0.741	0.625	0.879	<0.001**

\* P-values <0.05.  
 \*\* P-values <0.01.  
 Treatment is included in Cox proportional hazard model as covariate.

**Table 29: Sponsor’s Primary Endpoints with PP Time-Varying Covariate**

	Crude Rate				Covariates In The Model	Hazard Ratio	95% CI		p-Value
	Losartan (N=4605)		Atenolol (N=4588)				Lower	Upper	
	n	(%)	n	(%)					
Composite	508	(11.0)	588	(12.8)	Pulse Pressure	1.009	1.006	1.013	<0.001**
					Treatment	0.871	0.773	0.981	0.023*
Cardiovascular mortality	204	(4.4)	234	(5.1)	Pulse Pressure	1.005	0.999	1.011	0.078
					Treatment	0.876	0.726	1.057	0.167
MI (fatal/nonfatal)	198	(4.3)	188	(4.1)	Pulse Pressure	1.014	1.008	1.020	<0.001**
					Treatment	1.083	0.887	1.323	0.432
Stroke (fatal/nonfatal)	232	(5.0)	309	(6.7)	Pulse Pressure	1.013	1.008	1.018	<0.001**
					Treatment	0.765	0.645	0.907	0.002**

\* P-values <0.05.  
 \*\* P-values <0.01.  
 Treatment is included in Cox proportional hazard model as covariate.

The sponsor’s summary of these analyses is the following: “Higher systolic blood pressure was associated with a significant increase in the risk of the primary composite endpoint, as well as an increase in the risk of MI and stroke. The results were reversed for diastolic blood pressure with a tendency for higher diastolic blood pressures to be associated with a decrease in the risk of the primary composite endpoint (NS, p=0.087) and higher diastolic pressure associated with a significant decrease in the risk of cardiovascular mortality and MI. There was no apparent relationship between diastolic pressure and the risk of stroke. The results for pulse pressure were similar to those observed for systolic pressure but with the additional tendency for higher pulse pressure to be associated with an increase in cardiovascular mortality (NS, p=0.078).”

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Note that the sponsor's Cox regressions with time-varying covariates do not include the baseline covariates of degree of LVH and Framingham risk score. When the reviewer added these baseline covariates to the sponsor's time-varying models, the statistical significance of the treatment covariate is reduced slightly in the time-varying models compared to the Cox models without the time-varying covariates. The reviewer's results when SBP was included as a time-varying covariate are shown in the table below.

**Table 30: Reviewer's Cox Regression Results for the Primary Composite Endpoint with SBP as a Time-Varying Covariate**

Covariate	Hazard ratio	95% Confidence		p
		Lower	Upper	
Treatment	0.87	0.78	0.98	0.027
SBP	1.004	1.001	1.008	0.012
Cornell	1.012	1.01	1.02	<0.001
Sokolow-Lyon	1.016	1.01	1.022	<0.001
Framingham	1.049	1.043	1.055	<0.001

The time-varying covariate with the strongest relationship to the primary composite endpoint was not blood pressure but pulse. The results for a Cox regression model including blood pressure and pulse as time-varying covariates is shown in the table below.

**Table 31: Reviewer's Cox Regression Results for the Primary Composite Endpoint with S/DBP and Pulse as Time-Varying Covariates**

Covariate	Hazard ratio	95% Confidence		p
		Lower	Upper	
Treatment	0.78	0.69	0.88	<0.001
SBP	1.004	1	1.008	0.04
DBP	1.001	0.99	1.007	0.86
Pulse	1.018	1.013	1.023	<0.001
Cornell	1.012	1.007	1.017	<0.001
Sokolow-Lyon	1.017	1.011	1.023	<0.001
Framingham	1.05	1.04	1.06	<0.001

COMMENT: A major limitation of these analyses is that the blood pressures were recorded only at trough. It is interesting that pulse is the most significant time-varying covariate, but one can only speculate on possible explanations.

While the NDA summarizes well mean BP and attempts to relate the BP levels to outcomes through these Cox regression analyses, it does not otherwise attempt to relate levels of BP or degree of BP control to the outcomes. The reviewer explored the relationship between BP and outcomes further as follows.

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Patients who suffered primary endpoints tended to have higher baseline SBP than patients who did not. The mean baseline SBPs by primary endpoint are shown in the following table.

**Table 32: Reviewer’s Mean Baseline SBP by Primary Endpoint Category**

Endpoint	Atenolol	Losartan
None	174.2	174.0
MI	175.5	176.5
CV death	175.3	176.7
Stroke	178.4	176.5

Note that the mean baseline SBP is highest in patients treated with atenolol who eventually had a primary stroke endpoint. The mean baseline DBPs do not vary significantly by endpoint category. Mean baseline pulse rates tend to be slightly higher in patients who suffered a CV death.

Baseline isolated systolic hypertension, defined as SBP  $\geq$  160 with DBP  $<$  90, occurred more frequently in patients with primary endpoints treated with atenolol than with losartan. The rates of baseline isolated systolic hypertension are shown in the following table.

**Table 33: Reviewer’s Rates of Baseline Isolated Systolic Hypertension by Endpoint Category**

Endpoint	Atenolol	Losartan
None	14.1%	14.3%
MI	19.0%	15.5%
CV death	17.5%	15.3%
Stroke	16.9%	13.7%

For the following analyses the reviewer examined mean SBPs recorded prior to a primary endpoint event or the last recorded SBP for patients without primary endpoint events. If the SBP prior to a primary endpoint event was recorded within 30 days of the event, then the reviewer used the previous SBP in order to avoid BP values that may have been influenced by the event. The reviewer selected values that were recorded between 22 and 26 hours after the last dose of study medication. For brevity the reviewer refers to these SBPs as “at end”.

Mean SBPs recorded at end were higher in patients with primary endpoints than in those without them. The mean SBPs were consistently higher in atenolol patients as shown in the following table.

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**Table 34: Reviewer's Mean SBP at End**

Endpoint	Atenolol	Losartan
None	146.3	145.1
MI	155.4	150.1
CV death	153.9	151.6
Stroke	156.4	152.1
All patients	147.5	145.8

Investigators were to titrate patients to a target BP of < 140/90. The rates of patients achieving this goal at end are shown in the following table.

**Table 35: Reviewer's Rates of Achieving Target BP < 140/90 at End**

Endpoint	Atenolol	Losartan
None	34%	38%
MI	21%	25%
CV death	22%	29%
Stroke	20%	25%
All patients	32%	36%

Overall the rates of patients achieving the target BP were low. Blood pressure control was poorer with atenolol than with losartan.

The rates of poor BP control varied. Rates of poor BP control, defined as a SBP  $\geq$  160 or DBP  $\geq$  100, are shown in the following table.

**Table 36: Reviewer's Rates of Poor BP Control (SBP  $\geq$  160 or DBP  $\geq$  100) at End**

Endpoint	Atenolol	Losartan
None	21%	19%
MI	35%	32%
CV death	42%	39%
Stroke	44%	36%
All patients	24%	20%

For the vast majority (96 percent) of these patients SBP was poorly controlled, i.e., SBP  $\geq$  160. Note that poor control was more common for all endpoints. Poor control was more frequent with atenolol than with losartan.

The changes in BP from baseline varied in a pattern similar to the differences in absolute BP. Changes from baseline in SBP are shown in the following table.

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**Table 37: Reviewer’s Mean Changes in SBP from Baseline to End**

Endpoint	Atenolol	Losartan
None	-27.9	-28.9
MI	-20.0	-25.5
CV death	-21.3	-25.1
Stroke	-22.1	-24.3
All patients	-27.1	-28.5

The reductions in SBP from baseline to prior to a primary endpoint were less with atenolol than with losartan. A pertinent question is whether the variations in BP reduction are related to differential study drug usage. Study drug usage at the time of primary endpoint occurrence (in patients with primary endpoints) or at last follow-up (in patients without primary endpoints) is summarized in the following table.

**Table 38: Reviewer’s Study Drug Usage**

	Primary Endpoint		No Primary Endpoint	
	Atenolol	Losartan	Atenolol	Losartan
N	588	508	4000	4097
On primary drug	70%	74%	74%	78%
Mean primary dose	52	55	59	65
On HCTZ	48%	50%	57%	62%
Mean HCTZ dose	9	9	11	12

HCTZ = hydrochlorothiazide

Note that atenolol usage was slightly lower than losartan usage. Hydrochlorothiazide use was higher in patients not suffering a primary endpoint. Atenolol and hydrochlorothiazide use was slightly higher for patients with stroke primary endpoints compared to other endpoints.

Study drug usage varied by BP control and is shown in the following table.

**Table 39: Reviewer’s Study Drug Usage by BP Control at End**

	Good Control SBP<140 & DBP<90		Fair Control		Poor Control SBP≥160 or DBP≥100	
	Atenolol	Losartan	Atenolol	Losartan	Atenolol	Losartan
	N	1467	1671	2042	1995	1079
On primary drug	82%	85%	77%	81%	55%	59%
Mean primary dose	62	66	62	67	46	51
On HCTZ	60%	63%	60%	65%	42%	45%
Mean HCTZ dose	12	12	12	13	9	9

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Study drug usage was lowest in patients with poor control. It was slightly higher with losartan than with atenolol for all levels of control.

There are some interesting variations in dosing and BP control by country. Levels of control by country are shown in the following table.

**Table 40: Reviewer's Levels of BP Control at End by Country**

	Good	Fair	Poor
US white	48%	33%	19%
US black	41%	37%	22%
UK	33%	41%	25%
Scandinavia	31%	47%	22%

BP control was better in the US compared to non-US. Note that mean baseline BP levels were lower for US patients than non-US patients so that mean reductions in BP from baseline are similar for all countries. Primary study drug use was lower in the US than in other countries while hydrochlorothiazide use was lower in US whites and intermediate in US blacks and in the UK as shown in the following two tables.

**Table 41: Reviewer's Primary Study Drug Use at End by Country**

	Atenolol	Losartan
US white	63%	68%
US black	65%	70%
UK	67%	74%
Scandinavia	77%	81%

**Table 42: Reviewer's Study Hydrochlorothiazide Use at End by Country**

	Atenolol	Losartan
US white	46%	51%
US black	51%	59%
UK	48%	58%
Scandinavia	59%	62%

For patients on the primary study drug hydrochlorothiazide use was highest in blacks. Hydrochlorothiazide use was higher in patients treated with losartan than in patients treated with atenolol in the US and the UK and comparable in the two groups in Scandinavia.

Endpoint rates were particularly high for patients with poor control as shown in the following table.

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**Table 43: Reviewer’s Primary Endpoint Rates by Level of BP Control**

Control	Atenolol	Losartan
Good (SBP<140 & DBP<90)	8%	8%
Fair	11%	10%
Poor (SBP≥160 or DBP≥100)	22%	19%

If the blood pressure control distribution for losartan is used with the atenolol endpoint rates by level of blood pressure control, then one would estimate that 22 fewer primary endpoint events would have occurred for atenolol. This reduction in events is sufficient to eliminate the statistical significance of the difference in the endpoint rates between the two groups ( $p = 0.008$  by Fishers exact test for the observed rates,  $p = 0.055$  by Fishers exact test for the rates with 22 fewer atenolol events).

#### COMMENT:

Blood pressure control was slightly poorer in the atenolol group than in the losartan group. Study drug usage was also lower in the atenolol group. The difference in study drug use appears to be comparable to the difference in control. One can only speculate regarding the reasons for lower study drug usage in the atenolol group. It could be related to more side effects with atenolol, but the data are not available to prove or disprove that speculation.

Worse control, particularly poor control, is associated with worse outcomes. The difference in blood pressure control may account a significant portion of the difference in endpoint rates. If the BP control rates for atenolol were identical to those for losartan, then the expected differences in endpoint rates would not be statistically significant.

One major limitation of these observations regarding blood pressure control is that they are based on blood pressure measurements at only one point in time during the dosing interval, i.e., trough. It would be very interesting to have BP measurements at other times during the dosing interval.

#### 4.2.7. Stroke Endpoint Differences

Most of the difference in the primary composite endpoint is due to strokes. Hence it is informative to examine differences in factors associated with strokes. For these comparisons it is more appropriate to consider all stroke events rather than strokes that happened to occur first as a primary endpoint. The numbers of stroke primary endpoints, adjudicated strokes, and patients with strokes are shown in the following table.

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**Table 44: Reviewer’s Numbers of Stroke Endpoints, Strokes, and Patients with Strokes**

	Atenolol	Losartan
Primary stroke endpoint	266	197
Adjudicated strokes	359	255
Patients with strokes	308	228
% of patients with strokes	6.7%	5.0%

As can be seen from the table, strokes were not infrequent in this high-risk hypertensive population, occurring in about six percent of subjects over the four-year follow-up. Multiple strokes also were not rare.

Stroke rates increased with age, particularly with atenolol, as shown in the following table. Strokes were slightly more frequent in females than males in both groups, probably due to the older age of females in the study.

**Table 45: Reviewer’s Stroke Rates by Age**

Age	Atenolol	Losartan
<65	3%	3%
65-74	8%	5%
≥75	13%	9%

The type of stroke is also worth examining. Embolic strokes, particularly ones secondary to atrial fibrillation, may not be as directly related to hypertension as ischemic strokes. The Endpoint Classification Committee’s (ECC’s) classification of stroke types is shown in the following table:

**Table 46: Reviewer’s Endpoint Classification Committee’s Type of Stroke by Treatment Group**

		Ischemic		Hemorrhagic	Other	Total
		Embolic	Non-embolic			
Atenolol	N	52	269	34	4	359
	%	14%	75%	9%	1%	100%
Losartan	N	38	186	30	1	255
	%	15%	73%	12%	0%	100%

Note that the distributions of the types of strokes are similar between the two treatment groups even though the stroke rate is significantly higher in the atenolol group. After reviewing case report forms of the stroke endpoints, the reviewer believes that the ECC was conservative in classifying strokes as embolic, e.g., the ECC classified strokes as ischemic even though atrial fibrillation was documented. The reviewer believes that this conservative classification tends to obscure differences in the stroke types.

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Classifying strokes as embolic or ischemic based on clinical history and findings is frequently difficult. It is doubly difficult in this study because of the limited information in the case report forms. As a surrogate for embolic stroke the reviewer examined stroke rates in patients with atrial fibrillation or flutter, reported either by baseline history or as an adverse event. Rates of atrial fibrillation or flutter are shown in the following table.

**Table 47: Reviewer's Rates of Atrial Fibrillation or Flutter**

	Atenolol	Losartan
History	4.0%	3.5%
Adverse event	7.9%	6.8%
Either	10.7%	9.4%

Atrial fibrillation was not uncommon in the study population. It was slightly more frequent in atenolol patients. It was also more frequent among US white patients (15.9%) and Danish and Swedish patients (11.1 and 12.1% respectively) and less frequent among the rest (e.g., US blacks 6.7%).

Patients with evidence of atrial fibrillation were older (mean age 69.6 vs 66.6), more frequently male (53 vs. 45%), higher risk (mean Framingham risk score 24.8 vs. 22.1), with more isolated systolic hypertension (18.8 vs 13.9%), and had more frequent histories of stroke (7.4 vs. 4.0%), myocardial infarction (9.3 vs. 5.8%), heart failure (6.1 vs. 1.3%), and diabetes (17.8 vs. 12.5%) than patients without evidence of atrial fibrillation. These baseline factors were not different by evidence of atrial fibrillation between the atenolol and losartan groups.

Strokes occurred in about 15% of patients with a history or adverse event of atrial fibrillation, about three times as frequent as in patients without evidence of atrial fibrillation. Strokes associated with atrial fibrillation were more frequent with atenolol than with losartan as shown in the following table.

