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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 28: Sponsor's Last Vital Signs Using Primary Endpoint Censoring Rule

	Atenolol	Losartan	Difference
SBP	145.4	144.1	1.3
DBP	80.9	81.3	-0.4
PP	64.5	62.8	1.7
SBP change	-29.1	-30.2	1.1
DBP change	-16.8	-16.6	-0.2
PP change	-12.4	-13.6	1.2
SBP SD	17.2	16.4	0.8
DBP SD	9.5	9.6	-0.1
HR	66	72.1	-6.1
HR change	-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 29: Sponsor's Primary Endpoints with SBP Time-Varying

	Crude Rate				Covariates in the Model	Hazard Ratio	95% CI		p-Value
	Losartan (N=4695)		Atenolol (N=4588)				Lower	Upper	
	n	(%)	n	(%)					
Composite	508	(11.0)	588	(12.8)	Systolic BP Treatment	1.007	1.003	1.010	<0.001**
Cardiovascular mortality	204	(4.4)	234	(5.1)	Systolic BP Treatment	0.861	0.765	0.970	0.014*
MI (fatal/nonfatal)	198	(4.3)	188	(4.1)	Systolic BP Treatment	0.999	0.994	1.005	0.775
Stroke (fatal/nonfatal)	232	(5.0)	309	(6.7)	Systolic BP	1.009	1.003	1.014	0.003**
					Treatment	1.063	0.870	1.297	0.551
					Treatment	1.012	1.007	1.017	<0.001**
					Treatment	0.755	0.637	0.895	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 30: Sponsor's Primary Endpoints with DBP Time-Varying Covariate

	Crude Rate				Adjusted [†] Hazard Ratio	95% CI		p-Value [†]
	Losartan (N=4605)		Atenolol (N=4588)			Lower	Upper	
	n	(%)	n	(%)				
Composite	508	(11.0)	588	(12.8)	0.858	0.762	0.966	0.012*
Cardiovascular mortality	204	(4.4)	234	(5.1)	0.879	0.728	1.060	0.177
MI (fatal nonfatal)	198	(4.3)	188	(4.1)	1.062	0.870	1.297	0.555
Stroke (fatal nonfatal)	232	(5.0)	309	(6.7)	0.741	0.625	0.879	<0.001**

* p-Values <0.05.
 ** p-Values <0.01.
 † The 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 diastolic blood pressure as time-varying covariate.

Table 31: Sponsor's Primary Endpoints with PP Time-Varying Covariate

	Crude Rate				Adjusted [†] Hazard Ratio	95% CI		p-Value [†]
	Losartan (N=4605)		Atenolol (N=4588)			Lower	Upper	
	n	(%)	n	(%)				
Composite	508	(11.0)	588	(12.8)	0.871	0.773	0.981	0.023*
Cardiovascular mortality	204	(4.4)	234	(5.1)	0.876	0.726	1.057	0.167
MI (fatal nonfatal)	198	(4.3)	188	(4.1)	1.083	0.887	1.323	0.432
Stroke (fatal nonfatal)	232	(5.0)	309	(6.7)	0.765	0.645	0.907	0.002**

* p-Values <0.05.
 ** p-Values <0.01.
 † The 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 pulse pressure as time-varying 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 32: 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 33: 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 for the vast majority of patients 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.

Four Danish centers did perform ambulatory blood pressure monitoring (ABPM) in 82 patients at baseline and again at year 1. The sponsor provided the ABPM data from these patients in a submission date December 20, 2002, and a brief summary of the data. While the curves of blood pressure over 24-hours appear to be parallel in the atenolol and losartan groups, the data suggest that these patients are not representative of the study patients as a whole: "at year 1 both systolic and diastolic blood pressure were

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approximately 3 mm Hg lower in the atenolol group than in the losartan group.” Recall that in the study as a whole SBP was slightly lower in the losartan group while DBP was slightly higher in the atenolol group, particularly at the 1 year visit. (See Figure 6.) This Danish substudy does not appear to be representative of the study as a whole.

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.

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 34: 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 35: 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

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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.

Table 36: 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 37: 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 38: 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%

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For the vast majority (96 percent) of these patients SBP was poorly controlled, i.e., SBP ≥ 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.

Table 39: 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 40: 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.

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Table 41: 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

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 42: 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 43: 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 44: 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%

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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.

Table 45: 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 helpful to have BP measurements at other times during the dosing interval. The Danish ABPM substudy results do not provide information relevant to the whole study.

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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 some 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.

Table 46: Reviewer's Numbers of Stroke Endpoints, Strokes, and Patients with Strokes

	Atenolol	Losartan
Primary endpoint stroke	266	197
Primary endpoint stroke or stroke death	295	218
Adjudicated strokes	368	267
Patients with adjudicated strokes	309	232
% of patients with adjudicated 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. Note that the reviewer has updated the table above and all subsequent tables in this section of the amended review to include five patients for whom the adjudicated stroke was reported only as a stroke death that were not included as strokes in the original review. The updates are minimal, e.g., the percent of patients with adjudicated strokes to one decimal place in the table above does not change at all.

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 47: Reviewer's Rates of Patients with Stroke 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, excluding 11 strokes not classified, is shown in the following table.

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Table 48: 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.

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 and endpoint narratives. As a surrogate for embolic stroke the reviewer examined stroke rates in patients with atrial fibrillation or flutter, reported by baseline history, as an adverse event, or on the annual ECGs. (Note that the reviewer was not able to include the data on atrial fibrillation on ECGs in the original review.) Rates patients with evidence of atrial fibrillation or flutter are shown in the following table.

Table 49: Reviewer's Rates of Patients with Evidence of Atrial Fibrillation or Flutter

	Atenolol	Losartan
History	4.0%	3.5%
Adverse event	7.9%	6.8%
ECG	7.9%	5.7%
Any	12.5%	10.6%

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 (17%) and Danish and Swedish patients (12 and 13% respectively) and less frequent among the rest (e.g., US blacks 7%).

In the LIFE study electrocardiograms (ECGs) were obtained yearly. These ECGs should represent the most objective evidence of atrial fibrillation rates for the study. The annual ECGs were read by a central laboratory and encoded per the Minnesota code. The Minnesota code for atrial fibrillation and flutter is 8-3. In the following discussion this code reported on the annual ECGs is referenced as "afib".

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At baseline 1.6% of atenolol patients and 1.3% of losartan patients had afib on their ECGs. Compare these rates to the rates of prior history of atrial fibrillation: 4.0% in atenolol patients and 3.5% in losartan patients. The atenolol group shows a slight excess of afib by either measure.

Rates of afib increased continuously during the study period. The rates at the annual examinations are shown in the following figure.