**Table 48: Reviewer's Rates of Patients with Stroke by Evidence of Atrial Fibrillation**

	Atenolol	Losartan
No atrial fibrillation	5.3%	4.3%
Atrial fibrillation	18.3%	11.6%
Total	6.7%	5.0%

29% of the atenolol and 22% of the losartan patients with strokes had evidence of atrial fibrillation.

The majority (67%) of strokes classified as embolic were associated with evidence of atrial fibrillation. The 30 strokes classified as embolic but not associated with atrial fibrillation included strokes associated with myocardial infarction and strokes associated with revascularization procedures.

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Stroke patients on atenolol were slightly older than stroke patients on losartan, particularly for strokes associated with atrial fibrillation. Stroke patients, particularly in the atenolol group, had higher baseline SBP but similar baseline DBP. Poor control was more frequent in patients both with strokes associated with atrial fibrillation and with those that were not. Aspirin use was less frequent in stroke patients on atenolol than those on losartan while warfarin use was more frequent. These differences are quantified in the following tables.

**Table 49: Reviewer’s Mean Ages by Stroke and Atrial Fibrillation**

	Atenolol	Losartan
Neither	66.4	66.6
Atrial fibrillation	69.6	69.5
Stroke	70.1	69.0
Both	72.3	70.9
Total	66.9	66.9

**Table 50: Reviewer’s Rates of Poor Control by Stroke and Atrial Fibrillation**

	Atenolol	Losartan
Neither	22%	19%
Atrial fibrillation	27%	22%
Stroke	42%	38%
Both	50%	40%
Total	24%	21%

**Table 51: Reviewer’s Rates of Aspirin Use by Stroke and Atrial Fibrillation**

	Atenolol	Losartan
Neither	30%	30%
Atrial fibrillation	49%	51%
Stroke	61%	70%
Both	64%	72%
Total	34%	34%

**Table 52: Reviewer’s Rates of Warfarin Use by Stroke and Atrial Fibrillation**

	Atenolol	Losartan	Total
Neither	4%	3%	3%
Atrial fibrillation	45%	39%	42%
Stroke	15%	8%	12%
Both	56%	50%	54%
Total	9%	6%	8%

The case report forms collected general information on the type of neurologic deficit, i.e., visual disturbance, motor disorder, etc., but they did not try to capture the severity of the

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stroke. One metric of stroke severity is whether the stroke is associated with death. In 34 patients, 23 in the atenolol group and 11 in the losartan group, death occurred within 30 days of the stroke. Hence death was more frequent following stroke with atenolol (7.5% of patients with strokes) than with losartan (4.8% of patients with strokes).

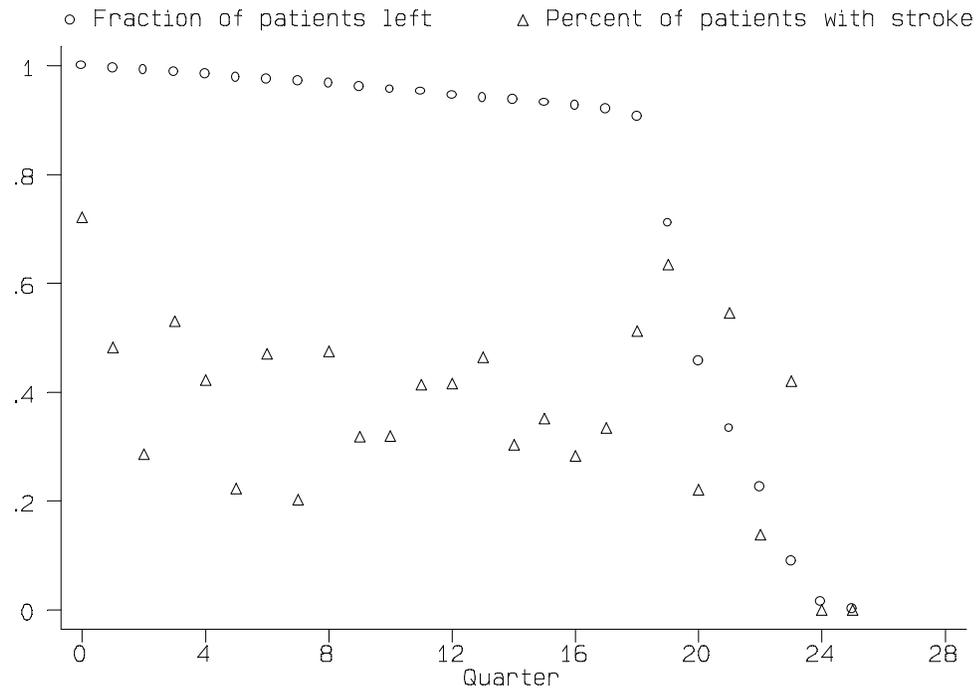
The timing of the occurrence of strokes is interesting. The reviewer calculated stroke rates by group and by quarter (90-day intervals) to provide reasonable stability of stroke rates. These quarterly stroke rates are shown in the following two figures. Note that stroke rates in the atenolol group appear to be greater in the first quarter and possibly also at the end of the study. Stroke rates do not seem to vary similarly for losartan. Quarterly rates of myocardial infarction (MI) or angina for both atenolol and losartan also do not show similar peaks. Quarterly rates of MI by treatment group are shown in the two figures following the quarterly stroke rates.

Strokes that occurred early, i.e., in the first quarter, were more frequently associated with atrial fibrillation than later occurring strokes (37% for atenolol and 50% for losartan). Otherwise there are no consistent variations in the types of stroke by time.

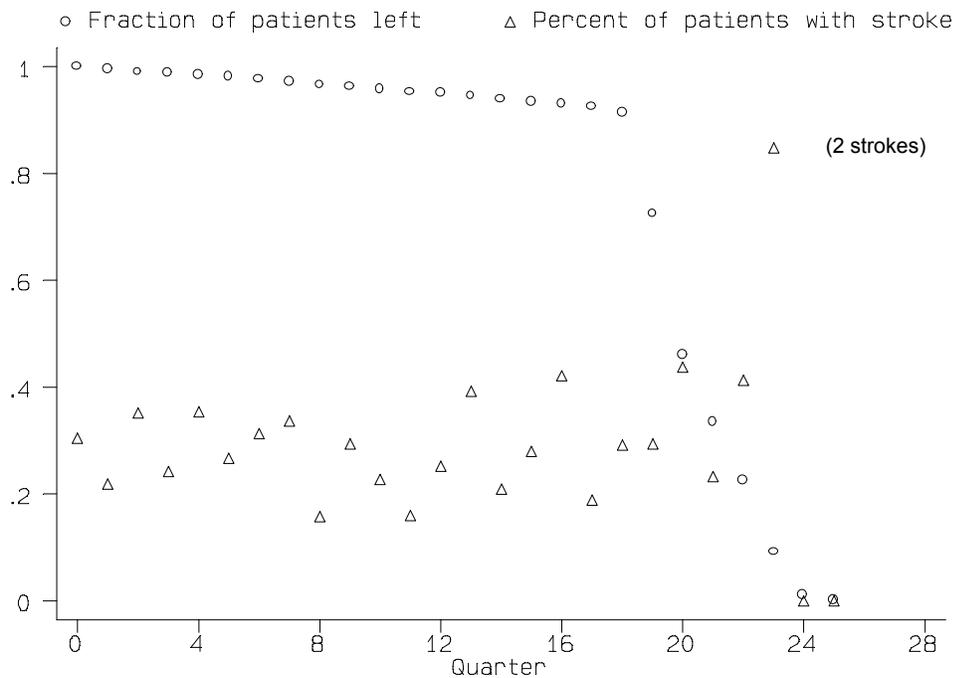
The timing of the occurrence of atrial fibrillation adverse events (afib AEs) is also interesting. The quarterly rates of afib AEs are shown in the two figures following the ones with MI rates. The rates of afib AEs appear to be slowly increasing with time with a cyclical variation. What appear to be dramatic are the increased rates of afib AEs in the atenolol group at the end of the study.

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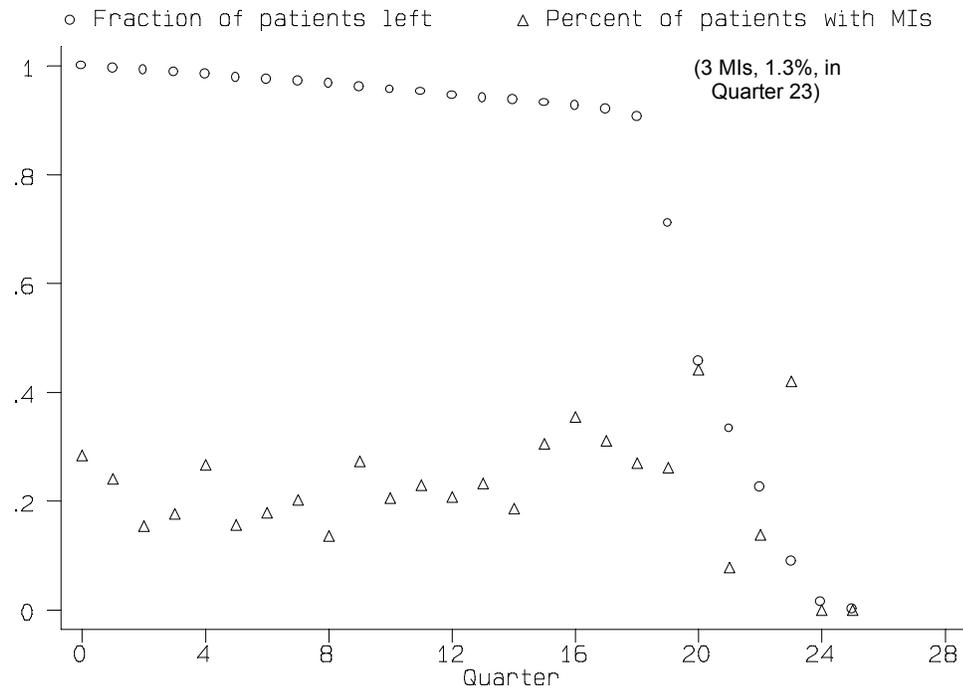
**Figure 7: Reviewer's Quarterly Stroke Rate for Atenolol Group**



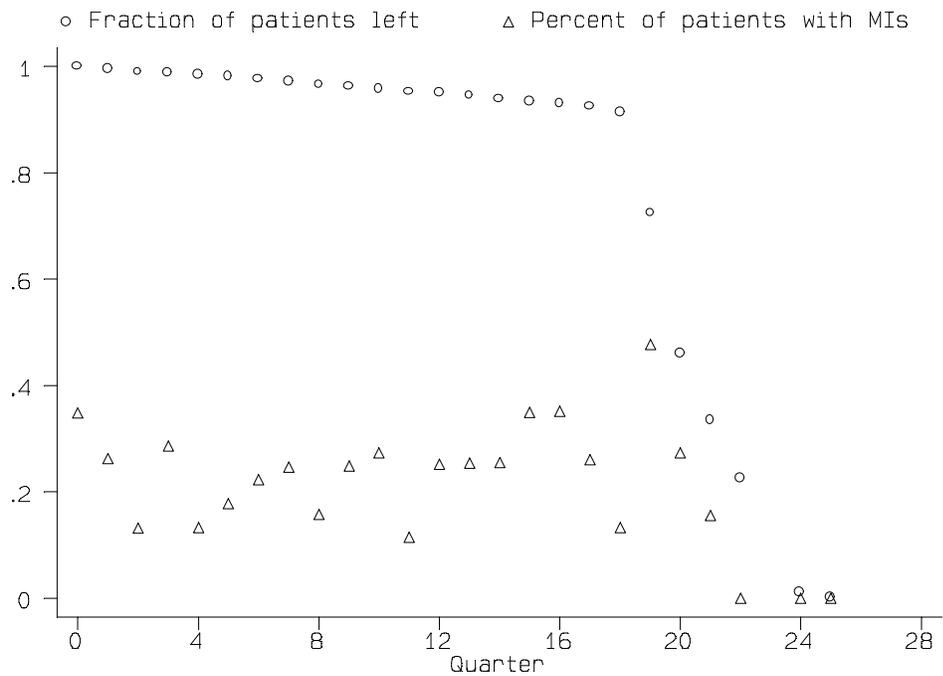
**Figure 8: Reviewer's Quarterly Stroke Rate for Losartan Group**

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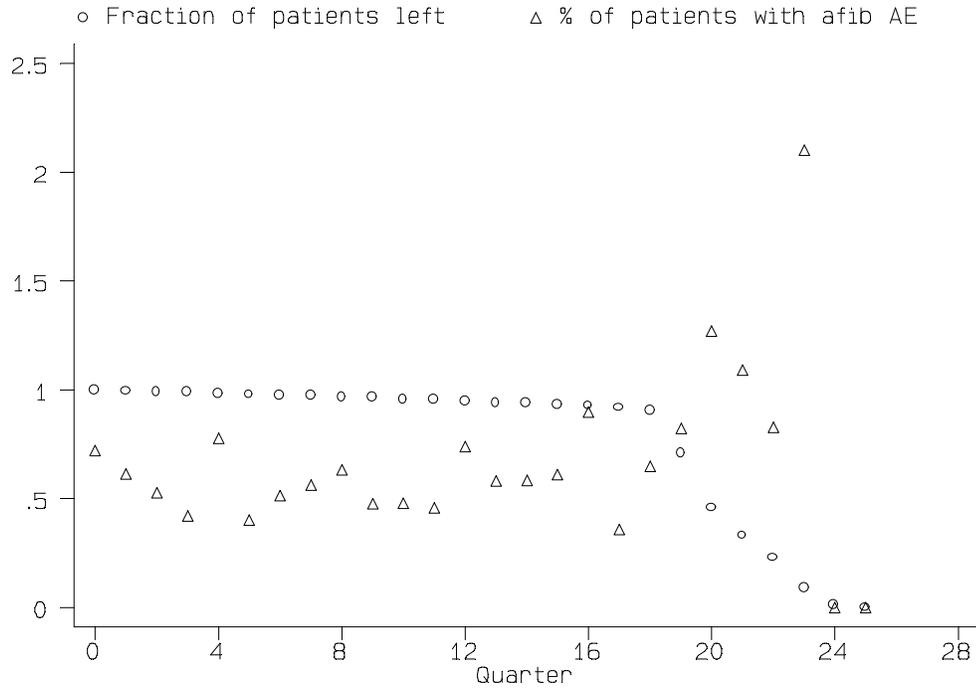
**Figure 9: Reviewer's Quarterly MI Rate for Atenolol Group**