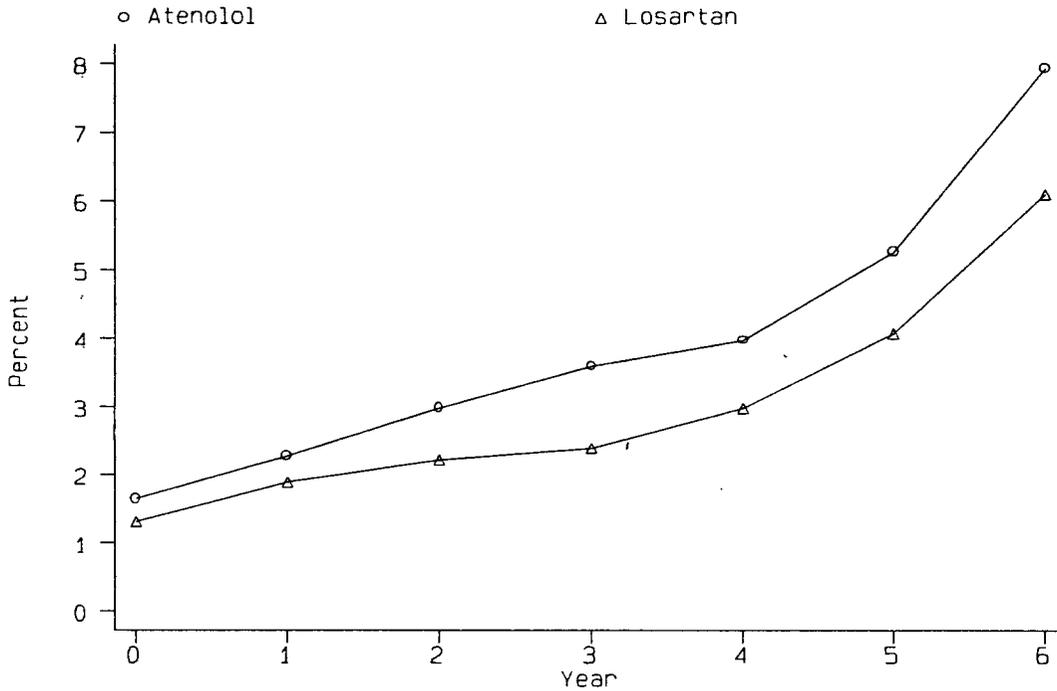


Figure 7: Rates of Atrial Fibrillation/Flutter on ECG

The rates in the previous figure are based on the ECGs done at each timepoint. The cumulative rates of patients having at least one ECG showing afib are shown in the following figure. Overall 7.9% of atenolol patients and 5.7% of losartan patients had afib on at least one of their ECGs.

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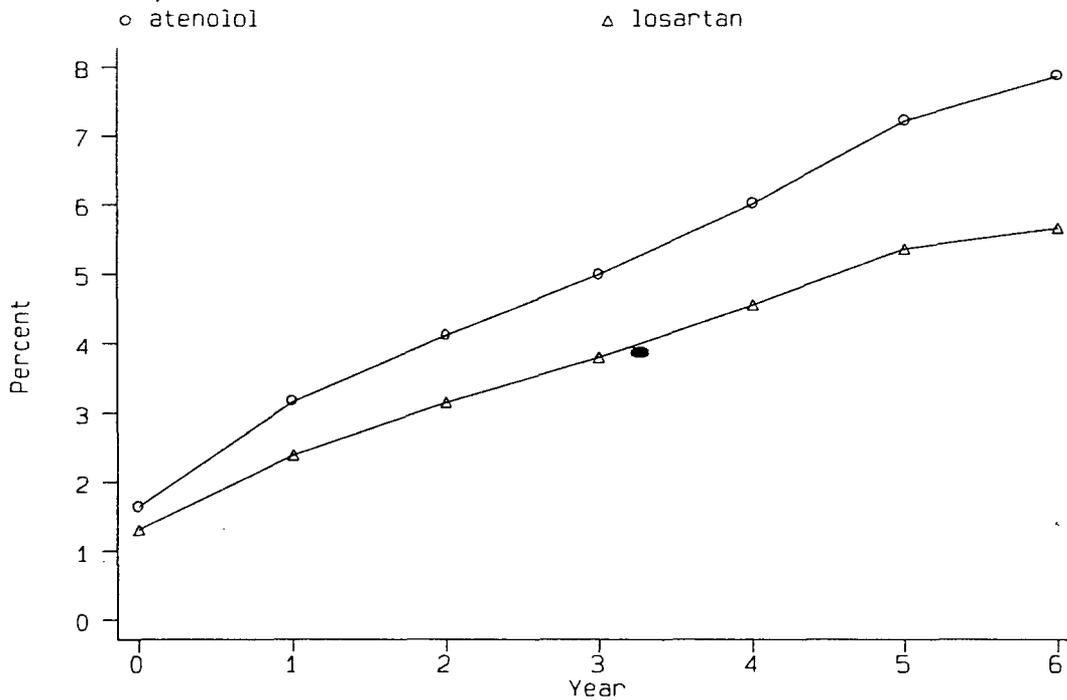


Figure 8: Cumulative Rates of Patients with at Least One ECG Showing Atrial Fibrillation/Flutter

COMMENT: The AE and ECG data suggest that atenolol is associated with more atrial fibrillation than losartan. The one confounder is that the baseline rates of atrial fibrillation are slightly higher in the atenolol group than in the losartan group.

Patients with evidence of atrial fibrillation were older (mean age 70.0 vs 66.5), more frequently male (53 vs. 45%), higher risk (mean Framingham risk score 24.9 vs. 22.1), with more isolated systolic hypertension (19 vs 14%), and had more frequent histories of stroke (7 vs. 4%), myocardial infarction (9 vs. 6%), heart failure (6 vs. 1%), and diabetes (18 vs. 12%) than patients without evidence of atrial fibrillation. These baseline factors were not different by evidence of atrial fibrillation between the atenolol and losartan groups.

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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. 32% of the atenolol and 25% of the losartan patients with strokes had evidence of atrial fibrillation. Strokes associated with atrial fibrillation were more frequent with atenolol than with losartan as shown in the following table.

Table 50: Reviewer's Rates of Patients with Stroke by Evidence of Atrial Fibrillation

	Atenolol	Losartan
No atrial fibrillation	5.2%	4.3%
Atrial fibrillation	17.3%	11.7%
Total	6.7%	5.0%

Stroke rates were highest in the atenolol patients with afib, intermediate in the losartan patients with afib, and slightly higher in the atenolol patients without afib (5.3%) than in the losartan patients without afib. Using ECG data alone the difference in rates is even more dramatic as shown in the following table.

Table 51: Rates of Patients with Strokes by Atrial Fibrillation/Flutter on ECG

	No afib	Afib
Atenolol	5.6%	20.5%
Losartan	4.5%	13.4%

Afib = Atrial fibrillation/flutter (Minnesota code 8-3) on any ECG

The majority 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.

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.

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Table 52: Reviewer's Mean Ages by Stroke and Atrial Fibrillation

	Atenolol	Losartan
Neither	66.3	66.5
Atrial fibrillation	69.7	69.7
Stroke	70.1	68.7
Both	72.1	71.2
Total	66.9	66.9

Table 53: Reviewer's Rates of Poor Control by Stroke and Atrial Fibrillation

	Atenolol	Losartan
Neither	22%	19%
Atrial fibrillation	26%	25%
Stroke	42%	38%
Both	49%	40%
Total	24%	21%

Table 54: Reviewer's Rates of Aspirin Use by Stroke and Atrial Fibrillation

	Atenolol	Losartan
Neither	30%	30%
Atrial fibrillation	48%	50%
Stroke	61%	70%
Both	63%	68%
Total	34%	34%

Table 55: Reviewer's Rates of Warfarin Use by Stroke and Atrial Fibrillation

	Atenolol	Losartan
Neither	3%	2%
Atrial fibrillation	41%	36%
Stroke	13%	7%
Both	55%	47%
Total	9%	6%

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 stroke. One metric of stroke severity is whether the stroke is associated with death. Strokes were followed by death within 30 days in 111 patients, 64 in the atenolol group and 47 in the losartan group. Death following stroke was similar in both groups, occurring within 30 days in 20.7% of atenolol patients with strokes and in 20.3% of losartan patients with strokes. (Note: The original review counted only strokes that were primary endpoints.)