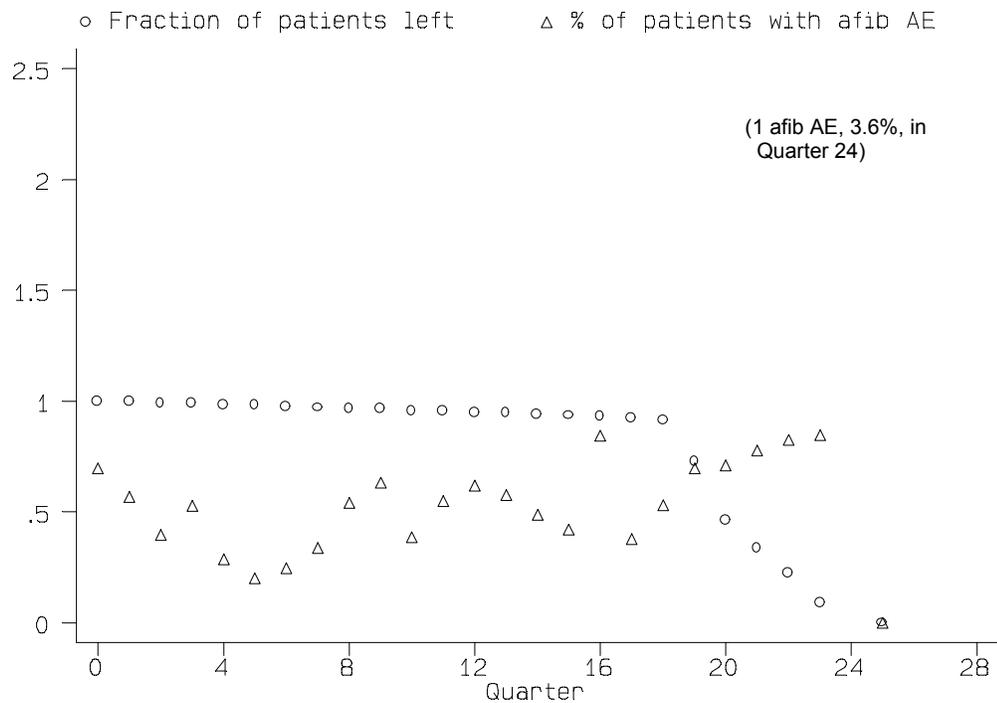
**Figure 10: Reviewer's Quarterly MI Rate for Losartan Group**

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**Figure 11: Reviewer’s Quarterly Atrial Fibrillation Adverse Event Rates for Atenolol Group**



**Figure 12: Reviewer’s Quarterly Atrial Fibrillation Adverse Event Rates for Losartan Group**

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The increased stroke rate with atenolol at the beginning and at the end of study raises the question of whether atenolol dose changes increase the risk of stroke. Interpreting association between strokes and dose changes is difficult because it is difficult to determine whether a dose change preceding an event by a few days was initiated because of developing signs or symptoms of the event or whether the dose change was initiated for unrelated reasons. Strokes were preceded by a dose change on the day before the event in 29 cases, 22 with atenolol and 7 with losartan. All but one of these dose changes were discontinuations of the study drug. Strokes were preceded by a dose change within 30 days prior to the event in 100 cases, 67 on atenolol and 33 on losartan. Of these latter dose changes 16 were initial dosing, 12 were increases in dosage, and 6 were restarts of dosing. Twenty-three of these 34 changes were in atenolol patients. These statistics suggest that atenolol dose changes are associated with strokes more frequently than losartan dose changes.

The relationship between changes in dose and atrial fibrillation adverse events (afib AE) does not appear to differ for atenolol and losartan. For 27 atenolol and 34 losartan patients an afib AE was reported on the day following a dosage change. For 106 atenolol and 90 losartan patients an afib AE was reported 1-30 days following a dosage change. The distribution of types of dose changes preceding afib AEs are similar for the two treatment groups.

An interesting analysis that the reviewer was unable to accomplish because of lack of data is the relationship between patient compliance, stroke, and atrial fibrillation. One wonders whether patient-initiated discontinuations are associated with either event.

The NDA did not include any discussion of a possible association of atrial fibrillation and stroke with atenolol use. That the sponsor may be aware of this association is shown by the topic of one of the proposed initial publications from the LIFE study listed at the December 10, 2001, meeting of the Steering Committee: "A fib, Rx and outcome".

COMMENT: Atenolol patients had more strokes associated with atrial fibrillation. This appears to represent a second mechanism that explains the differences in outcomes.

#### 4.2.3. Subgroup Analyses

##### 4.2.3.1. Country

Subgroup analyses by country are potentially useful to understand how the study results are relevant to the US population. Note that as documented in Section 4.1.2.2 there are some baseline differences among the subjects in the various countries. The rates of the primary composite endpoint by country are shown in the following table.

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**Table 53: Reviewer' Primary Composite Endpoint Rates by Country**

Country	Atenolol	Losartan
Denmark	14.2%	10.7%
Finland	8.8%	7.8%
Iceland	8.8%	12.3%
Norway	16.7%	12.2%
Sweden	13.0%	11.5%
US	13.7%	13.1%
UK	9.5%	9.6%
Total	12.8%	11.0%

Please note that Iceland is included in the table above and subsequent ones for completeness, but so few subjects were enrolled in Iceland that the Iceland results have extremely wide confidence limits. For the primary composite endpoint only the UK results favor atenolol very slightly, while the advantage of losartan is lower in the US. The results are more consistent for stroke as shown in the following table.

**Table 54: Reviewer's Primary Endpoint Stroke Rates by Country**

Country	Atenolol	Losartan
Denmark	7.9%	5.3%
Finland	4.5%	3.2%
Iceland	2.9%	1.5%
Norway	7.6%	3.9%
Sweden	6.0%	5.1%
US	4.9%	4.5%
UK	3.4%	2.7%
Total	5.8%	4.3%

From Section 4.1.2.2 one can appreciate that the US study population is not homogeneous. Baseline characteristics of US blacks differ significantly from US whites and from the subjects in other countries. If one treats US blacks and US whites as different subgroups, then the primary composite endpoint and stroke endpoint rates are as shown in the following two tables.

**Table 55: Reviewer' Primary Composite Endpoint Rates by Country/Race**

	Atenolol	Losartan
Denmark	14.2%	10.7%
Finland	8.8%	7.8%
Iceland	8.8%	12.3%
Norway	16.7%	12.2%
Sweden	13.0%	11.5%
US white	14.9%	11.2%
US black	11.2%	17.4%
UK	9.5%	9.6%

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	Atenolol	Losartan
Total	12.8%	11.0%

**Table 56: Reviewer's Primary Endpoint Stroke Rates by Country/Race**

	Atenolol	Losartan
Denmark	7.9%	5.3%
Finland	4.5%	3.2%
Iceland	2.9%	1.5%
Norway	7.6%	3.9%
Sweden	6.0%	5.1%
US white	5.5%	3.6%
US black	3.5%	6.4%
UK	3.4%	2.7%
Total	5.8%	4.3%

The results for whites in all countries are consistent with the possible exception of the neutral results for the composite endpoint in the UK. If total mortality is substituted for cardiovascular mortality in the composite endpoint, then the results are more consistent for whites as shown in the following table.

**Table 57: Reviewer's Primary Composite Endpoint with Total Mortality Rates by Country/Race**

	Atenolol	Losartan
Denmark	18.5%	15.3%
Finland	10.7%	10.2%
Iceland	11.8%	13.8%
Norway	19.5%	16.1%
Sweden	16.6%	13.8%
US white	18.8%	15.9%
US black	15.4%	23.5%
UK	14.8%	12.8%
Total	16.4%	14.5%

Note that the UK now shows an advantage to losartan, although the advantage of losartan in Finland is reduced.

COMMENT: If one accepts that US blacks are a substantially different population, then the results are reasonably consistent for whites by country particularly for the primary composite endpoint using total mortality in place of cardiovascular mortality. The results in US whites are consistent with the overall study. The differences in US blacks are explored further in the next section.

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### 4.2.3.2. Race

The sponsor did not specify assessing the influence of race or ethnicity as one of its secondary or tertiary endpoints but did include subgroup analyses by ethnicity in its Data Analysis Plan. The sponsor’s summary of its initial approach to examining ethnicity is the following:

“Although there was not a significant effect of ethnic background on the risk of an event in the prespecified groups, there was a suggestion of interaction between ethnic background and treatment (p=0.057). The prespecified test for the interaction between ethnic background and treatment was based on a comparison of the effect of losartan among the 5 different ethnic background categories: White (n=8503), Black (n=533), Hispanic (n=100), Asian (n=43), and Other (n=14). White patients appeared to have lower risk with losartan (hazard ratio: 0.819 [95% CI 0.724 to 0.928]), while Black patients appeared to have lower risk with atenolol (hazard ratio: 1.598 [95% CI 1.004 to 2.543]) (Table 19). The amount of data for all but the White and Black groups was very limited, which made the prespecified test for interaction unreliable. A further exploratory analysis dichotomizing patients into Black (N=533) and non-Black (N=8660) yielded a statistically significant interaction (p=0.005). Further, a test for qualitative interaction (i.e., effect of losartan differs in direction between Blacks and non-Blacks, not just in magnitude) was also statistically significant (p=0.016).”

Because of the suggestion of a qualitative interaction the sponsor performed additional analyses, the major ones of which are summarized in the following table.

**Table 58: Sponsor’s Primary Composite Endpoint and Components for Blacks and Non-Blacks**

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

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

Please see the FDA statistician’s review for a complete discussion of these analyses. However, the validity of these analyses is dependent upon assuming that the black and

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white subgroups are relatively homogeneous for factors not included in the analyses and that the statistical model employed, in this case Cox regression, adequately adjusts for the factors included in the model. Because quantitative tests of these assumptions are not available, it is helpful to examine differences in factors between the black and white subgroups and the two treatment groups in the black subgroup.

Baseline characteristics of US blacks are summarized in Section 4.1.2.3. Black were younger and heavier, more likely to be male and smokers, and less likely to use alcohol and to exercise. They had higher Sokolow-Lyon voltage but lower Cornell voltage duration products. They were intermediate between US non-blacks and non-US cases for heart disease and prior cardiovascular drug use (except beta blockers, for which they have the lowest prior use.) They had histories of more strokes and diabetes. While these differences do not prove that blacks and whites are nonhomogeneous populations that should not be analyzed in combination, they do provide support for looking at the black subgroup separately.

Baseline characteristics are reasonably well balanced between the two treatment groups in blacks. There are minor imbalances shown in the following table that are not statistically significant. Note, however, the age and gender differences.

**Table 59: Reviewer's Selected Baseline Characteristic in Blacks**

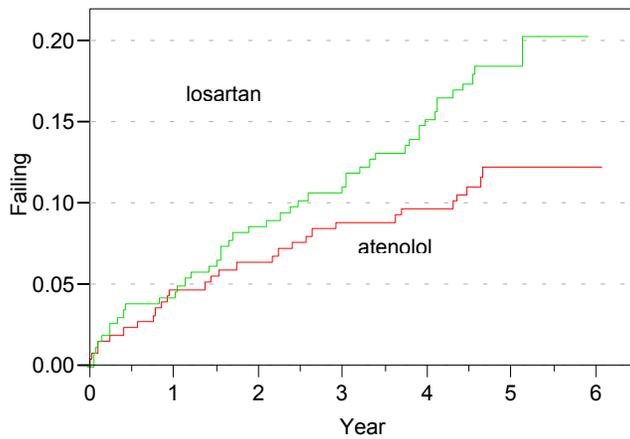
	Atenolol	Losartan	p*
Mean age	64.4	65.5	
Median age	63	66	0.07
Age <65	56%	46%	
Female	50%	43%	0.09
SBP	172	172	0.9
Isolated systolic hypertension	15%	17%	0.5
Framingham risk score	22.2	22.2	0.7
Smoker	17%	16%	0.2
Prior angina	11%	14%	0.3
Prior myocardial infarction	7%	9%	0.3
Prior heart failure	3.5%	3.8%	0.8
Prior stroke	9%	9%	0.9
Prior diabetes	27%	23%	0.3
Aspirin use	41%	48%	0.2

\*p by Chi square for categorical, rank sum for continuous variables

A Kaplan-Meier plot for the primary composite endpoint in blacks is shown in the figure below.

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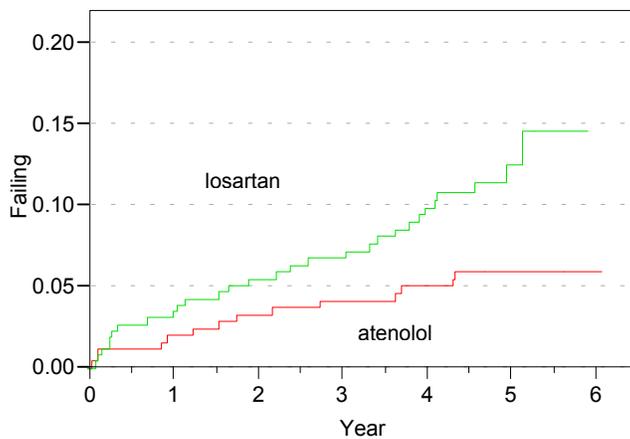
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**Figure 13: Reviewer's Kaplan-Meier Plot of Primary Composite Endpoint in Blacks**

Note that the curves diverge after about 1.5 years. There appears to be a substantial benefit to atenolol (log rank  $p = 0.02$ ). The results are similar if total mortality is incorporated into the composite endpoint.

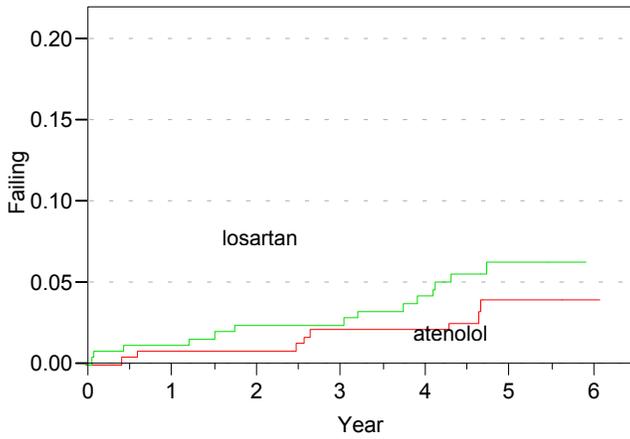
Kaplan-Meier plots for the components of the composite endpoint and for total mortality in blacks are shown in the following four figures.



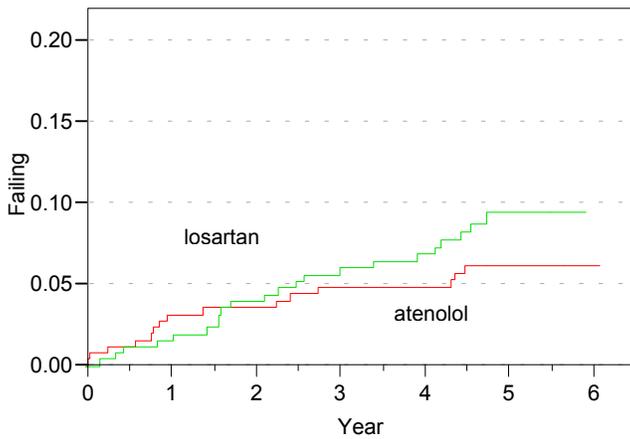
**Figure 14: Reviewer's Kaplan-Meier Plot of Strokes in Blacks**

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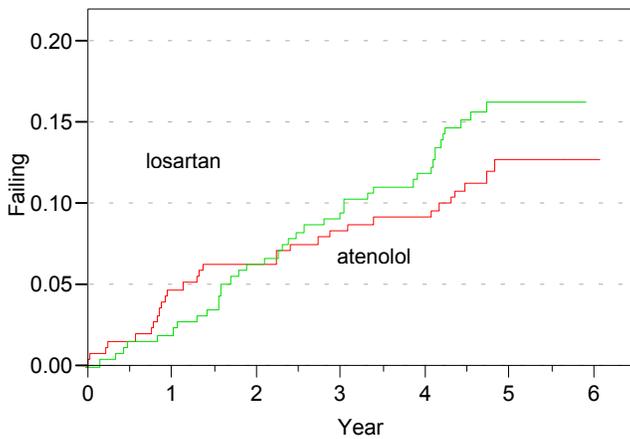
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**Figure 15: Reviewer's Kaplan-Meier Plot of Myocardial Infarctions in Blacks**



**Figure 16: Reviewer's Kaplan-Meier Plot of CV Mortality in Blacks**



**Figure 17: Reviewer's Kaplan-Meier Plot of Total Mortality in Blacks**

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Note that the curves for both cardiovascular and total mortality cross at about two years, with atenolol having a small survival advantage prior to two years and losartan having a survival advantage thereafter. However, the differences in survival are not statistically significant. The difference in stroke rates for blacks is statistically significant (log rank  $p = 0.02$ ).