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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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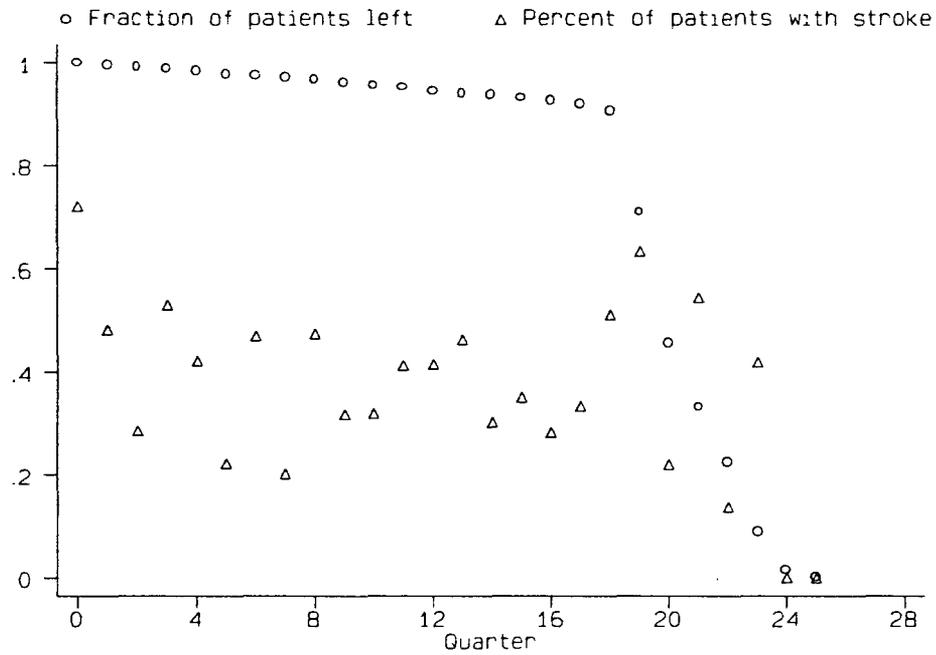


Figure 9: Reviewer's Quarterly Stroke Rate for Atenolol Group

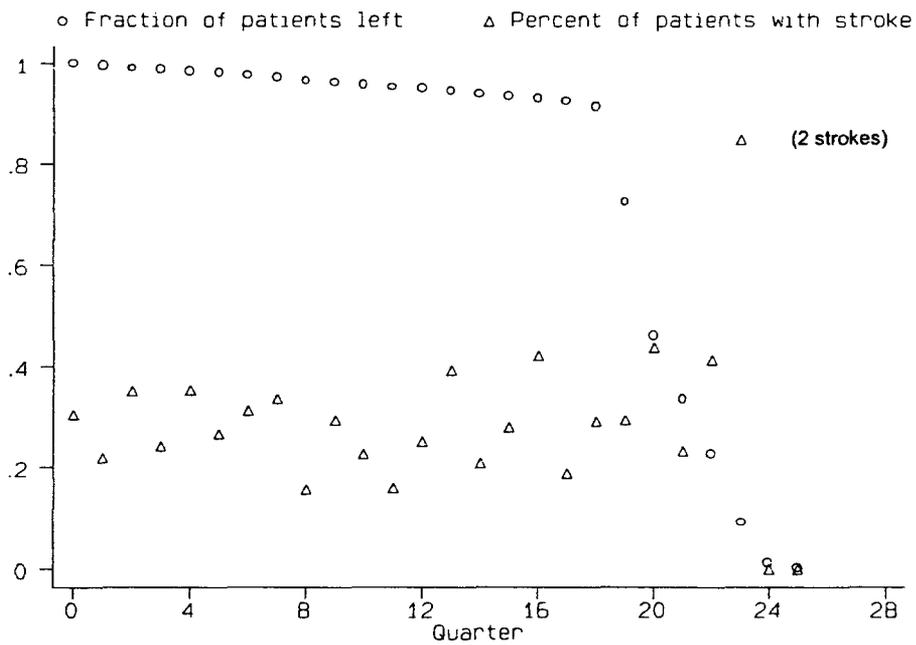


Figure 10: Reviewer's Quarterly Stroke Rate for Losartan Group

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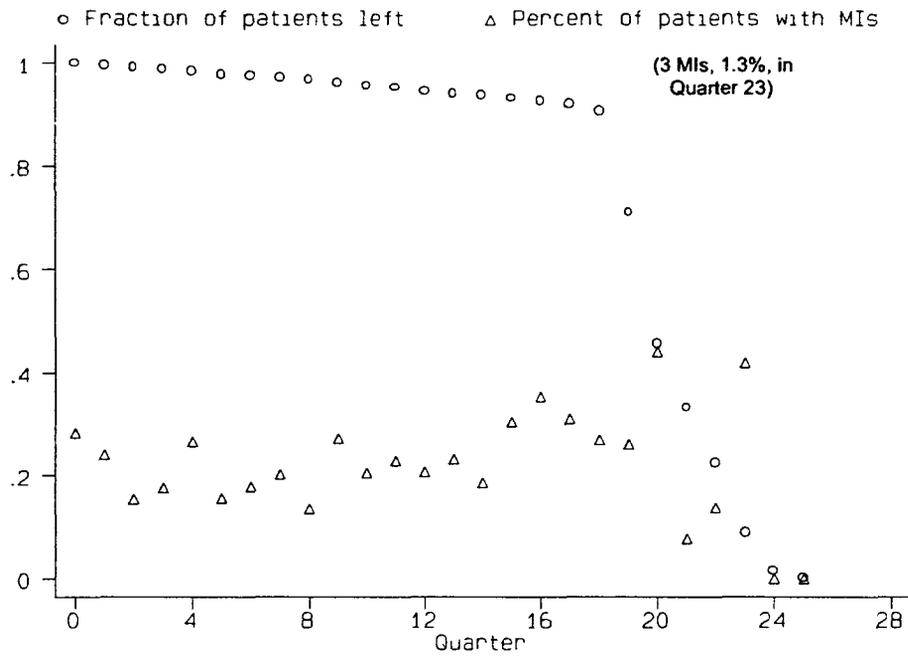