The number of events is relatively small and all components of the composite contribute to the benefit of atenolol in blacks as shown in the following table.

**Table 60: Reviewer's Primary Composite Endpoint Events in Blacks**

	MI	CV death	Stroke	Total
Atenolol	6	14	9	29
Losartan	11	18	17	46
Total	17	32	26	75

MI = myocardial infarction

The difference in primary composite endpoints between the two groups is statistically significant ( $p = 0.03$ ) by the sponsor's usual Cox regression including LVH and Framingham risk score as covariates, although the LVH measures are not significant covariates for the regression. If age is substituted as a covariate, age is a highly significant covariate and group loses significance ( $p = 0.07$ ). Gender is not a significant covariate.

There are slight differences in treatment and response to treatment. Fewer black patients than white were on their primary study drugs at the time of an endpoint or end of study (68 vs. 76%). Fewer black atenolol patients were on primary study drug at the end than black losartan patients (65 vs 70%). Blood pressure control in blacks was mixed. Good control was more frequent with losartan (42 vs. 39%) but so was poor control (24 vs 19%). The mean SBP at end was slightly lower with atenolol (144.2 vs. 145.0) corresponding to a slightly greater SBP reduction with atenolol (-27.6 vs -27.0). Heart rate change in blacks differed from those in whites, with blacks showing less of a reduction in heart rate on atenolol (-5.8 vs -8.5) and an increase rather than a decrease with losartan (1.0 vs. -1.5).

The Kaplan-Meier plots suggest that there is a difference, favoring atenolol, in the rates of stroke by treatment. In addition to the 26 primary composite endpoint strokes there were 17 other strokes, for a total of 17 strokes in blacks in the atenolol group and 26 strokes in the losartan group.

There appear to be only subtle differences in the characteristics of strokes in blacks vs. whites. The distribution of types of strokes is similar, with the majority of strokes in both races being classified as ischemic (blacks 77%, whites 74%). Strokes followed by death within 30 days were more frequent with losartan in blacks, but the numbers are too small

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to have significance (3 vs. 0). Any evidence of atrial fibrillation was reported less frequently in blacks (7%) than whites (10%). It was slightly but not significantly more frequent with losartan in blacks while it was slightly and significantly more frequent with atenolol in whites. More strokes associated with atrial fibrillation occurred in blacks on losartan than on atenolol, but the numbers are too small (4 vs. 2) to have any significance.

The LIFE study included an echocardiographic substudy at selected centers that enrolled 916 patients (459 atenolol and 457 losartan). This substudy oversampled blacks, but the numbers of blacks enrolled were still low (65 atenolol, 64 losartan). Patients in this substudy underwent baseline and annual echocardiograms to estimate left ventricular mass and left ventricular mass index (LVMI—left ventricular mass divided by body surface area). LVMI is greater in men than women. (Shub, Klein et al. 1994) Various thresholds for defining LVH by increased LVMI have been published, ranging from 111 to 134 g/m<sup>2</sup> in men and from 100 to 125 g/m<sup>2</sup> in women.

**Table 61: Sponsor’s Baseline LVMI and Changes at Final Visit**

	Atenolol			Losartan		
	N	Baseline	Change	N	Baseline	Change
<b>All</b>	459	123	-18	457	125	-22
<b>Black</b>	65	130	-19	64	126	-16
<b>US white</b>	55	123	-16	50	121	-19
<b>All white</b>	394	121	-18	393	125	-23
<b>Female</b>	184	115	-15	193	119	-20
<b>Male</b>	275	127	-19	264	129	-23

Blacks in the atenolol group experienced a greater LVMI reduction compared with blacks in the losartan group. Note that atenolol blacks had the highest baseline LVMI so that final visit LVMI in blacks are very similar in both groups. Whites, including US whites analyzed separately, had greater reduction in LVMI on losartan than atenolol.

In contrast to the echocardiographic measures, a similar pattern of change in the ECG measures of LVH (Cornell product and Sokolow-Lyon voltage) was seen in black and white echocardiographic substudy patients and was consistent with the results in blacks and whites in the main LIFE population. Reduction in Cornell product was less in blacks than in whites for both treatments. The reduction in Sokolow-Lyon voltage was greater in blacks than whites in both treatment groups. The reduction of both ECG measures of LVH in both racial groups was greater with losartan than with atenolol.

COMMENT: The black population in this study does appear to be a different population than the white population with regard to baseline characteristics, response to therapy, and outcomes. Some of the difference in outcomes may be explained by the differences in age and gender between the two groups. The critical question in this reviewer’s opinion is whether the difference in outcomes represents a reversal of the apparent beneficial effect of losartan in hypertensive whites with LVH or a lack of difference between the two drugs in hypertensive blacks with LVH confounded by random baseline differences.

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This reviewer does not believe that the evidence is sufficient to conclude that there is an actual reversal of the effect seen in whites.

#### 4.2.3.3. Age and Gender

The overall study population was well represented with the elderly (61% age 65 or older, 17% age 75 or older) and with both genders (54% female). Females tended to be older than males as is shown in the following table.

**Table 62: Reviewer's Age Categories by Gender**

		Female	Male
<65	N	1677	1812
	%	34%	43%
65-74	N	2268	1854
	%	46%	44%
≥75	N	1018	564
	%	21%	13%

Baseline SBP was higher for older ages (mean 171 for ages <65 vs. 174 for ages ≥ 75) while DBP was lower for older ages (mean 100 for ages <65 vs. 94 for ages ≥ 75). Hence isolated systolic hypertension was more frequent at older ages (7.5% for ages <65 vs. 26% for ages ≥ 75). Blood pressure control worsened with age in both treatment groups. Rates of poor control by age category are shown in the following table.

**Table 63: Reviewer's Rates of Poor Blood Pressure Control (SBP≥160 or DBP≥100) by Age**

	Atenolol	Losartan
<65	18%	15%
65-74	25%	22%
≥75	31%	27%

The treatment groups were well balanced for age and gender. However, rates of the primary composite endpoint varied by age and treatment group as shown in the following table.

**Table 64: Reviewer's Primary Composite Endpoint Rates by Age Category**

	Atenolol	Losartan
<65	6.9%	7.4%
65-74	14.2%	11.3%
≥75	22.5%	18.2%

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Note that losartan was slightly less beneficial than atenolol for ages < 65 as measured by the sponsor's primary composite endpoint. However, if total mortality rather than cardiovascular mortality is incorporated into the composite endpoint, then there is no difference in the endpoint rate for ages < 65 between atenolol and losartan as shown in the following table.

**Table 65: Reviewer's Primary Composite Endpoint with Total Mortality Rates by Age Category**

	Atenolol	Losartan
<65	9.1%	9.1%
65-74	17.8%	15.1%
≥75	28.8%	24.9%

Losartan appears to show the greatest net benefit over atenolol in the older age groups. This pattern is also present with regard to the stroke and mortality components of the primary composite endpoint. Stroke rates are slightly lower (2.7 vs 3.2%) with atenolol for ages < 65. Myocardial infarction rates vary slightly and inconsistently between the two groups by age.

Gender differences appear to reflect the age differences by gender noted above, although females have slightly higher SBP and slightly lower DBP than males in the same age category. Both genders show a beneficial effect of losartan compared to atenolol by the primary composite endpoint as shown in the following table.

**Table 66: Reviewer's Primary Composite Endpoint Rates by Gender**

	Atenolol	Losartan
Female	10.5%	8.6%
Male	15.5%	13.8%

The beneficial effect of losartan appears reduced in males when total mortality is incorporated into the composite endpoint as shown in the following table.

**Table 67: Reviewer's Primary Composite Endpoint with Total Mortality Rates by Gender**

	Atenolol	Losartan
Female	14.1%	11.1%
Male	19.1%	18.6%
Total	16.4%	14.5%

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Total mortality in males was the same for both treatment groups for males, while females on atenolol had a higher total mortality rate (8.4%) than females on losartan (6.4%). Note that mean ages were nearly identical in the two groups but were higher for females (67.7) vs. males (66.1) in both groups.

Calculating primary composite endpoint with total mortality rates by gender and age produces the results shown in the following table.

**Table 68: Reviewer’s Primary Composite Endpoint with Total Mortality Rates by Gender and Age**

Gender	Age	N	Atenolol	Losartan
Female	<65	1539	7.4%	5.6%
	65-74	2190	13.6%	10.1%
	≥75	991	26.3%	21.0%
Male	<65	1685	10.6%	12.3%
	65-74	1732	23.1%	20.6%
	≥75	533	33.3%	31.9%

Note that losartan is less beneficial than atenolol in younger males (age <65). There also appears to be a reduced benefit in elderly males (age ≥75) but the number of cases is small.

COMMENT: One must be cautious about overinterpreting these subgroup analyses. Losartan appears to be more effective in higher risk individuals such as the elderly. Losartan may be less beneficial in males, particularly younger males (age <65).

### 4.2.3.4. Diabetics

The sponsor analyzed various endpoint results in patients with diabetes at baseline. The sponsor’s analyses are summarized in the following table.

**Table 69: Sponsor’s Endpoint Results for Baseline Diabetics**

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

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

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Losartan appears to be even more beneficial in this subgroup, with a risk reduction for the composite endpoint of about 25%. The pattern of benefit is different from the study as a whole, with a dramatic difference in total mortality in diabetics between the two groups. The atenolol group had more deaths due to heart failure (10 vs. 5), myocardial infarction (17 vs. 13), sudden death or arrest (20 vs. 8), stroke (12 vs. 6), and pneumonia or other infection (12 vs. 1), while the losartan group had a clear excess of deaths only for respiratory failure (7 vs. 0).

#### 4.2.3.5. Isolated Systolic Hypertension

The sponsor also analyzed various endpoint results in patients with isolated systolic hypertension (ISH) at baseline. The sponsor's analyses are summarized in the following table.

**Table 70: Sponsor's Endpoint Results for Patients with Isolated Systolic Hypertension**

	Crude Rate						Hazard <sup>‡</sup> Ratio	95% CI		p-Value <sup>§</sup>
	Losartan (N=660)			Atenolol (N=666)				Lower	Upper	
	Rate <sup>†</sup>	n	(%)	Rate <sup>†</sup>	n	(%)				
Composite	25.1	75	(11.4)	35.4	104	(15.6)	0.750	0.557	1.011	0.059
Cardiovascular mortality	8.7	27	(4.1)	16.9	52	(7.8)	0.543	0.340	0.867	0.010*
MI (fatal/nonfatal)	10.2	31	(4.7)	11.9	36	(5.4)	0.890	0.550	1.442	0.637
Stroke (fatal/nonfatal)	10.6	32	(4.8)	18.9	56	(8.4)	0.595	0.385	0.921	0.020*
Total mortality	21.2	66	(10.0)	30.2	93	(14.0)	0.725	0.528	0.995	0.046*
Hospitalization due to angina	11.3	34	(5.2)	7.6	23	(3.5)	1.475	0.868	2.507	0.151
Hospitalization due to heart failure	8.5	26	(3.9)	13.3	40	(6.0)	0.665	0.405	1.093	0.107

\* p-Values <0.05.  
<sup>†</sup> Per 1000 patient-years of follow-up.  
<sup>‡</sup> Baseline LVH degree (Cornell product and S-L) and baseline Framingham risk score are included in Cox proportional hazard model as covariates.  
<sup>§</sup> The p-values and estimates of hazard ratio of experiencing the endpoint on losartan compared to atenolol are based on Cox proportional hazard model.

ISH appears to be one surrogate for the effects of age. Rates of ISH increase substantially with increasing age as shown in the following table.

**Table 71: Reviewer's Rates of Isolated Systolic Hypertension by Age**

Age	Atenolol	Losartan
<65	7%	8%
65-74	16%	16%
≥75	27%	25%

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COMMENT: Both subgroup analyses in diabetics and patients with isolated systolic hypertension are interesting ones that must be interpreted with caution. If real they would be clinically useful because the distinguishing characteristics are easy to determine. The difficult question is how much to trust these subgroup results. ISH may be a surrogate for age.

### 4.2.3. Secondary Endpoints

The most important secondary endpoints, the components of the primary composite endpoint and total mortality, have been discussed in conjunction with the primary endpoint. The sponsor also defined a number of secondary endpoints that are summarized briefly below.

#### 4.2.3.1. Other Endpoint Classification Committee Endpoints

The Endpoint Classification Committee also adjudicated several other events that the sponsor judged to be relevant to the interpretation of the study results. The sponsor's summary of the these other secondary endpoints are shown in the following table.

**Table 72: Sponsor's Other Secondary Endpoints Classified by the Endpoint Classification Committee**

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

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

The reviewer has discussed total mortality results in conjunction with the primary endpoint. There are no statistically significant differences in these secondary endpoints.

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#### 4.2.3.2. Left Ventricular Hypertrophy

The sponsor postulated based on other evidence that losartan might improve LVH more than atenolol. The results appear to support this hypothesis. The sponsor's summary of changes in LVH by ECG criteria are shown in the following table.

**Table 73: Sponsor's Changes in ECG Measures of LVH**

	Losartan (N=4605)				Atenolol (N=4588)				p-Value <sup>†</sup>
	n	Mean			n	Mean			
		Baseline	Follow-up	Change		Baseline	Follow-up	Change	
<b>ECG Estimate of LVH (Cornell Product mm x msec)</b>									
Month 6	3926	2826.4	2624.6	-201.8	3906	2804.7	2738.2	-66.6	<0.001**
Year 1	4079	2823.6	2568.1	-255.6	4042	2811.8	2702.6	-109.3	<0.001**
Year 2	3882	2817.9	2498.5	-319.4	3848	2813.5	2644.4	-169.1	<0.001**
Year 3	3731	2806.0	2492.1	-313.9	3633	2807.0	2635.6	-171.4	<0.001**
Year 4	3598	2813.4	2507.6	-305.8	3546	2797.7	2635.6	-162.0	<0.001**
Year 5	1365	2877.0	2549.9	-327.2	1365	2892.3	2710.1	-182.2	<0.001**
<b>ECG Estimate of LVH (Sokolow-Lyon mm)</b>									
Month 6	3964	30.0	27.4	-2.5	3960	29.9	29.2	-0.7	<0.001**
Year 1	4127	29.8	26.7	-3.1	4086	29.9	28.6	-1.3	<0.001**
Year 2	3929	29.8	25.9	-3.9	3909	29.9	27.8	-2.1	<0.001**
Year 3	3767	29.8	25.5	-4.3	3709	29.9	27.4	-2.6	<0.001**
Year 4	3638	29.8	25.1	-4.7	3596	29.9	26.9	-3.0	<0.001**
Year 5	1376	28.8	24.2	-4.6	1378	29.4	26.2	-3.2	<0.001**
** p-Values <0.01.									
† The p-values are based on Wilcoxon test.									
n = Total number of patients with available data at each designated study time point.									
ECG = Electrocardiogram.									
LVH = Left ventricular hypertrophy.									

The sponsor also incorporated the ECG criteria for LVH as time-varying covariates into its Cox regression analyses of the primary endpoint and components. The results are shown in the following table.

**Table 74: Sponsor's Primary Composite Endpoint and Components Adjusted for ECG Criteria for LVH as Time-Varying Covariates**

	Crude Rate				Adjusted Hazard Ratio <sup>†</sup>	95% CI		p-Value <sup>†</sup>
	Losartan (N=4605)		Atenolol (N=4588)			Lower	Upper	
	n	(%)	n	(%)				
Composite	508	(11.0)	588	(12.8)	0.902	0.801	1.106	0.090
Cardiovascular Mortality	204	(4.4)	234	(5.1)	0.936	0.775	1.130	0.493
MI (fatal/nonfatal)	198	(4.3)	188	(4.1)	1.094	0.895	1.337	0.380
Stroke (fatal/nonfatal)	232	(5.0)	309	(6.7)	0.782	0.659	0.928	0.005**
** p-Values <0.01.								
† p-Values and estimates of hazard ratio of experiencing the endpoint on losartan compared to atenolol are based on Cox proportional hazard model that includes Cornell Voltage Product and Sokolow-Lyon as time-varying covariates.								

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After adjustment for ECG criteria for LVH as time-varying covariates treatment effect for the composite endpoint and for stroke are slightly smaller, while the treatment effect for MI becomes slightly larger.

### 4.2.3.3. Hospitalizations

The sponsor defined the rate of hospitalization for any reason as a tertiary endpoint. The reviewer includes hospitalizations here as one available measure of whether overall patient morbidity was different between the two groups. Hospitalization numbers were similar in the two groups and are shown in the following table.

**Table 75: Sponsor’s Numbers of Hospital Admissions**

Number of Hospital Admissions	Losartan (N=4605)		Atenolol (N=4588)		p-Value <sup>†</sup>
	n	(%)	n	(%)	
No hospitalization	2345	(50.9)	2256	(49.2)	0.095
At least one hospital admission	2260	(49.1)	2332	(50.8)	
One admission	916	(19.9)	947	(20.6)	
Two admissions	473	(10.3)	449	(9.8)	
Three admissions	272	(5.9)	306	(6.7)	
Four or more admissions	599	(13.0)	630	(13.7)	

<sup>†</sup> The p-value is based on Wilcoxon rank-sum test for ordered categories.

First hospitalization rates by reason for hospitalization are shown in the following table.

**Table 76: Sponsor’s Rates of First Hospitalizations by Reason**

Reason for Hospitalization	Crude Rate						Kaplan-Meier Rates								Hazard <sup>†</sup> Ratio	95% Confidence Interval		p-Value <sup>‡</sup>
	Losartan (N=4605)			Atenolol (N=4588)			Losartan				Atenolol					Lower	Upper	
	Rate <sup>§</sup>	n	(%)	Rate <sup>§</sup>	n	(%)	1 Year	2 Year	3 Year	4 Year	1 Year	2 Year	3 Year	4 Year				
Any reason	140	2239	(48.6)	146	2315	(50.5)	15.5	26.7	35.4	42.8	15.7	26.6	35.8	44.0	0.964	0.909	1.021	0.211
Angina	10.0	213	(4.6)	8.0	171	(3.7)	1.5	2.4	3.3	4.1	1.3	2.0	2.7	3.3	1.261	1.031	1.542	0.024*
Coronary revascularization	6.0	131	(2.8)	6.2	133	(2.9)	0.6	1.3	1.9	2.5	0.4	1.1	1.7	2.3	1.001	0.787	1.274	0.992
Heart failure	9.1	196	(4.3)	9.5	203	(4.4)	1.1	1.8	2.6	3.5	1.4	2.1	2.8	3.7	0.981	0.806	1.194	0.846
Myocardial infarction	8.4	182	(4.0)	7.5	161	(3.5)	0.9	1.6	2.2	3.2	0.7	1.4	2.1	2.9	1.148	0.929	1.419	0.202
Non-coronary arterial vascular surgery	5.1	110	(2.4)	6.0	129	(2.8)	0.5	1.0	1.4	1.9	0.3	1.0	1.6	2.3	0.870	0.674	1.122	0.282
Stroke	11.4	244	(5.3)	14.8	314	(6.8)	1.4	2.6	3.3	4.4	2.0	3.1	4.2	5.7	0.779	0.659	0.921	0.003**
Death	4.8	106	(2.3)	5.5	121	(2.6)	0.3	0.7	1.4	1.8	0.3	0.6	1.3	1.9	0.886	0.682	1.150	0.362
Non-endpoint	107	1838	(39.9)	112	1898	(41.4)	11.4	20.8	28.2	34.9	11.4	20.8	29.0	36.6	0.961	0.901	1.024	0.219

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

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Times to first hospitalization for any reasons were similar in the two groups. Times to first hospitalization were shorter in the losartan group for angina and in the atenolol group for stroke.

COMMENT: The secondary endpoint analyses do not reveal any other major differences between atenolol and losartan, although there is a suggestion of slight differences in hospitalizations for angina. The LVH analyses suggest that losartan is superior to atenolol in reducing LVH. The unknown factor is whether there were differences in blood pressure control, including differences in 24-hour control, that might explain the observed differences in LVH reduction.

#### **D. Efficacy Conclusions**

##### 1. Primary Endpoint

The reviewer believes that there are two critical questions to ask regarding the primary results of the LIFE study:

- (a) Does the LIFE study show that a losartan regimen is robustly superior to an atenolol regimen in reducing cardiovascular morbidity and mortality?
- (b) Were the LIFE regimens realistic enough and the conduct of the trial adequate to support transfer of the results into routine clinical practice?

The reviewer judges that the answer to both questions is a qualified yes.

The sponsor's pre-specified analysis for its primary composite endpoint of cardiovascular mortality, myocardial infarction, and stroke was a Cox regression in including treatment group, baseline Cornell and Sokolow-Lyon ECG LVH scores, and Framingham risk score as covariates. For this Cox regression the hazard ratio for losartan treatment is 0.869 with  $p=0.21$ . Without the baseline covariates the hazard ratio is 0.854 with  $p=0.009$ .

Because all three components of the primary composite endpoint have a degree of subjectivity in their ascertainment, the reviewer examined case report forms and reclassified all endpoints for which the Endpoint Classification Committee (ECC) changed the investigator's assignment. The results based on the reviewer's reclassifications are nearly identical for the sponsor's primary composite endpoint and the reviewer did not identify any biases in the ECC's assignments.

The reviewer believes that the Division's original recommendation to use total mortality rather than cardiovascular mortality in the primary composite endpoint is appropriate because of subjectivity in assessing cardiovascular mortality and the unquestionable

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importance of mortality regardless of cause. Using a modified composite endpoint incorporating total mortality  $p=0.029$  for the Cox regression with baseline LVH and risk score covariates and  $p=0.018$  for an unadjusted log rank analysis. For the reviewer's reclassifications  $p=0.051$  for the Cox regression and  $p=0.023$  for an unadjusted log rank analysis. The primary composite endpoint results are not statistically extreme.

The sponsor appropriately performed the pre-specified primary endpoint analysis and the reviewer performed all endpoint analyses discussed so far using a strict, as-randomized intention-to-treat approach. The sponsor also performed a per-protocol analysis and the reviewer performed an on-study drug analysis. These analyses are relevant because discontinuation of study drug was not uncommon: 170 (29%) atenolol and 130 (26%) losartan primary endpoint events occurred more than 30 days after study drug discontinuation. All Cox regression analyses by per-protocol or on-study drug approaches are non-significant ( $p=0.053$  to  $0.12$ ).

The sponsor refers to the reduction in the secondary endpoint of stroke, an adjusted risk reduction of about 25%,  $p=0.001$ , as robust. However, the reviewer does not consider a selected secondary endpoint to be robust in view of non-robustness of the primary endpoint. Furthermore, if components of the primary endpoint are to be highlighted, then one must also consider the relevance of the point estimate of the hazard ratio for myocardial infarction with losartan, 1.07. While this hazard ratio is not statistically significant, it is arguably consistent with the positive impact beta blockers have shown upon cardiovascular morbidity and mortality in post-myocardial infarction studies.

The reviewer's conclusion regarding the first question is that the LIFE study does show that an antihypertensive regimen including losartan is superior to one including atenolol for reducing cardiovascular morbidity and mortality in hypertensive patients with LVH. The qualification is that the evidence is not very robust. It is also a single study. However, the magnitude of the point estimate of the benefit is reasonable. An adjusted risk reduction of about 10% for a composite endpoint of total mortality, myocardial infarction, and stroke is clinically significant. Repetition of the trial would be difficult.

The second question, whether the LIFE regimens were realistic enough and the conduct of the trial adequate, has several subordinate questions. The first is how much impact the small difference in blood pressure (BP) control had on the results. Mean systolic BP (SBP) at year 4 was 1.5 mm Hg higher in the atenolol group while diastolic BP (DBP) was 0.3 mm Hg lower. These mean differences translate into small differences in control, e.g., 24% of atenolol and 20% of losartan patients had poor control defined as  $SBP \geq 160$  or  $DBP \geq 100$ . Endpoint rates were substantially higher with poor control, e.g., 2-3 fold higher than in patients with good control defined as  $SBP < 140$  and  $DBP < 90$ . If the atenolol group had achieved the same level of BP control as the losartan group, then 22 fewer endpoints would be expected in the atenolol group. The difference in the primary composite endpoint rates would not be statistically significant.

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By the reviewer's calculations BP control in the LIFE study was only fair. Prior to the endpoint in patients with primary endpoints or at last recording for patients without primary endpoints only about a third of patients had good control. This level of control is probably typical of routine practice, so one can argue that the LIFE results will transfer into routine practice.

Study drug usage was slightly lower in the atenolol group. The magnitude of the difference is about the same as the magnitude of the difference in control. While the study was blinded, the effect of atenolol on heart rate is observable. Whether the differences in drug dosage and BP control are consequences of adverse effects, differing efficacy, or investigator perception is impossible to unravel.

The reviewer's conclusion regarding the second question is that the LIFE regimens were realistic enough and the conduct of the trial adequate to support transfer of the results into practice. The qualification regarding the second question is similar to that for the first—the reviewer's confidence in the affirmative answer is not great. The potential for neutralizing the benefit with a small increase in BP control for the atenolol group is not reassuring. On the other hand, the LIFE study is probably similar to routine practice so its results may transfer well.

#### 2. Atrial Fibrillation and Strokes

One of the possible surprise findings of the LIFE study may be that atenolol is associated with more atrial fibrillation and consequently more strokes. The evidence is not conclusive but includes the following:

- Atrial fibrillation and flutter adverse events reported at any time during the study were slightly more common in the atenolol group (7.9%) than in the losartan group (6.8%). Atrial fibrillation led to discontinuation in about 1% of atenolol patients vs. 0.5% of losartan patients.
- Strokes occurred in about 18% of atenolol patients with some evidence of atrial fibrillation, 12% of losartan patients with some evidence of atrial fibrillation, and 5% of patients without evidence of atrial fibrillation.
- Stroke rates in the atenolol group peaked in the first quarter and at year five as patients were being discontinued. Atrial fibrillation adverse event rates also peaked at year five. The losartan group did not show these peaks.
- Strokes were preceded by a dose change on the day before the event in 22 atenolol and 7 losartan patients. Strokes were preceded by a dose change within 30 days prior to the event in 67 patients and 33 losartan patients.

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This association between atenolol use and atrial fibrillation and stroke appears to explain some of the difference in outcomes not explained by the difference in blood pressure control. Confirmation, or refutation, of this association is needed from other studies.

#### 3. Differential Effect in Blacks

Although the sponsor did not pre-specify the comparison, there is a significant interaction between race, characterized as black and white, and treatment ( $p=0.005$ ). Blacks fared worse with losartan (hazard ratio 1.666,  $p=0.033$ , by the sponsor's usual Cox regression analysis with baseline covariates) than with atenolol. A test for a qualitative interaction (i.e., that the effect of losartan differs in direction, not just in magnitude, between blacks and whites) was statistically significant ( $p=0.016$ ).

However, the interpretation of these analyses is confounded because the blacks in the LIFE study have different baseline characteristics than the whites and the blacks in the losartan groups have different baseline characteristics than the blacks in the atenolol group. There are some inconsistencies in the results between the two racial groups. The pertinent findings are the following:

- The vast majority of blacks were enrolled only in the US. To take into account this difference the sponsor also compared US blacks to US whites and still noted the difference in effect. However, US blacks are also dissimilar from US whites.
- Baseline characteristics of US blacks differ from the other ethnic subgroups. Blacks were younger and heavier, more likely to be male and smokers, and less likely to use alcohol and to exercise. They had higher Sokolow-Lyon voltage but lower Cornell voltage duration products. They had histories of more strokes and diabetes.
- Blacks in the losartan group were older and more likely to be male. While these differences are not statistically significant, the maldistributions of baseline risk factors probably influence the results. If primary endpoints in blacks are analyzed by the sponsor's usual Cox regression with covariates of baseline ECG LVH measures and Framingham risk score, then treatment group is a significant factor (hazard ratio 1.66,  $p=0.033$ ). As with the overall study and white subgroup analyses, Framingham risk score is a highly significant covariate. Different from the overall study and white subgroup analyses, baseline ECG LVH measures are not significant covariates. If age is added as a covariate, then treatment group becomes insignificant ( $p=0.07$ ).
- Blacks were treated differently and responded differently to treatment. Fewer blacks than whites were on their primary study drugs at the time of an endpoint or end of study (68 vs. 76%). Fewer black atenolol patients were on primary study drug at the end than black losartan patients (65 vs 70%). Blood pressure control in

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blacks was mixed. Good control was more frequent with losartan (42 vs. 39%) but so was poor control (24 vs 19%). The mean SBP at end was slightly lower with atenolol (144.2 vs. 145.0). Heart rate change in blacks differed from those in whites, with blacks showing less of a reduction in heart rate on atenolol (-5.8 vs -8.5) and an increase rather than a decrease with losartan (1.0 vs. -1.5).

- Blacks in the atenolol group in the echocardiographic substudy had a greater reduction in left ventricular mass index (LVMI) compared to blacks in the losartan group, although the absolute values at final visit were similar. Whites had greater reductions in LVMI with losartan. Reductions in electrocardiographic left ventricular hypertrophy measures were greater with losartan for both ethnic groups, although blacks had greater reductions in Sokolow-Lyon voltage and lesser reductions in Cornell products than whites.
- Blacks on atenolol had fewer adverse events, serious adverse events, and discontinuations for adverse events than blacks on losartan. Rates of adverse events for blacks on losartan were very similar to rates for whites. While it is conceivable that the same mechanism that led to better efficacy with atenolol in blacks also produced fewer adverse events, it is simpler to conclude that blacks on atenolol were lower risk.

The reviewer concludes that blacks in the LIFE study were a different population than whites. They had different baseline characteristics and responded differently to treatment. There were baseline imbalances in important risk factors, i.e., age and gender, between the two treatment groups in blacks. While the LIFE study results suggest that losartan is not superior to atenolol in reducing cardiovascular morbidity and mortality in black hypertensives with LVH, it does not provide sufficient consistent evidence that losartan is inferior to atenolol in this subgroup.

#### 4. Differential Effects by Age and Gender

The LIFE study was well represented with the elderly (61% age 65 or older, 17% age 75 or older) and with both genders (54% female). Females were older than males on the average (mean age for females 67.7, for males 66.1). Older patients had higher baseline SBP (mean 171 for ages <65 vs. 174 for ages ≥ 75), lower baseline DBP (mean 100 for ages <65 vs. 94 for ages ≥ 75), and hence more isolated systolic hypertension (7.5% for ages <65 vs. 26% for ages ≥ 75). Blood pressure control declined with age.

The rates of the primary composite endpoint, with or without total mortality, varied by age and gender. The rates of the primary composite endpoint with total mortality are shown in the following table.