Figure 11: Reviewer's Quarterly MI Rate for Atenolol Group

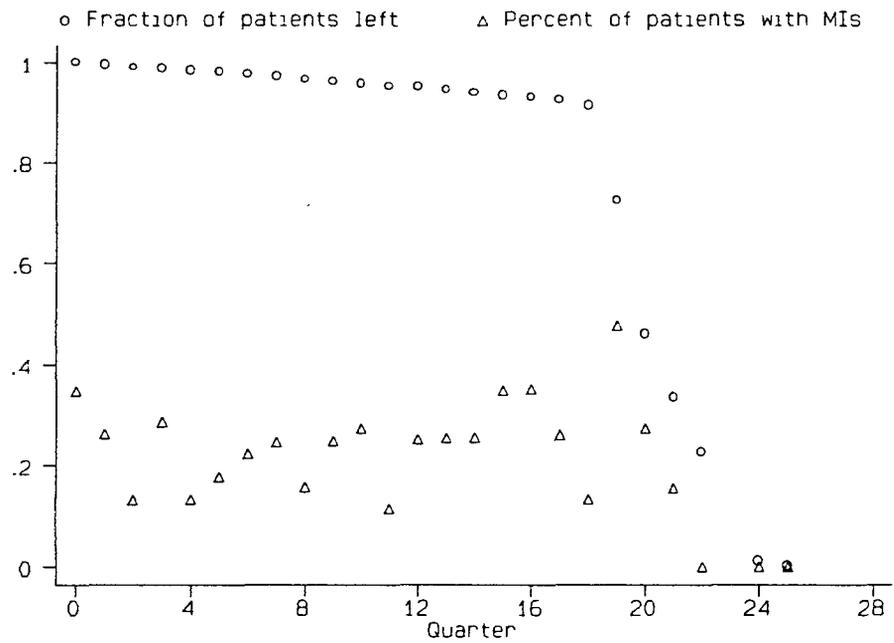


Figure 12: Reviewer's Quarterly MI Rate for Losartan Group

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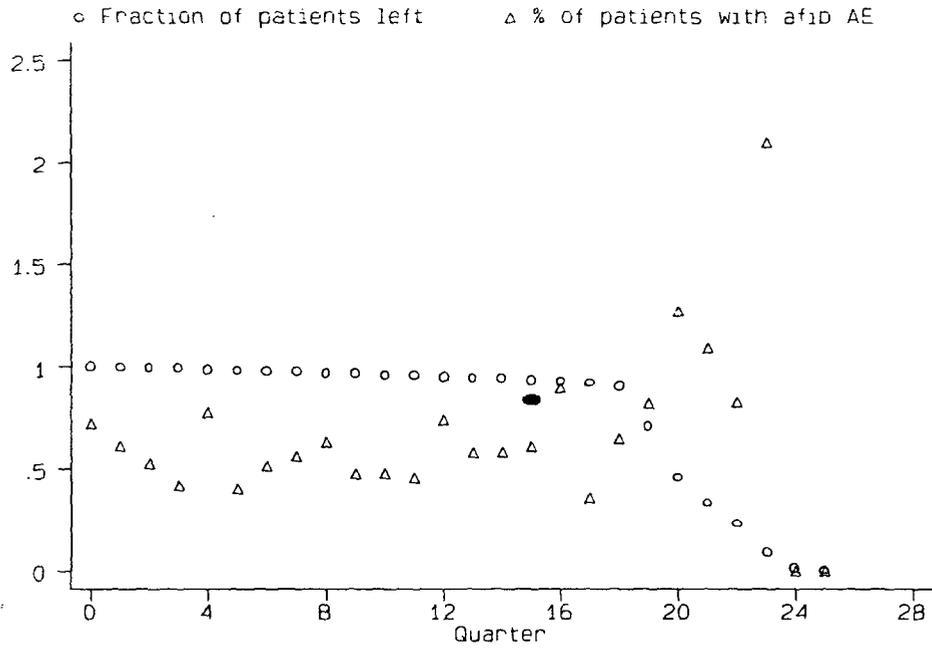


Figure 13: Reviewer's Quarterly Atrial Fibrillation Adverse Event Rates for Atenolol Group

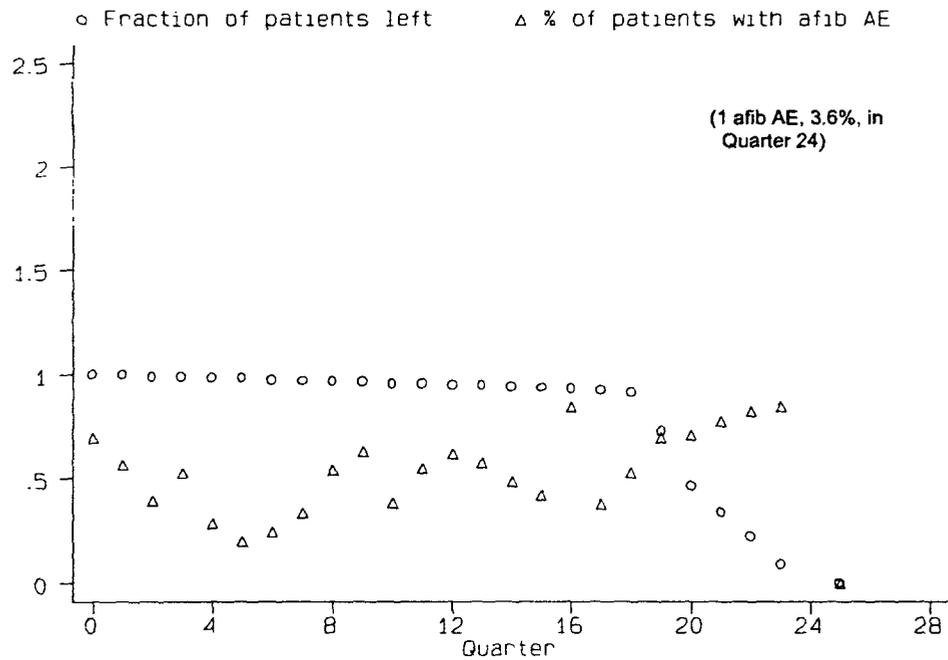


Figure 14: Reviewer's Quarterly Atrial Fibrillation Adverse Event Rates for Losartan Group

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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 30 events, 23 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 138 events, 83 on atenolol and 55 on losartan. Of these latter dose changes 9 were initial dosing, 5 were increases in dosage, and 4 were restarts of dosing. These latter changes were evenly distributed between the two groups. Discontinuations were more frequent with atenolol (84 vs. 46). (Note: The original review included erroneous statistics on dose changes preceding strokes.)

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 56: 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 57: 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 58: 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 59: 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 60: 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 61: Sponsor's Primary Composite Endpoint and Components for Blacks and Non-Blacks

Endpoint	Losartan (N=271)		Atenolol (N=263)		Kaplan-Meier Rates								Hazard Ratio	95% CI		p Value
	Rate	n/N	Rate	n/N	Losartan				Atenolol					Lower	Upper	
	1-Yr	2-Yr	3-Yr	4-Yr	1-Yr	2-Yr	3-Yr	4-Yr								
Comparison of Primary Composite Endpoint Secondary Endpoints																
Cardiovascular Mortality	1.1	22 (8.1)	1.1	15 (5.7)	2.5	3.8	5.5	6.7	3.1	3.9	4.8	4.9	1.64	0.764	2.9%	0.244
MI (fatal/nonfatal)	1.8	15 (4.8)	0.5	6 (2.3)	1.6	2.4	2.4	4.1	0.4	0.4	1.8	1.8	2.74	0.786	5.4%	0.141
Stroke (fatal/nonfatal)	21.9	26 (9.5)	1.0	12 (4.4)	2.3	4.5	5.8	7.9	2.0	3.3	3.7	4.6	2.1%	1.070	4.4%	0.036*
Overall Non-Black Patients																
Endpoint	Losartan (N=4354)		Atenolol (N=4325)		Kaplan-Meier Rates								Hazard Ratio	95% CI		p Value
	Rate	n/N	Rate	n/N	Losartan				Atenolol					Lower	Upper	
	1-Yr	2-Yr	3-Yr	4-Yr	1-Yr	2-Yr	3-Yr	4-Yr								
Comparison of Primary Composite Endpoint Secondary Endpoints																
Cardiovascular Mortality	8.7	182 (4.2)	10.5	239 (5.5)	0.6	1.5	2.1	3.1	0.7	1.7	2.8	3.7	0.842	0.692	1.025	0.067
MI (fatal/nonfatal)	9.6	185 (4.3)	8.5	182 (4.2)	0.8	1.7	2.4	3.5	0.9	1.7	2.4	3.3	1.0%	0.844	1.2%	0.734
Stroke (fatal/nonfatal)	11.2	206 (4.8)	14.7	297 (6.9)	1.6	2.2	3.1	3.9	1.9	3.1	4.1	4.7	0.7%	0.586	1.4%	0.001**

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. Note in particular the age and gender differences.

Table 62: Reviewer's Selected Baseline Characteristic in Blacks

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

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

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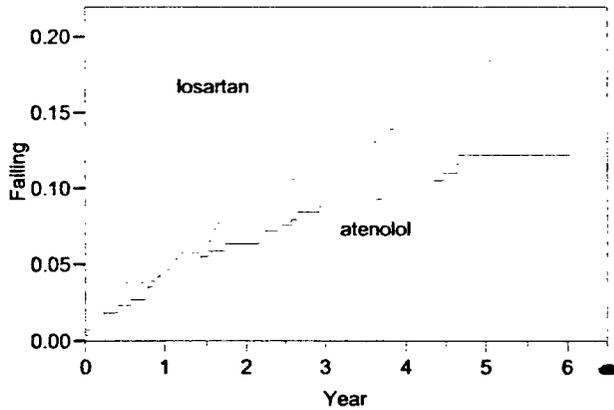


Figure 15: Reviewer's Kaplan-Meier Plot of Primary Composite Endpoint in Blacks

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.

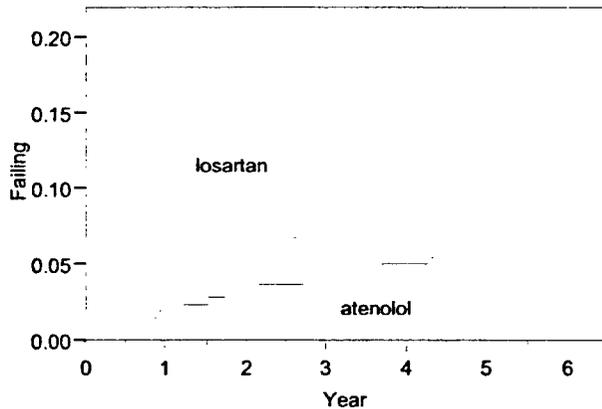


Figure 16: Reviewer's Kaplan-Meier Plot of Strokes in Blacks

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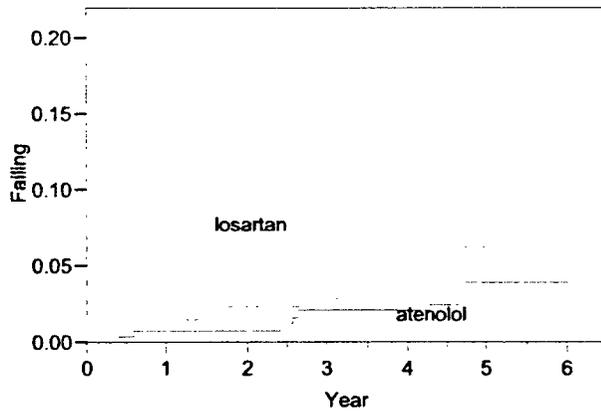


Figure 17: Reviewer's Kaplan-Meier Plot of Myocardial Infarctions in Blacks

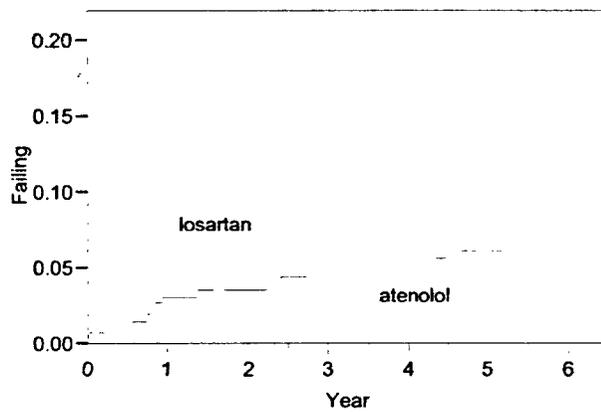


Figure 18: Reviewer's Kaplan-Meier Plot of CV Mortality in Blacks

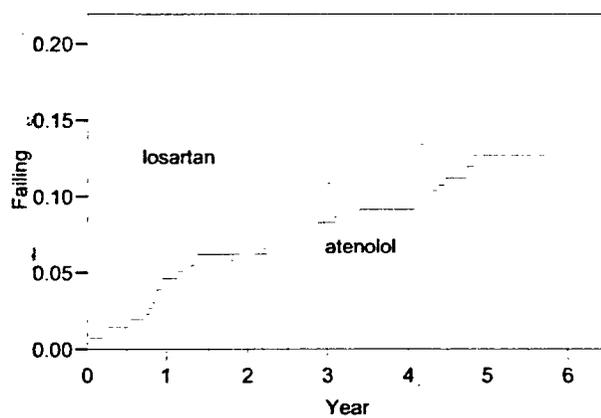


Figure 19: Reviewer's Kaplan-Meier Plot of Total Mortality in Blacks

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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 63: 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 43 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/m² in men and from 100 to 125 g/m² in women.

Table 64: Sponsor's Baseline LVMI and Changes at Final Visit

	Atenolol			Losartan		
	N	Baseline	Change	N	Baseline	Change
All	459	123	-18	457	125	-22
Black	65	130	-19	64	126	-16
US white	55	123	-16	50	121	-19
All white	394	121	-18	393	125	-23
Female	184	115	-15	193	119	-20
Male	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 65: 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 66: 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 67: 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 68: 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 69: 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 70: 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 71: 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 72: Sponsor's Endpoint Results for Baseline Diabetics

	Crude Rate						Kaplan Meier Rates								Hazard Ratio	95% CI		p-Value
	Losartan (N=580)			Atenolol (N=600)			Losartan				Atenolol					Lower	Upper	
	Rate	n	(%)	Rate	n	(%)	1-Yr	2-Yr	3-Yr	4-Yr	1-Yr	2-Yr	3-Yr	4-Yr				
Composite	39.2	193	33.3	43.6	239	39.8	3.9	7.9	9.5	14.5	6.6	9.3	14.2	18.1	0.755	0.585	0.975	0.014
Cardiovascular mortality	13.6	68	11.7	21.8	119	19.0	0.9	1.4	2.1	4.3	1.5	3.0	5.4	6.8	0.634	0.422	0.951	0.028*
Myocardial infarction	15.2	77	13.3	18.7	99	16.3	1.6	2.6	3.3	5.0	2.5	3.2	5.5	7.4	0.829	0.548	1.243	0.373
Stroke (fatal/nonfatal)	19.0	97	16.7	24.5	126	20.7	2.2	4.7	5.4	7.6	3.7	4.9	6.9	8.9	0.788	0.546	1.138	0.204
Total mortality	22.5	114	19.8	37.2	194	32.0	1.5	2.2	4.7	7.8	2.6	4.9	8.6	11.6	0.813	0.443	0.839	0.024*
Hospitalization due to angina	11.1	56	9.6	11.1	59	9.8	1.7	2.4	3.2	4.3	1.3	1.9	2.8	4.4	1.058	0.677	1.749	0.828
Hospitalization due to heart failure	11.8	60	10.4	20.7	110	18.3	1.0	2.3	3.5	4.8	2.5	4.6	6.5	8.4	0.594	0.384	0.914	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 ratios (expressed as the ratio 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 73: Sponsor's Endpoint Results for Patients with Isolated Systolic Hypertension

	Crude Rate						Hazard ² Ratio	95% CI		p-Value ¹
	Losartan (N=660)			Atenolol (N=665)				Lower	Upper	
	Rate ³	n	(%)	Rate ³	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.
¹ Per 1000 patient-years of follow-up.
² Baseline LVH degree (Cornell product and S-L) and baseline Framingham risk score are included in Cox proportional hazard model as covariates.
³ 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 74: 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 these other secondary endpoints are shown in the following table.

Table 75: Sponsor's Other Secondary Endpoints Classified by the Endpoint Classification Committee

	Crude Rate						Kaplan-Meier Rates								Hazard Ratio	95% CI		p-Value ^c
	Losartan (N=4567)			Atenolol (N=4568)			Losartan				Atenolol					Lower	Upper	
	Rate ^a	n	n (%)	Rate ^a	n	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	6.5	1.3	2.7	4.0	6.7	0.592	1.783	1.131	0.128
Hospitalization due to angina (including probable MI)	7.4	160	(3.5)	8.8	191	(4.1)	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	1.208	0.765
Coronary revascularization	7.8	169	(3.7)	7.8	168	(3.7)	0.9	1.5	2.2	3.1	0.8	1.3	2.1	2.9	1.022	0.826	1.265	0.941
Noncoronary arterial vascular surgery	4.7	102	(2.2)	6.0	129	(2.8)	0.5	0.9	1.3	1.8	0.5	1.0	1.6	2.3	0.809	0.624	1.049	0.118
Cardiac arrest, resuscitated ^b	0.5	11	(0.2)	0.5	11	(0.2)												

^a Per 1000 patient-years of follow-up
^b Baseline left ventricular hypertrophy degree (Cornell product and Sokolow-Lyon) and baseline Framingham risk score are included in Cox proportional hazard model as covariates
^c The p-values and estimates of hazard ratio of experiencing the endpoint on losartan compared to atenolol are based on Cox proportional hazard model
^d 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 76: Sponsor's Changes in ECG Measures of LVH