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**Table 77: Reviewer's Primary Composite Endpoint with Total Mortality Rates by Gender and Age**

Gender	Age	N	Atenolol	Losartan
Female	<65	1539	7.4%	5.6%
	65-74	2190	13.6%	10.1%
	≥75	991	26.3%	21.0%
Male	<65	1685	10.6%	12.3%
	65-74	1732	23.1%	20.6%
	≥75	533	33.3%	31.9%

While one must be cautious about overinterpreting these subgroup analyses, losartan appears to be more beneficial in the elderly. Losartan may be less beneficial in males, particularly younger males (age <65).

#### 5. Other Subgroups

Losartan appears to be even more beneficial in diabetics at baseline, with a risk reduction for the composite endpoint of about 25%. The pattern of benefit is different from the study as a whole, with a dramatic difference in total mortality in diabetics between the two groups. Atenolol use was also associated with more new onset diabetes as is discussed in the Safety section.

Losartan also appears to be more beneficial in patients with isolated systolic hypertension (ISH) at baseline, with a risk reduction for the composite endpoint also of about 25%. ISH appears to be one surrogate for age, increasing from about 7% for ages <65 to 27% for ages ≥ 75.

#### 6. Other Endpoints

The sponsor postulated based on other evidence that losartan might improve left ventricular hypertrophy (LVH) more than atenolol. At the last visit before a primary endpoint or at the last recording the Cornell product was reduced by 4.4% in the atenolol group and 10% in the losartan group. The Sokolow-Lyon voltage was reduced by 9% in the atenolol group and 15% in the losartan group. While these results also may be confounded by differences in blood pressure control, they appear to support the sponsor's hypothesis.

The sponsor defined the rate of hospitalization for any reason as a tertiary endpoint. Rates of hospitalizations are informative as one available measure of whether overall patient morbidity was different between the two groups. Rates of hospitalizations were similar in the two groups, with 50.8% of atenolol patients and 49.1% of losartan patients having at least one hospital admission. Times to first hospitalization for any reasons were similar in the two groups. Times to first hospitalization were shorter in the losartan group for angina and in the atenolol group for stroke.

### **VII. Integrated Review of Safety**

#### **A. Brief Statement of Conclusions**

The tolerability of atenolol and losartan appears comparable when judged by total adverse event (AE) rates, AEs leading to hospitalization, and serious AE rates. Only for AEs leading to discontinuation and investigator-classified drug-related AEs, rates that are more susceptible to investigator subjectivity, are losartan rates lower than atenolol rates. Overall both drugs were tolerated well.

The most common AEs were ones that would be expected with these drugs. Dizziness was the most frequently reported AE with both drugs. Bradycardia was common with atenolol. Bradycardia was the most frequent reason, and fatigue and dyspnea were other common reasons, for discontinuation with atenolol.

This large, long-term study helps to define better rarer complications of both drugs. Atenolol was associated with an increase in atrial fibrillation. Atenolol also raised uric acid and glucose levels slightly and was associated with slightly increased rates of gout and greater risk of diabetes. Losartan lowered hemoglobin levels slightly and was associated with slightly increased rates of anemia.

#### **B. Review of Safety Data in the LIFE Study**

##### **1. Exposure**

The sponsor's summary statistics on drug exposure, including dosages at the final visit, are provided in the Efficacy section. The dosages by study visit are listed in the following table.

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**Table 78: Sponsor's Study Drug Dosages by Visit**

Visit	Total Daily Dose	Losartan (N=4605)		Atenolol (N=4588)	
	Dose	n	(%) Mean(Std)	n	(%) Mean(Std)
Month 1	50 mg	3665	(79.6)	3575	(77.9)
	50 mg + Other	684	(14.9)	682	(14.9)
	100 mg + Other	125	(2.7)	93	(2.0)
	All Doses (mg)	4474	(97.2)	4350	(94.8)
Month 2	50 mg	2182	(47.4)	2179	(47.5)
	50 mg + Other	1628	(35.4)	1585	(34.5)
	100 mg + Other	575	(12.5)	475	(10.4)
	All Doses (mg)	4385	(95.2)	4239	(92.4)
Month 4	50 mg	1273	(27.6)	1279	(27.9)
	50 mg + Other	1562	(33.9)	1587	(34.6)
	100 mg + Other	1433	(31.1)	1254	(27.3)
	All Doses (mg)	4268	(92.7)	4120	(89.8)
Month 6	50 mg	845	(18.3)	840	(18.3)
	50 mg + Other	1112	(24.1)	1160	(25.3)
	100 mg + Other	2046	(44.4)	1806	(39.4)
	All Doses (mg)	4003	(86.9)	3806	(83.0)
Year 1	50 mg	743	(16.1)	716	(15.6)
	50 mg + Other	999	(21.7)	1062	(23.1)
	100 mg + Other	2117	(46.0)	1846	(40.2)
	All Doses (mg)	3859	(83.8)	3624	(79.0)
Year 1.5	50 mg	665	(14.4)	668	(14.6)
	50 mg + Other	947	(20.6)	958	(20.9)
	100 mg + Other	2119	(46.0)	1861	(40.6)
	All Doses (mg)	3731	(81.0)	3487	(76.0)
Year 2	50 mg	614	(13.3)	613	(13.4)
	50 mg + Other	882	(19.2)	913	(19.9)
	100 mg + Other	2134	(46.3)	1840	(40.1)
	All Doses (mg)	3630	(78.8)	3366	(73.4)
Year 2.5	50 mg	586	(12.7)	596	(13.0)
	50 mg + Other	844	(18.3)	878	(19.1)
	100 mg + Other	2120	(46.0)	1850	(40.3)
	All Doses (mg)	3550	(77.1)	3324	(72.4)
Year 3	50 mg	557	(12.1)	561	(12.2)
	50 mg + Other	783	(17.0)	853	(18.6)
	100 mg + Other	2117	(46.0)	1825	(39.8)
	All Doses (mg)	3457	(75.1)	3239	(70.6)
Year 3.5	50 mg	524	(11.4)	517	(11.3)
	50 mg + Other	734	(15.9)	829	(18.1)
	100 mg + Other	2135	(46.4)	1821	(39.7)
	All Doses (mg)	3393	(73.7)	3167	(69.0)
Year 4	50 mg	452	(9.8)	453	(9.9)
	50 mg + Other	657	(14.3)	727	(15.8)
	100 mg + Other	2004	(43.5)	1720	(37.5)
	All Doses (mg)	3113	(67.6)	2900	(63.2)
16-Sep 2001	50 mg	442	(9.6)	436	(9.5)
	50 mg + Other	643	(14.0)	718	(15.6)
	100 mg + Other	2109	(45.8)	1805	(39.3)
	All Doses (mg)	3194	(69.4)	2959	(64.5)

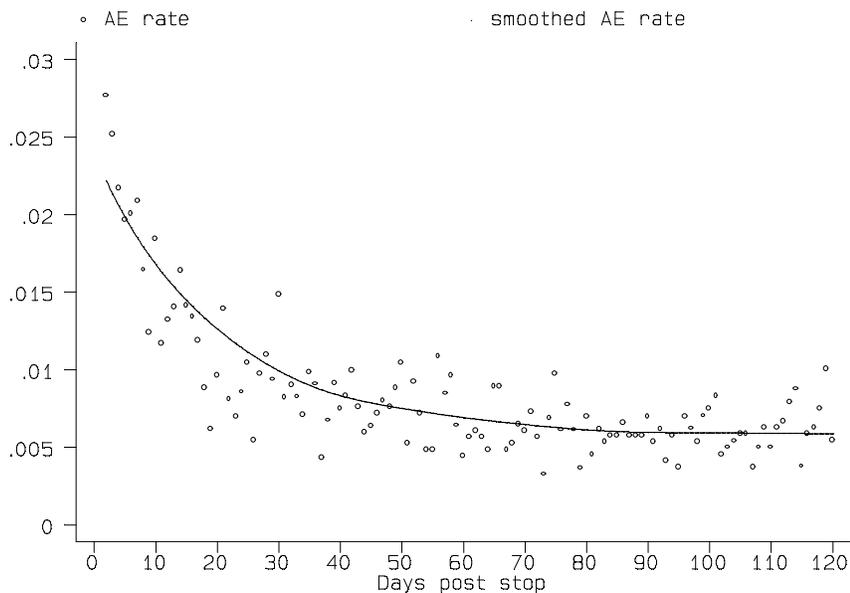
The reviewer calculated that the atenolol patients remained on study drug for a mean of 3.94 years (18,076 person exposure years) and losartan patients remained on study drug for a mean of 4.12 years (19,006 person exposure years).

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Investigators reported adverse events during the screening period prior to the initiation of treatment, during treatment with study drug, and after treatment with study drug until termination of follow-up. The sponsor restricted safety analyses to the period while the patients were receiving study drug and the 14-day periods immediately following study drug discontinuation. The sponsor's description of this restriction is as follows: "Safety analyses included laboratory measurements and adverse experiences that 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." This sponsor did not include this restriction in the original protocol but it does appear in the Data Analysis Plan dated November 1, 2001.

The sponsor's justification for not analyzing adverse events (AEs) occurring more than 14 days after discontinuation of study medication is the following: "Since patients who discontinued blinded study medication often took another antihypertensive medication that had its own set of potential adverse experiences, the adverse experiences that occurred during the period following discontinuation would tend to obscure the true differences between losartan and atenolol. For this reason, the adverse experience results summarized below do not include adverse experiences that occurred more than 14 days after the patient discontinued study medication or more than 14 days after the start of a gap in study therapy." It is not obvious how long AEs may be delayed after study drug discontinuation. The reviewer examined AE rates in the days following discontinuation to determine how soon the rates would stabilize. A graph of daily AE rates post discontinuation is shown in the following figure. The curve was drawn using a lowess smoothing algorithm.



**Figure 18: Fraction of Patients with Adverse Events by Day Post Study Drug Discontinuation**

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AE rates do not stabilize until 90 days post discontinuation. Although not shown, the reviewer also graphed AE rates post-discontinuation for atenolol and losartan separately; the graphs for both drugs are very similar to the above and to each other. The AE rates around 14 days post-continuation are still substantially higher than the stabilized rates. Because the excess AEs from days 15 through 90 may help differentiate atenolol from losartan toxicities and because the sponsor has analyzed the AEs excluding them and provided good summaries of its analyses, the reviewer analyzed AEs including all ones occurring up to 90 days post-discontinuation.

#### 2. Serious Adverse Events

The sponsor counted serious adverse events (SAEs) in 36.2% of atenolol and 37.2% of losartan patients using its 14-day criteria; the reviewer counted SAEs in 37.7% of atenolol patients and 38.4% of losartan patients using his 90-day criteria. The sponsor's tabulation of SAEs occurring in  $\geq 0.5\%$  of patients is shown in the following table.

Specific SAEs were uncommon, i.e.,  $< 2\%$ . The one SAE that occurred with a frequency  $\geq 2\%$  in both groups was atrial fibrillation, with nearly identical rates in both groups.

The patterns of SAEs in the reviewer's analyses including SAEs through 90 days post treatment are very similar to those in the table above. One slight difference is worthy of comment: Atrial fibrillation SAEs through 90 days show a slight excess in the atenolol group (0.89/100 PEY with atenolol vs 0.74/100 PEY with losartan). A second comparison is noteworthy because of a lack of difference: depression SAEs were rare in both groups and comparable in frequency.

COMMENT: Rates of SAEs were similar in both treatment groups. There may be some minor distinguishing SAEs, such as more bradycardia and atrial arrhythmic events in the atenolol group. The greater differences in atrial fibrillation with atenolol when a longer period post-treatment discontinuation is included raises the question again of whether discontinuing atenolol increases event rates.

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**Table 79: Sponsor's Serious Adverse Events with Frequencies  $\geq 0.5\%$  of Patients**

	Losartan (N=4605)		Atenolol (N=4588)	
	n	(%)	n	(%)
Patients with one or more adverse experiences	1715	(37.2)	1660	(36.2)
Patients with no adverse experience	2890	(62.8)	2928	(63.8)
<b>Body as a Whole/Site Unspecified</b>	<b>414</b>	<b>(9.0)</b>	<b>398</b>	<b>(8.7)</b>
Abdominal pain	24	(0.5)	31	(0.7)
Chest pain	21	(0.5)	26	(0.6)
Drug overdose	88	(1.9)	65	(1.4)
Inguinal hernia	29	(0.6)	28	(0.6)
Syncope	59	(1.3)	49	(1.1)
<b>Cardiovascular System</b>	<b>357</b>	<b>(7.8)</b>	<b>396</b>	<b>(8.6)</b>
Atrial fibrillation	96	(2.1)	93	(2.0)
Bradycardia	9	(0.2)	43	(0.9)
Deep venous thrombosis	30	(0.7)	21	(0.5)
Pulmonary embolism	18	(0.4)	25	(0.5)
Transient ischemic attack	35	(0.8)	49	(1.1)
<b>Digestive System</b>	<b>287</b>	<b>(6.2)</b>	<b>261</b>	<b>(5.7)</b>
Colonic malignant neoplasm	26	(0.6)	21	(0.5)
<b>Endocrine System</b>	<b>39</b>	<b>(0.8)</b>	<b>39</b>	<b>(0.9)</b>
<b>Eyes, Ears, Nose, and Throat</b>	<b>92</b>	<b>(2.0)</b>	<b>93</b>	<b>(2.0)</b>
Cataract	27	(0.6)	22	(0.5)
<b>Hemic and Lymphatic System</b>	<b>53</b>	<b>(1.2)</b>	<b>50</b>	<b>(1.1)</b>
Anemia	31	(0.7)	16	(0.3)
<b>Hepatobiliary System</b>	<b>107</b>	<b>(2.3)</b>	<b>79</b>	<b>(1.7)</b>
Cholecystitis	29	(0.6)	24	(0.5)
Cholelithiasis	51	(1.1)	46	(1.0)
<b>Metabolism and Nutrition</b>	<b>26</b>	<b>(0.6)</b>	<b>28</b>	<b>(0.6)</b>
<b>Musculoskeletal System</b>	<b>385</b>	<b>(8.4)</b>	<b>367</b>	<b>(8.0)</b>
Hip osteoarthritis	35	(0.8)	33	(0.7)
Knee osteoarthritis	33	(0.7)	16	(0.3)
Musculoskeletal chest pain	26	(0.6)	24	(0.5)
<b>Nervous System</b>	<b>122</b>	<b>(2.6)</b>	<b>124</b>	<b>(2.7)</b>
Vertigo	41	(0.9)	39	(0.9)
<b>Psychiatric Disorder</b>	<b>57</b>	<b>(1.2)</b>	<b>37</b>	<b>(0.8)</b>
<b>Respiratory System</b>	<b>189</b>	<b>(4.1)</b>	<b>193</b>	<b>(4.2)</b>
Lung malignant neoplasm	29	(0.6)	12	(0.3)
Pneumonia	75	(1.6)	96	(2.1)
<b>Skin and Skin Appendages</b>	<b>127</b>	<b>(2.8)</b>	<b>129</b>	<b>(2.8)</b>
Basal cell carcinoma	66	(1.4)	58	(1.3)
<b>Urogenital System</b>	<b>318</b>	<b>(6.9)</b>	<b>274</b>	<b>(6.0)</b>
Breast malignant neoplasm	37	(0.8)	36	(0.8)
Prostatic disorder	28	(0.6)	22	(0.5)
Prostatic malignant neoplasm	58	(1.3)	42	(0.9)

Although a patient may have had 2 or more serious adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

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### 2.1. Deaths

Total mortality rates are presented in the Efficacy section. The death rate was slightly higher in the atenolol group (431 deaths, 9.4%) than in the losartan group (383 deaths, 8.3%).