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

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

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

	Crude Rate				Adjusted Hazard Ratio†	95% CI		p-Value*
	Losartan (N=4605)		Atenolol (N=4588)			Lower	Upper	
	n	(%)	n	(%)				
Composite	508	(11.0)	588	(12.8)	0.902	0.804	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	0.008**

** 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 78: Sponsor's Numbers of Hospital Admissions

Number of Hospital Admissions	Losartan (N=4605)		Atenolol (N=4588)		p-Value [†]
	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)	

[†] 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 79: Sponsor's Rates of First Hospitalizations by Reason

Reason for Hospitalization	Losartan (N=4605)						Atenolol (N=4588)						Kaplan-Meier Rates								Hazard Ratio	95% Confidence Interval		p-Value [†]
	Rate [‡]		Rate		Rate		1 Year				2 Year				3 Year				Lower	Upper				
	n	(%)	n	(%)	n	(%)	1 Year	2 Year	3 Year	4 Year	1 Year	2 Year	3 Year	4 Year	1 Year	2 Year	3 Year	4 Year						
Any reason	246	5.3	229	4.9	146	3.1	15.5	26.7	37.4	42.5	15.7	26.8	37.8	44.1	0.964	0.959	1.021	0.211						
Angina	19	0.4	213	4.6	84	1.8	1.5	2.4	3.3	4.1	1.5	2.5	2.7	3.3	1.261	1.051	1.542	0.024*						
Coronary revascularization	6	0.1	171	3.7	62	1.3	0.6	1.1	1.5	2.4	0.4	1.1	1.7	2.3	1.961	1.787	1.274	0.002						
Heart failure	9	0.2	196	4.3	95	2.0	1.1	1.8	2.6	3.4	1.4	2.1	2.8	3.7	0.981	0.806	1.194	0.446						
Myocardial infarction	9	0.2	152	3.3	75	1.6	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	5	0.1	110	2.4	68	1.4	0.5	1.0	1.4	1.9	0.5	1.5	1.8	2.3	0.670	0.674	1.122	0.282						
vascular surgery																								
Stroke	11	0.2	244	5.3	148	3.1	1.4	2.6	3.3	4.4	2.0	3.1	4.2	5.7	0.779	0.694	0.921	0.003**						
Death	4	0.1	156	3.4	72	1.5	0.7	0.7	1.4	1.8	4.3	6.6	7.3	7.8	0.806	0.682	1.150	0.162						
Non-fatal	10	0.2	189	4.1	112	2.4	1.1	2.0	2.8	3.9	11.4	21.8	29.0	36.8	0.961	0.961	1.024	1.229						

[†] p-Value < 0.05
^{**} p-Value < 0.01
[‡] For 100 patient-years of follow-up
 † Baseline left ventricular hypertrophy degree of overall product and Salsitrol 100mg and baseline Framingham risk score are included as Cox proportional hazard model as covariates.
 ‡ The p-values and estimates of this table are of separate by the treatment in a separate comparison and 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 $p=0.021$. 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 atenolol 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. 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 blacks was mixed. Good control was more frequent with losartan (42 vs. 39%) but

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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 80: 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.

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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 81: Sponsor's Study Drug Dosages by Visit

Visit	Total Daily	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)	51.4 (8.24)	4350	(94.8)	51.0 (7.31)
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)	56.6 (17.06)	4239	(92.4)	55.5 (15.55)
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)	66.8 (23.66)	4120	(89.8)	65.2 (23.09)
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)	76.0 (26.35)	3806	(83.0)	74.0 (26.21)
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)	77.5 (25.40)	3624	(79.0)	75.4 (25.41)
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)	78.3 (24.87)	3487	(76.0)	76.6 (25.38)
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)	79.3 (24.85)	3366	(73.4)	77.3 (25.64)
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)	79.8 (24.82)	3324	(72.4)	77.4 (25.49)
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)	80.5 (24.63)	3239	(70.6)	77.6 (25.72)
Year 3.5	50 mg	524	(11.4)		517	(11.3)	
	50 mg + Other	734	(15.9)		529	(11.6)	
	100 mg + Other	2135	(46.4)		1821	(39.7)	
	All Doses (mg)	3393	(73.7)	81.3 (24.73)	3167	(69.0)	78.1 (25.89)
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)	81.9 (24.39)	2900	(63.2)	79.0 (25.79)
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)	82.8 (24.24)	2959	(64.5)	79.9 (25.58)

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.

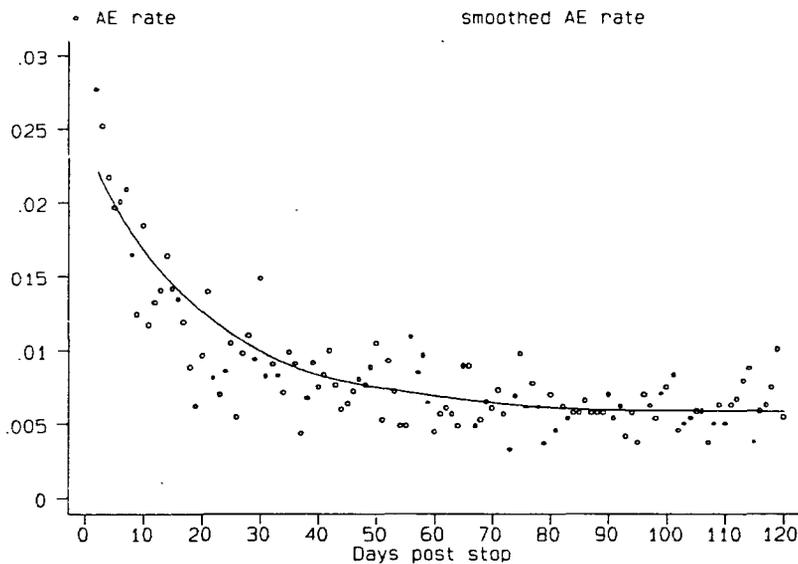


Figure 20: Fraction of Patients with Adverse Events by Day Post Study Drug Discontinuation

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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 82: Sponsor's Serious Adverse Events with Frequencies ≥ 0.5% of Patients

	Losartan (N=4665)		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)
Body as a Whole/Site Unspecified	414	(9.0)	398	(8.7)
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)
Cardiovascular System	357	(7.8)	396	(8.6)
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)
Digestive System	287	(6.2)	261	(5.7)
Colonic malignant neoplasm	26	(0.6)	21	(0.5)
Endocrine System	39	(0.8)	39	(0.9)
Eyes, Ears, Nose, and Throat	92	(2.0)	93	(2.0)
Cataract	27	(0.6)	22	(0.5)
Hemic and Lymphatic System	53	(1.2)	50	(1.1)
Anemia	31	(0.7)	16	(0.3)
Hepatobiliary System	107	(2.3)	79	(1.7)
Cholecystitis	29	(0.6)	24	(0.5)
Cholelithiasis	51	(1.1)	46	(1.0)
Metabolism and Nutrition	26	(0.6)	28	(0.6)
Musculoskeletal System	385	(8.4)	367	(8.0)
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)
Nervous System	122	(2.6)	124	(2.7)
Vertigo	41	(0.9)	39	(0.9)
Psychiatric Disorder	57	(1.2)	37	(0.8)
Respiratory System	189	(4.1)	193	(4.2)
Lung malignant neoplasm	29	(0.6)	12	(0.3)
Pneumonia	75	(1.6)	96	(2.1)
Skin and Skin Appendages	127	(2.8)	129	(2.8)
Basal cell carcinoma	66	(1.4)	58	(1.3)
Urogenital System	318	(6.9)	274	(6.0)
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 83: 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 84: Reviewer's Top 20 Adverse Events Leading to Hospitalization