Causes of death were similar in the two groups with the exception of more stroke deaths in the atenolol group. The major causes of death are listed in the following table.

**Table 80: Reviewer’s Death Causes**

	Atenolol		Losartan	
	N	%	N	%
Aortic aneurysm	13	3.0%	10	2.6%
Heart failure	29	6.7%	24	6.3%
Myocardial infarction	74	17.2%	68	17.8%
Cancer	111	25.8%	115	30.0%
Other	91	21.1%	83	21.7%
Stroke	59	13.7%	35	9.1%
Sudden	54	12.5%	48	12.5%
Total	431	100.0%	383	100.0%

In the above table cardiac arrests and a few deaths reported as arrhythmias have been lumped into the “Sudden” death category. A few other deaths reported as cardiac hypertrophy have been placed into the “Heart failure” category. These consolidations were done to eliminate small, imprecise categories. Aortic aneurysm, uncommon but not rare as a cause of death, did not fit clearly into any other category. It is a not rare cause of death in both treatment groups in these high risk hypertensives with LVH.

The “Other” category includes a diverse range of non-cardiovascular diagnoses with only the following diagnoses comprising more than 1% of deaths: pneumonia (4.1%), other infections (2.7%), other respiratory failure (2.7%), gastrointestinal bleeds (1.4%), pulmonary embolism (1.2%), and renal failure (1.1%). There are no significant differences or unusual patterns of noncardiovascular deaths in either group.

For 220 atenolol and 202 losartan patients the investigators reported AEs as resulting in death. For none of these AEs did the investigators consider the study medication to be the cause. About half of these deaths were cancer related in each group. The other deaths were due to the causes noted in the previous paragraph. There is no obvious pattern to the causes in either group.

### 2.2. Hospitalizations

Hospitalization rates are presented in the Efficacy section as secondary endpoints.

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Overall 3,128 adverse events led to one or more hospitalizations in 1,587 (33.9%) atenolol patients and 3,266 adverse events led to one or more hospitalizations in 1,609 (34.9%) losartan patients. The top 20 adverse events leading to hospitalization for each group are shown in the following table.

**Table 81: Reviewer’s Top 20 Adverse Events Leading to Hospitalization**

Rank	Atenolol AE	N	Losartan AE	N
1	atrial fibrillation	101	atrial fibrillation	95
2	pneumonia	98	pneumonia	81
3	syncope	47	syncope	59
4	transient ischemic attack	46	cholelithiasis	52
5	cholelithiasis	46	vertigo	40
6	bradycardia	43	hip osteoarthritis	35
7	vertigo	40	anemia	34
8	hip osteoarthritis	33	transient ischemic attack	34
9	breast malignant neoplasm	32	knee osteoarthritis	33
10	abdominal pain	32	breast malignant neoplasm	33
11	inguinal hernia	27	cholecystitis	30
12	musculoskeletal chest pain	27	abdominal pain	30
13	pulmonary embolism	26	inguinal hernia	29
14	chest pain	26	prostatic malignant neoplasm	29
15	cholecystitis	25	deep venous thrombosis	28
16	prostatic malignant neoplasm	24	colonic malignant neoplasm	28
17	cataract	24	prostatic disorder	28
18	prostatic disorder	23	musculoskeletal chest pain	28
19	colonic malignant neoplasm	22	cataract	27
20	spinal stenosis	21	lung malignant neoplasm	24

Note that same three adverse event are the leading reasons for hospitalization for both treatment groups. Some adverse events are more frequently associated with hospitalizations in one treatment group vs. the other: TIAs and bradycardia in the atenolol group and anemia in the losartan group.

COMMENT: Overall rates of AEs leading to hospitalization are similar in the two groups. There appear to be minor differences in the types of AEs leading to hospitalization. Anemia appears to be an uncommon but clinically important adverse effect of losartan.

### 2.3. Other Serious Adverse Events

The reviewer did not identify any other serious adverse events of interest other than those already presented.

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#### 3. Events Leading to Discontinuation

Adverse events reported by the investigator as resulting in study drug discontinuation occurred in 831 (18.1%) of atenolol patients and 604 (13.1%) of losartan patients. (These numbers include temporary discontinuations for AEs after which the study drug was restarted.) The AEs leading to discontinuation with a frequency  $\geq 0.5\%$  in either group are shown in the following table. Note that asthenia, atrial fibrillation, bradycardia, and dyspnea were substantially more frequent causes for discontinuation in the atenolol group than the losartan group.

**Table 82: Sponsor' Adverse Events Leading to Discontinuation at Rates  $\geq 0.5\%$**

	Losartan (N=4605)		Atenolol (N=4588)	
	n	(%)	n	(%)
Patients with one or more adverse experiences	604	(13.1)	831	(18.1)
Patients with no adverse experience	4001	(86.9)	3757	(81.9)
<b>Body as a Whole/Site Unspecified</b>	<b>143</b>	<b>(3.1)</b>	<b>201</b>	<b>(4.4)</b>
Asthenia/fatigue	32	(0.7)	76	(1.7)
Dizziness	32	(0.7)	41	(0.9)
<b>Cardiovascular System</b>	<b>182</b>	<b>(4.0)</b>	<b>327</b>	<b>(7.1)</b>
Atrial fibrillation	24	(0.5)	44	(1.0)
Bradycardia	11	(0.2)	122	(2.7)
Congestive heart failure	7	(0.2)	23	(0.5)
<b>Digestive System</b>	<b>51</b>	<b>(1.1)</b>	<b>83</b>	<b>(1.8)</b>
<b>Musculoskeletal System</b>	<b>35</b>	<b>(0.8)</b>	<b>38</b>	<b>(0.8)</b>
<b>Nervous System</b>	<b>90</b>	<b>(2.0)</b>	<b>85</b>	<b>(1.9)</b>
Headache	29	(0.6)	23	(0.5)
Vertigo	28	(0.6)	19	(0.4)
<b>Psychiatric Disorder</b>	<b>44</b>	<b>(1.0)</b>	<b>41</b>	<b>(0.9)</b>
<b>Respiratory System</b>	<b>68</b>	<b>(1.5)</b>	<b>123</b>	<b>(2.7)</b>
Dyspnea	22	(0.5)	79	(1.7)
<b>Skin and Skin Appendages</b>	<b>20</b>	<b>(0.4)</b>	<b>27</b>	<b>(0.6)</b>
<b>Urogenital System</b>	<b>48</b>	<b>(1.0)</b>	<b>45</b>	<b>(1.0)</b>

Although a patient may have had 2 or more adverse experiences leading to discontinuation, the patient is counted only once within a category. The same patient may appear in different categories.

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### 4. Events of Special Interest

The sponsor specified the following AEs to be of special interest:

- angioedema (angioedema, tongue edema)
- bradycardia (bradycardia, sinus bradycardia)
- sleep disturbance (dream abnormality)
- hypotension (blood pressure decreased, hypotension, orthostatic hypotension)
- dizziness (dizziness, orthostatic dizziness, presyncope, orthostatic presyncope)
- sexual dysfunction (sexual dysfunction, impotence, erectile dysfunction, libido decreased)
- cold extremities (peripheral vascular disorder, skin cool to touch, Raynaud's phenomenon)
- cough (ACE inhibitor induced cough, dry cough)
- cancer

The sponsor's analysis of these events of special interest is shown in the following table.

**Table 83: Sponsor's Rates of Events of Special Interest**

	Losartan (N=4605)		Atenolol (N=4588)		Losartan - Atenolol			p-Values <sup>†</sup>
	n	(%)	n	(%)	Risk	95% CI		
					Difference	Lower	Upper	
Angioedema	6	(0.1)	11	(0.2)	-0.0011	-0.0029	0.0007	0.237
Bradycardia	66	(1.4)	391	(8.5)	-0.0709	-0.0797	-0.0621	<0.001**
Cancer	358	(7.8)	320	(7.0)	0.0080	-0.0027	0.0187	0.151
Cold extremities	178	(3.9)	269	(5.9)	-0.0200	-0.0288	-0.0112	<0.001**
Cough	133	(2.9)	113	(2.5)	0.0043	-0.0023	0.0108	0.220
Dizziness	771	(16.7)	727	(15.8)	0.0090	-0.0061	0.0241	0.247
Hypotension	121	(2.6)	75	(1.6)	0.0099	0.0040	0.0158	0.001**
Sexual dysfunction	164	(3.6)	214	(4.7)	-0.0110	-0.0191	-0.0029	0.009**
Sleep disturbance	30	(0.7)	38	(0.8)	-0.0018	-0.0053	0.0017	0.333

\*\* p-Values <0.01.  
<sup>†</sup> The p-values are based on Fisher exact test.

More atenolol patients experienced bradycardia, cold extremities, and sexual dysfunction; more losartan patients experienced hypotension.

The reviewer re-analyzed the sponsor's events of special interest by the alternative approach considering all events through 90 days after study drug discontinuation and expressing the rates per 100 person exposure years (PEYs). The reviewer added additional events regarding anemia (a label note for losartan), atrial and ventricular arrhythmias, hepatic and renal insufficiency, fatigue, depression, hyperkalemia, and hyponatremia. The reviewer's rates for these events are shown in the following table.

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**Table 84: Reviewer’s Rates of Patients with Events of Special Interest per 100 Person-Exposure Years**

	Atenolol	Losartan
anemia	1.21	1.72
angioedema	0.07	0.03
atrial arrhythmia	2.07	1.78
bradycardia	2.20	0.39
cancer	1.85	1.99
cold extremities	1.81	1.16
cough	1.82	1.84
depression	1.67	1.62
dizziness	4.13	4.11
fatigue	4.53	3.72
hepatic disorder	0.77	0.67
hyperkalemia	0.18	0.22
hyponatremia	0.26	0.27
hypotension	0.45	0.66
renal dysfunction	0.32	0.43
sexual dysfunction	1.21	0.87
sleep disturbance	0.57	0.48
ventricular arrhythmia	0.23	0.42

COMMENT: The reviewer confirmed the sponsor’s observations of more bradycardia, cold extremities, and sexual dysfunction in the atenolol patients and slightly more hypotension in the losartan patients. The reviewer also found more fatigue and atrial arrhythmias in the atenolol patients and more anemia, ventricular arrhythmias, and renal dysfunction in the losartan patients. However, the differences are small (< 1 event per 100 PEYs) except for bradycardia.

The sponsor defined new onset diabetes mellitus as a tertiary endpoint. Because diabetes mellitus is also considered to be an adverse event, the sponsor’s analysis of diabetes mellitus is shown in the table below.

**Table 85: Sponsor’s Rates of New Onset Diabetes Mellitus**

	Crude Rate						Kaplan-Meier Rates								Hazard <sup>‡</sup> Ratio	95% CI		p-Value <sup>§</sup>
	Losartan (N <sup>†</sup> =4019)			Atenolol (N <sup>†</sup> =3979)			Losartan				Atenolol					Lower	Upper	
	Rate <sup>‡</sup>	n	(%)	Rate <sup>‡</sup>	n	(%)	1-Yr	2-Yr	3-Yr	4-Yr	1-Yr	2-Yr	3-Yr	4-Yr				
New-onset diabetes mellitus	13.0	242	(6.0)	17.4	320	(8.0)	1.1	2.7	3.9	4.9	1.0	3.1	4.9	6.5	0.749	0.634	0.885	<0.001**

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

The sponsor analyzed new onset diabetes similarly to other endpoints. Losartan patients had about a 25% lower risk of developing diabetes than atenolol patients. Note the effects of atenolol upon blood glucose presented in the Clinical Laboratory Tests section.

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#### 5. Overall Adverse Events

Adverse event (AE) reports were common in this elderly, high-risk study population followed for more than four years. Investigators reported 39,161 AEs in 4,376 atenolol patients and 39,623 AEs in 4,375 losartan patients. AEs occurring at rates of greater than 1 per 100 PEYs in either group are shown in the following table.

**Table 86: Reviewer's AE Rates Greater than 1 per 100 Person Exposure Years**

	Atenolol	Losartan
abdominal pain	1.7	1.8
albuminuria	1.7	1.1
asthenia/fatigue	4.5	3.7
atrial fibrillation	1.5	1.3
back pain	2.7	3.1
bradycardia	2.0	0.3
bronchitis	2.3	2.1
cataract	1.1	1.1
chest pain	2.7	2.8
cough	1.8	1.8
cystitis	1.2	1.3
depression	1.7	1.6
diabetes mellitus	1.2	1.0
diarrhea	1.8	1.8
dizziness	3.9	3.9
dyspnea	3.7	2.5
eczematous dermatitis	1.6	1.3
gout	1.1	0.6
headache	3.4	3.4
hypercholesterolemia	1.6	1.5
hyperglycemia	1.7	1.3
hypokalemia	1.3	1.0
influenza-like disease	1.6	1.6
insomnia	1.3	1.2
knee pain	1.3	1.3
leg pain	1.0	1.2
lower extremity edema	3.7	3.0
muscular weakness	1.1	0.8
myalgia	1.2	1.3
nausea	1.6	1.6
peripheral vascular disorder	1.4	0.9
pneumonia	1.6	1.2
rash	1.1	1.2
shoulder pain	1.3	1.3
sinusitis	1.2	1.2
upper respiratory infection	4.6	4.5
uric acid increased	1.2	0.7

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	Atenolol	Losartan
urinary tract infection	1.8	1.7
vertigo	2.7	2.7

The sponsor also tabulated AEs that the investigator judged to be drug-related. Investigators reported drug-related AEs more frequently in the atenolol group (45%) than in the losartan group (37%).

COMMENT: Most of the AEs with rates greater than 1 per 100 PEYs are minor illnesses also common in the general population and probably not related to study treatment. Of the AEs with differential rates in the two groups only the greater rates of dyspnea, pneumonia, hyperglycemia, lower extremity edema, gout, and uric acid increased in the atenolol group have not been mentioned previously. The differences in rates are small.

The difference in the two treatment groups in drug-related AEs is similar to the difference in AEs leading to discontinuation. Given that rates of all AEs, SAEs, and AEs leading to hospitalization were similar, one wonders whether the differences in drug-related and AEs leading to discontinuation are real differences in tolerability or subjective judgments influenced by other factors. Reduction in heart rate was common with atenolol as would be expected. One wonders whether investigators might be more likely to call another AE in the same patient drug-related or to discontinue treatment because of concomitant reduced heart rate or borderline or frank bradycardia in the patient.

#### 6. Vital Signs

Changes in blood pressure and pulse are discussed in the Efficacy section. Mean pulse rates in beats/minutes decreased by 10.1 in the atenolol group and 1.2 in the losartan group at study end. Mean weight in kg increased by 0.4 in the atenolol group and decreased by 0.4 in the losartan group at study end.

#### 7. Clinical Laboratory Tests

During the study standard hematology and chemistry tests and urinary microalbumin were monitored. The tests with mean changes that appear to differ between the two treatment groups are shown in the following table.