Rank	Atenolol		Losartan	
	AE	N	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 85: 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)
Body as a Whole/Site Unspecified	143	(3.1)	201	(4.4)
Asthenia fatigue	32	(0.7)	76	(1.7)
Dizziness	32	(0.7)	41	(0.9)
Cardiovascular System	182	(4.0)	327	(7.1)
Atrial fibrillation	24	(0.5)	44	(1.0)
Bradycardia	11	(0.2)	122	(2.7)
Congestive heart failure	7	(0.2)	23	(0.5)
Digestive System	51	(1.1)	83	(1.8)
Musculoskeletal System	35	(0.8)	38	(0.8)
Nervous System	90	(2.0)	85	(1.9)
Headache	29	(0.6)	23	(0.5)
Vertigo	28	(0.6)	19	(0.4)
Psychiatric Disorder	44	(1.0)	41	(0.9)
Respiratory System	68	(1.5)	123	(2.7)
Dyspnea	22	(0.5)	79	(1.7)
Skin and Skin Appendages	20	(0.4)	27	(0.6)
Urogenital System	48	(1.0)	45	(1.0)
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 86: Sponsor's Rates of Events of Special Interest

	Losartan (N=4605)		Atenolol (N=4588)		Losartan - Atenolol			p-Values [†]
	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.
[†] 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 87: 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 88: Sponsor's Rates of New Onset Diabetes Mellitus

	Event Rate						Kaplan-Meier Rates								Hazard Ratio	95% CI		
	Losartan			Atenolol			Losartan				Atenolol					Lower	Upper	p-Value
	Rate	95% CI	N	Rate	95% CI	N	1-yr	2-yr	3-yr	4-yr	1-yr	2-yr	3-yr	4-yr				
New-onset diabetes mellitus	1.31	0.42	173	1.74	0.32	168	1.1	2.7	5.9	4.9	1.3	3.1	4.5	6.8	0.74 ^a	0.64	0.885	0.0021 ^b

^a p-Values < 0.01.
^b N = Patients with no prior history of diabetes.
^c Per 100 patient-years of follow-up.
 Based on left ventricular hypertrophy degree in atenolol product and Sokal and Jones baseline transplant risk score are included in Cox proportional hazard model as covariates.
 Hazard ratios and 95% confidence intervals are presented in the table. Hazard ratios and 95% confidence intervals 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 89: 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 90: 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
Hemoglobin (gm/dL)								
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
Glucose (mg/dL)								
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
Uric Acid (mg/dL)								
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
Urine Microalbumin (mg/dL)								
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 91: Sponsor's Patient's Exceeding Predefined Limits of Change in Lab Test Values

Predefined Laboratory Test	Limit of Change	Treatment	Number	Total ²	(%)
Hemoglobin (g/L)	Decrease ≥ 35	Atenolol	52	3480	(1.5)
		Losartan	100	3636	(2.8)
Creatinine ($\mu\text{mol/L}$)	Increase > 35	Atenolol	363	4202	(8.6)
		Losartan	451	4277	(10.5)
SGPT (ALT) ($\mu\text{kat/L}$)	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 ($\mu\text{mol/L}$)	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)

¹ Number of patients with both a valid prestudy and poststudy value.
² 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 original NDA submission did not provide data or discuss changes in electrocardiograms other than the changes in left ventricular hypertrophy criteria in the Efficacy section. A later submission provided data on atrial fibrillation and flutter on the annual ECGs. See Section VI.C.4.2.7 for a discussion of atrial fibrillation on ECG.

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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 (≥ 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.

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 ≥ 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 the question definitively, so another trial may be 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 “an antihypertensive regimen including losartan and hydrochlorothiazide is superior to one including atenolol and hydrochlorothiazide in reducing the incidence of stroke in non-black hypertensive patients 55 years of age or older with left ventricular hypertrophy.” The reviewer’s recommendations regarding the proposed labeling are given below.

Two issues need follow-up:

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- 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.

The following only includes sections of the label that should be modified based on this supplemental NDA. In the sponsor's proposed labeling text below, the reviewer's suggested deletions are indicated with strikethroughs and additions are underlined. Reviewer's comments and explanations are enclosed in square brackets and highlighted in gray.

CLINICAL PHARMACOLOGY

[The sponsor proposes to add the following new material last in this section.]

DRAFT

5 pages redacted from this section of
the approval package consisted of draft labeling

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XI. Appendix

A. References

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this page is the manifestation of the electronic signature.**

/s/

Thomas Marciniak
1/15/03 09:51:26 AM
MEDICAL OFFICER

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

Notes:

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

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

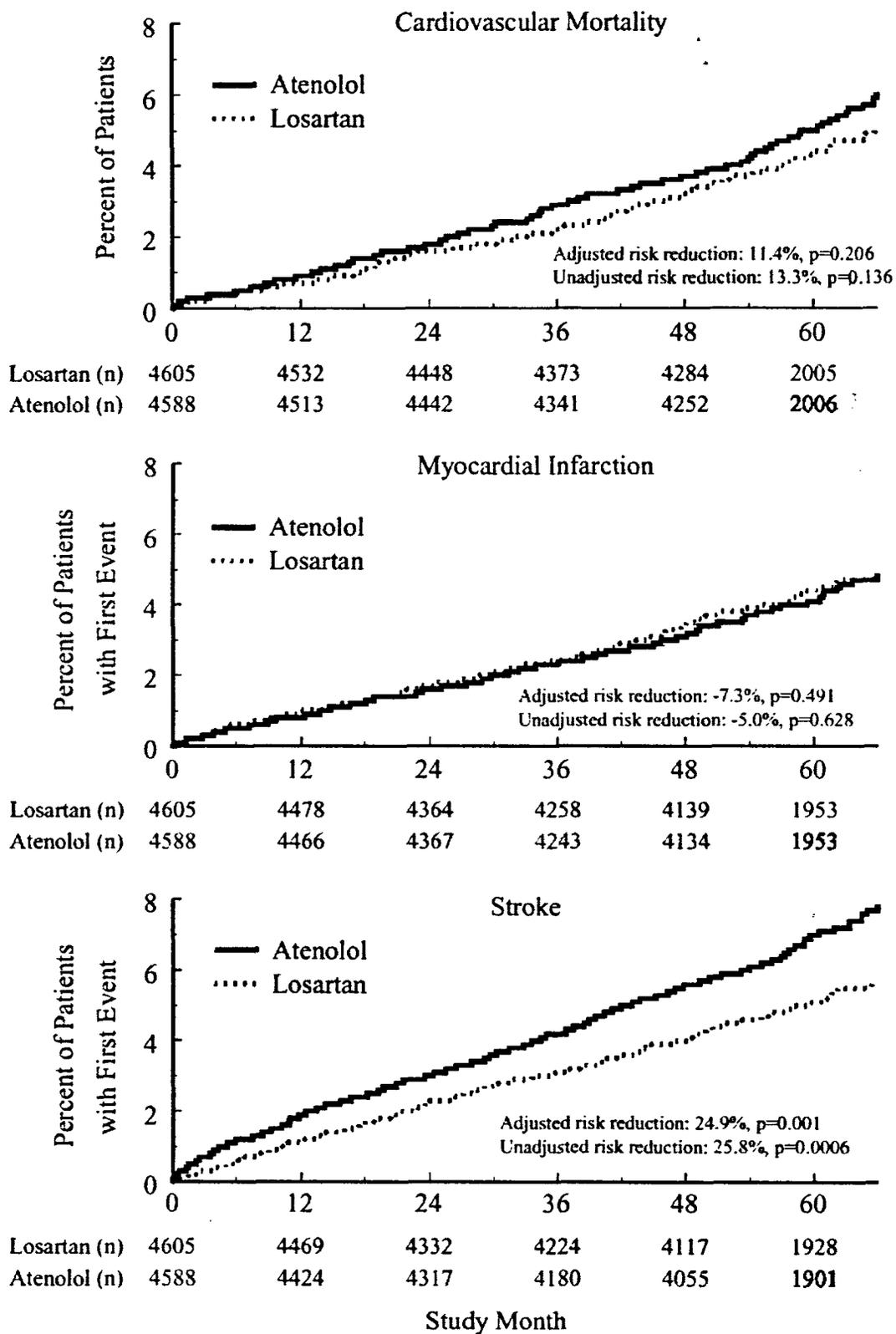


Figure 5: Sponsor's Kaplan-Meier Curves for Components of the Primary Composite Endpoint