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**Table 87: Sponsor's Mean Changes in Hemoglobin, Glucose, Uric Acid, and Urine Microalbumin by Study Year**

	Losartan (N=3899)				Atenolol (N=3740)			
	n	Mean			n	Mean		
		Baseline	Follow-up	Change		Baseline	Follow-up	Change
<b>Hemoglobin (gm/dL)</b>								
Year 1	3308	14.253	13.877	-0.376	3106	14.258	14.144	-0.114
Year 2	3017	14.261	13.749	-0.512	2851	14.273	14.052	-0.220
Year 3	2884	14.260	13.748	-0.513	2705	14.279	14.047	-0.232
Year 4	2733	14.256	13.884	-0.372	2597	14.286	14.181	-0.105
Year 5	2004	14.280	13.789	-0.491	1820	14.299	14.054	-0.245
<b>Glucose (mg/dL)</b>								
Year 1	3709	107.737	110.353	2.616	3532	108.466	114.789	6.322
Year 2	3409	107.526	110.008	2.483	3213	107.413	115.094	7.681
Year 3	3238	107.556	110.829	3.273	3027	106.479	114.857	8.378
Year 4	3075	107.052	111.686	4.634	2897	106.386	114.239	7.853
Year 5	2192	106.325	110.215	3.890	1994	104.805	114.726	9.921
<b>Uric Acid (mg/dL)</b>								
Year 1	3706	5.526	5.594	0.068	3510	5.541	6.166	0.625
Year 2	3427	5.523	5.417	-0.106	3203	5.545	5.985	0.440
Year 3	3238	5.509	5.661	0.152	3017	5.534	6.269	0.735
Year 4	3066	5.511	5.772	0.260	2882	5.518	6.347	0.830
Year 5	2186	5.476	5.944	0.468	1981	5.476	6.486	1.010
<b>Urine Microalbumin (mg/dL)</b>								
Year 1	3419	6.138	3.841	-2.297	3195	5.184	4.291	-0.894
Year 2	3122	5.778	3.820	-1.957	2945	4.756	4.323	-0.433
Year 3	2944	5.312	3.599	-1.713	2776	4.362	3.620	-0.743
Year 4	2779	5.105	3.697	-1.408	2633	4.334	4.095	-0.239
Year 5	2057	4.900	3.437	-1.463	1854	3.768	4.136	0.368

The sponsor pre-specified limits against which changes in lab values were checked. The rates of patients exceeding these pre-specified limits are shown in the following table.

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**Table 88: Sponsor's Patient's Exceeding Predefined Limits of Change in Lab Test Values**

Predefined Laboratory Test	Limit of Change	Treatment	Number <sup>†</sup> /Total <sup>‡</sup>	(%)
Hemoglobin (g/L)	Decrease $\geq$ 35	Atenolol	52/3480	(1.5)
		Losartan	100/3636	(2.8)
Creatinine ( $\mu$ mol/L)	Increase >35	Atenolol	363/4202	(8.6)
		Losartan	451/4277	(10.5)
SGPT (ALT) ( $\mu$ kat/L)	Increase >1.0	Atenolol	87/3058	(2.8)
		Losartan	74/3149	(2.3)
SGPT (ALT)—US (mU/mL)	Increase >25	Atenolol	22/633	(3.5)
		Losartan	29/711	(4.1)
Glucose (mmol/L)	Increase >3.33	Atenolol	496/3734	(13.3)
		Losartan	394/3897	(10.1)
Uric acid ( $\mu$ mol/L)	Increase >60	Atenolol	2480/3691	(67.2)
		Losartan	1610/3862	(41.7)
Sodium (mmol/L)	Increase >10	Atenolol	21/4105	(0.5)
		Losartan	14/4209	(0.3)
	Decrease >10	Atenolol	61/4105	(1.5)
		Losartan	57/4209	(1.4)
Potassium (mmol/L)	Increase >1.0	Atenolol	125/4094	(3.1)
		Losartan	155/4195	(3.7)
	Decrease >1.0	Atenolol	185/4094	(4.5)
		Losartan	132/4195	(3.1)
Total cholesterol (mmol/L)	Increase >1.0	Atenolol	708/3695	(19.2)
		Losartan	601/3861	(15.6)
HDL cholesterol (mmol/L)	Decrease >0.25	Atenolol	1933/3691	(52.4)
		Losartan	1643/3856	(42.6)

<sup>†</sup> Number of patients with both a valid prestudy and poststudy value.  
<sup>‡</sup> Total number of patients with changes in laboratory values that exceeded predefined limits.  
 Changes from baseline were limited only to valid treatment values, which were from laboratory records on-drug or off-drug no more than 14 days.

COMMENT: The atenolol group shows small increases in serum glucose and uric acid while the losartan group shows small decreases in serum hemoglobin and urine microalbumin. All of these changes appear to be related to differences in clinical event rates except the changes in urine microalbumin. The atenolol group had more incident cases of diabetes and gout adverse events. The losartan group had more anemia adverse events. The reduced urine microalbumin does not appear to be associated with a reduction in renal adverse events.

#### 8. Electrocardiograms

The NDA does not provide data or discuss changes in electrocardiograms other than the changes in left ventricular hypertrophy criteria in the Efficacy section.

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#### 9. Overdose

Overall 72 overdoses were reported in 69 atenolol patients and 93 overdoses were reported in 88 losartan patients. The overdoses are difficult to evaluate because other drugs may have been taken in addition to the study drug. Other AEs were reported with the overdose in about fourth of the losartan cases and included hypotension, dizziness, and vertigo. Details of the overdoses, e.g., dosages, are not provided.

#### 10. Special Populations

Elderly patients ( $\geq 65$ ) experienced more serious AEs than younger ( $< 65$ ) patients. For SAEs the rates in the elderly were 39% for atenolol and 41% for losartan; for younger patients the SAE rates were about 32% for both atenolol and losartan. Discontinuations due to AEs also were more frequent in the elderly and, as in the study as a whole, were more common with atenolol. In the elderly 21% of atenolol and 15% of losartan patients discontinued due to AEs; 14% of younger atenolol and 10% of younger losartan patients discontinued due to AEs. Overall about 95% of patients of either age or treatment group experienced at least one AE.

Males and females experienced AEs at similar rates in both treatment groups. Overall about 94% of males in both groups and 96% of females experienced one or more AEs. SAEs were slightly more frequent in males on losartan (38%) than on atenolol (37%) and than females of either treatment group (36%). Both males and females had fewer discontinuations due to AEs with losartan.

Blacks on atenolol had fewer AEs overall (90%) and SAEs (28%) than blacks on losartan. Rates of AEs and SAEs for blacks on losartan were very similar to rates for whites. More blacks on losartan (16%) than on atenolol (13%) discontinued treatment due to an AE. Rates of drug-related AEs were similar in blacks on losartan (39%) and on atenolol (40%).

COMMENT: The most pertinent finding regarding AEs in special populations is that blacks on atenolol had fewer AEs and SAEs. While it is conceivable that the same mechanism that led to better efficacy with atenolol in blacks also produced fewer AEs, it is simpler to conclude that blacks on atenolol were lower risk.

#### C. Summary of Critical Safety Findings and Limitations of Data

The tolerability of atenolol and losartan appears comparable when judged by total adverse event (AE) rates (about 95% of patients in each group or 39,161 vs. 39,623 AEs), AEs leading to hospitalization (34% vs. 35%), and serious adverse (SAE) event rates (38% vs. 38%). Only for AEs leading to discontinuation (losartan 13% vs. atenolol 18%)

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and investigator-classified drug-related AEs (losartan 37% vs. atenolol 45%) does losartan appear to be superior to atenolol. While these rates may appear high, they must be considered in view of the fact that this was a prolonged research study (4+ years) in high risk patients with mandated reporting of any suspected AE. Overall both drugs appeared to be tolerated well.

The common, expected AEs included bradycardia with atenolol (9%) and dizziness with both drugs (about 16%). Bradycardia was the most frequent reason, and fatigue and dyspnea were other common reasons, for discontinuation with atenolol.

One unexpected AE is that atrial fibrillation led to discontinuation in about 1% of atenolol patients vs 0.5% of losartan patients. Atrial fibrillation overall was only a slightly more common AE with atenolol (1.5/100 PEY) than with losartan (1.3/100 PEY). (PEY = person exposure year.) While the rates of and difference in reported atrial fibrillation are not great, see the discussion of atrial fibrillation in the Efficacy section for the possible implications regarding stroke.

An AE not totally unexpected but probably unappreciated is anemia with losartan. Losartan has a label caution regarding small decreases in hemoglobin. Such a decrease (about -0.5 gm/dL vs. -0.2 gm/dL with atenolol) was seen in this study. Losartan also was associated with more anemia AEs (1.7 vs. 1.2/100 PEY) and hospitalizations for anemia.

Atenolol also led to slightly greater increases uric acid (about 1 mg/dL) and glucose (about 4 mg/dL). These lab value changes appear to be associated with slightly increased AE rates for gout (1.1 vs. 0.6/100 PEY) and diabetes mellitus (1.7 vs 1.3/100 PEY) respectively.

The most pertinent finding regarding AEs in special populations is that blacks on atenolol had fewer AEs and SAEs. While it is conceivable that the same unknown mechanism that led to better efficacy with atenolol in blacks also produced fewer AEs, it is simpler to conclude that blacks in the atenolol group were lower risk.

The limitation of this study is that it is not a simple comparison of losartan to atenolol. The comparison is between regimens including losartan or atenolol and other antihypertensives, particularly hydrochlorothiazide. While one can presume that differences in AEs in one treatment group are probably related to the unique comparator in that treatment group, one is less confident that real differences in AE rates aren't obscured by the multiple co-treatments.

AE relationships to drug and discontinuations for AEs are subjective investigator judgments. Given that rates of all AEs, SAEs, and AEs leading to hospitalization were similar, the review wonders whether the differences in drug-related and AEs leading to discontinuation are real differences in tolerability or subjective judgments influenced by other factors. Reduction in heart rate was common with atenolol as would be expected.

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The reviewer suspects that investigators might have been more likely to call another AE drug-related or to discontinue treatment in patients with reduced heart rate or borderline or frank bradycardia. Overall the reviewer concludes that the losartan regimen was slightly better tolerated than the atenolol regimen in the LIFE study, but the evidence is not overwhelming.

### VIII. Dosing, Regimen, and Administration Issues

The LIFE study used standard dosages and once daily dosing regimens for all three specified study drugs (atenolol, losartan, and hydrochlorothiazide.) The dosing adjustment scheme in the protocol with a target blood pressure of <140/90 was reasonable. The once daily dosing is the most convenient for patients and approved for all three drugs.

While the dosing and regimen are reasonable, there are several issues regarding them:

- All three drugs are approved for once daily dosing but may be more effective with twice daily dosing. Could differences in 24-hour blood pressure control contribute to the outcome differences?
- The blood pressure goal was reasonable but not typically achieved. Would the outcome differences persist if blood pressure control had been more aggressive?
- Atenolol was discontinued more frequently than losartan. Was this due to real efficacy or safety problems or a perception of problems heightened by bradycardia? Would the outcomes be the same if atenolol and losartan exposures were equal?
- Additional antihypertensive use was not controlled. How much of the outcome difference is due to additional antihypertensive use?

COMMENT: Such what-if issues are easy to generate but hard to answer. All the questions above are unanswerable by the LIFE study. The reviewer's interpretation of the LIFE study as conducted is that it is a reasonable comparison of antihypertensive regimens including losartan to antihypertensive regimens including atenolol. The level of control and use of atenolol are similar to what is achieved in current practice. The results should be applicable to current practice.

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#### **IX. Use in Special Populations**

##### **A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation**

The LIFE study included a majority (54%) of females. The sponsor examined gender effects for both efficacy and safety. Neither the sponsor nor the reviewer identified differential effects by gender. The results of the LIFE study appear to be equally applicable to both genders.

##### **B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy**

The Efficacy section contains extensive evaluations of differential effects by age and ethnicity. The apparent beneficial effect of losartan overall appears to be eliminated or even reversed in blacks. Losartan appears to be more effective in the elderly (age  $\geq 65$ ). Please see the Efficacy section for detailed discussion of these assertions.

The Safety section contains a brief evaluation of differential safety findings by age and ethnicity. Adverse events are more common in the elderly but the patterns of adverse events for the two treatment groups are not different. Blacks in the atenolol group had fewer AEs and SAEs than blacks in the losartan group, while the rates of AEs and SAEs were similar for whites in both treatment groups and blacks in the losartan group. Please see the Safety section for the specifics.

##### **C. Evaluation of Pediatric Program**

The sponsor is requesting a waiver of pediatric studies for this indication with the following justification:

“Pursuant to 21 CFR 314.55(c), Merck is requesting a full waiver to the pediatric data requirement for the use of losartan to reduce the risk of cardiovascular morbidity and mortality in pediatric patients with hypertension and LVH. The rationale for this full waiver is that necessary studies are impossible or highly impractical because 1) the number of such patients is very small and 2) the occurrence of stroke and myocardial infarction in such patients is very rare.

“LIFE was an outcome study with a composite endpoint of cardiovascular death, myocardial infarction, and stroke. Since stroke and myocardial infarction are rare in pediatric patients with hypertension and LVH (Sorof, Cardwell et al. 2002), it would be impractical or impossible to conduct a study with sufficient power to measure a treatment effect in this population.

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“Please note that the FDA previously issued a Written Request for pediatric studies for the use of losartan in children with hypertension and that Merck submitted a sNDA fully responding to the WR. The FDA Pediatric Exclusivity Board determined on March 20, 2000, that Merck’s sNDA for losartan pediatric studies met the terms of the agency’s Written Request. Proposed labeling changes based on the sNDA are still under review at the FDA.”

COMMENT: The reviewer believes that the request for a waiver of pediatric studies for this new indication is justified.

#### **D. Comments on Data Available or Needed in Other Populations**

Two issues raised by the LIFE study are important ones that need additional data to confirm or refute:

- Is the beneficial effect of losartan reversed vs. reduced or neutral in blacks? The reviewer believes that this question can not be answered definitively with the LIFE data. There is probably no other existing data that can answer definitively, so another trial is needed.
- Is atenolol associated with more atrial fibrillation and strokes? There may be data from existing studies using atenolol for hypertension or angina that could provide additional evidence to answer this question.

### **X. Conclusions and Recommendations**

#### **A. Conclusions**

The LIFE study is not a simple study to interpret. If one focuses on the primary composite endpoint alone, then the LIFE study was successful in showing that regimens including losartan are superior to regimens including atenolol in the LIFE study population. However, the statistical significance is not extreme and the results are not terribly robust. There are several factors (differences in blood pressure control, differences in endpoint determinations, differences in study drug usage) that could make the results even more uncertain than the simple p value indicates. Overall, however, the reviewer believes that it is most reasonable to stick with the simple analysis of the primary composite, substituting only the Division’s recommendation of incorporating total mortality rather than cardiovascular mortality. By this standard the LIFE study was successful.

The LIFE study is the only study supporting the new indication. However, because the magnitude of the treatment effect (a 10% risk reduction) is reasonable and the endpoint is

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vital, the reviewer believes that a description of the beneficial effect of losartan 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. 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 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.

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

- Losartan appears to be more effective in the elderly. Losartan may be less effective in males younger than 65.
- Losartan appears to be more effective in patients with isolated systolic hypertension at baseline. Isolated systolic hypertension is more frequent in the elderly.
- Losartan appears to be more effective in patients with diabetes at baseline. Losartan 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.

This large, long-term study helps to define better the safety profiles of both losartan and atenolol. Overall the LIFE study confirms the tolerability of both drugs. The one additional detail regarding losartan safety that should be considered for the label is the rate of anemia. For atenolol, the increases rates of gout and diabetes should be considered for the label. The possible association of atenolol with increased rates of atrial fibrillation needs verification before being incorporated into labeling.

### **B. Recommendations**

The reviewer recommends that the new indication be approved as “to reduce the risk of death and cardiovascular morbidity as measured by the combined incidence of death, stroke, and myocardial infarction in hypertensive patients with left ventricular hypertrophy.” The reviewer will add more detailed recommendations on labeling in an addendum to this review.

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Two issues need follow-up:

- The LIFE study raises a question regarding whether the beneficial effect of losartan is reversed in blacks. Other data sources should be sought to help address this issue.
- The possible association of atenolol use with increased rates of atrial fibrillation and strokes needs verification. Other data sources should be consulted to address this issue as well.

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