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

	Crude Rate				Adjusted [†] Hazard Ratio	95% CI		p-Value [†]
	Losartan (N=4605)		Atenolol (N=4588)			Lower	Upper	
	n	(%)	n	(%)				
Composite	508	(11.0)	588	(12.8)	0.858	0.762	0.966	0.012*
Cardiovascular mortality	204	(4.4)	234	(5.1)	0.879	0.728	1.060	0.177
MI (fatal/nonfatal)	198	(4.3)	188	(4.1)	1.062	0.870	1.297	0.555
Stroke (fatal/nonfatal)	232	(5.0)	309	(6.7)	0.741	0.625	0.879	<0.001**

* p-Values <0.05.
 ** p-Values <0.01.
 † The 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 diastolic blood pressure as time-varying covariate.

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

	Crude Rate				Adjusted [†] Hazard Ratio	95% CI		p-Value [†]
	Losartan (N=4605)		Atenolol (N=4588)			Lower	Upper	
	n	(%)	n	(%)				
Composite	508	(11.0)	588	(12.8)	0.871	0.773	0.981	0.023*
Cardiovascular mortality	204	(4.4)	234	(5.1)	0.876	0.726	1.057	0.167
MI (fatal/nonfatal)	198	(4.3)	188	(4.1)	1.083	0.887	1.323	0.432
Stroke (fatal/nonfatal)	232	(5.0)	309	(6.7)	0.765	0.645	0.907	0.002**

* p-Values <0.05.
 ** p-Values <0.01.
 † The 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 pulse pressure as time-varying covariate.

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

Overall Black Patients																		
	Crude Rate						Kaplan-Meier Rates								Hazard [‡] Ratio	95% CI		p-Value [§]
	Losartan (N=270)			Atenolol (N=263)			Losartan				Atenolol					Low	Upper	
	Rate [†]	n	(%)	Rate [†]	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 [‡] Ratio	95% CI		p-Value [§]
	Losartan (N=4335)			Atenolol (N=4325)			Losartan				Atenolol					Low	Upper	
	Rate [†]	n	(%)	Rate [†]	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**

* p-Values < 0.05.

** p-Values < 0.01.

† Per 1000 patient-years of follow-up.

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

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

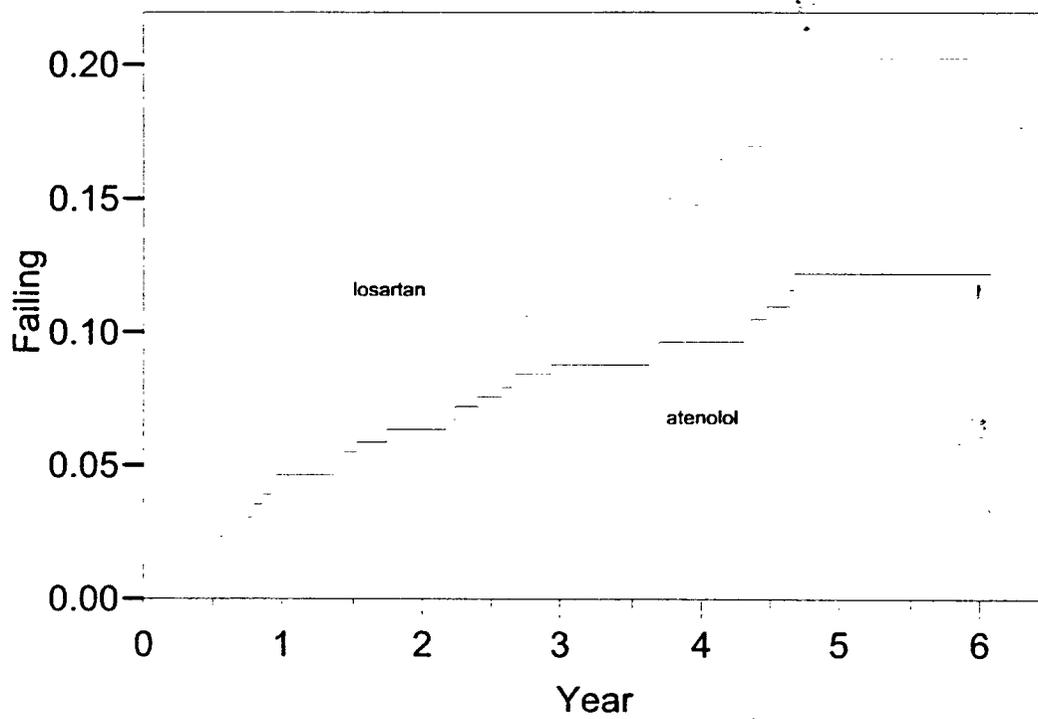


Figure 13: Reviewer's Kaplan-Meier Plot of Primary Composite Endpoint in Blacks

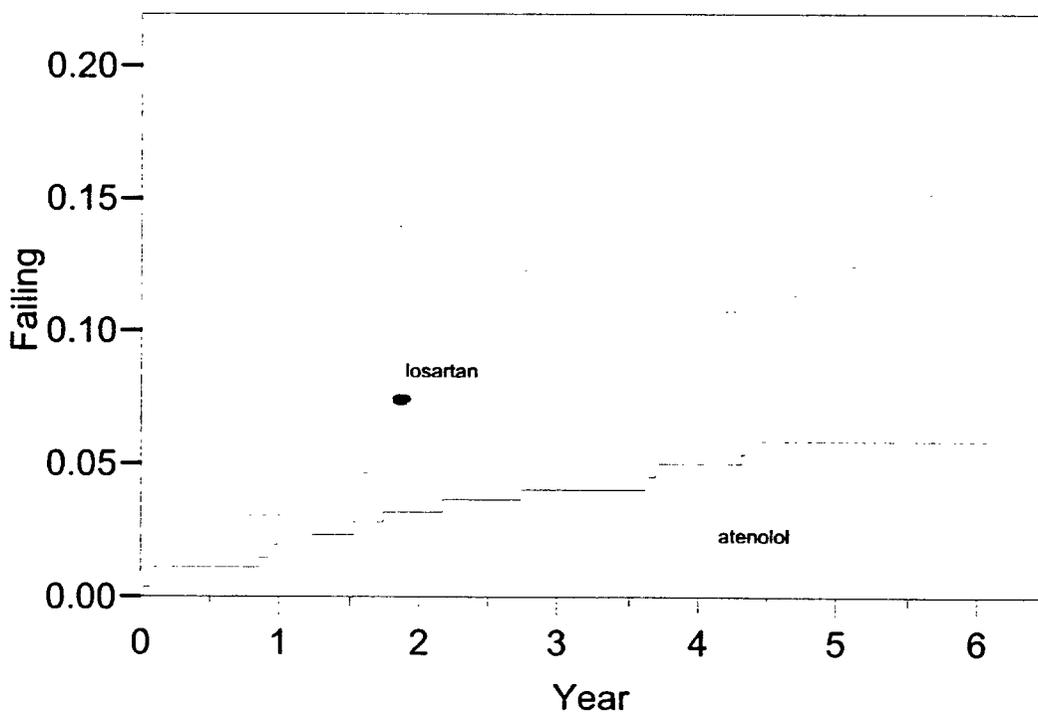


Figure 14: Reviewer's Kaplan-Meier Plot of Strokes in Blacks

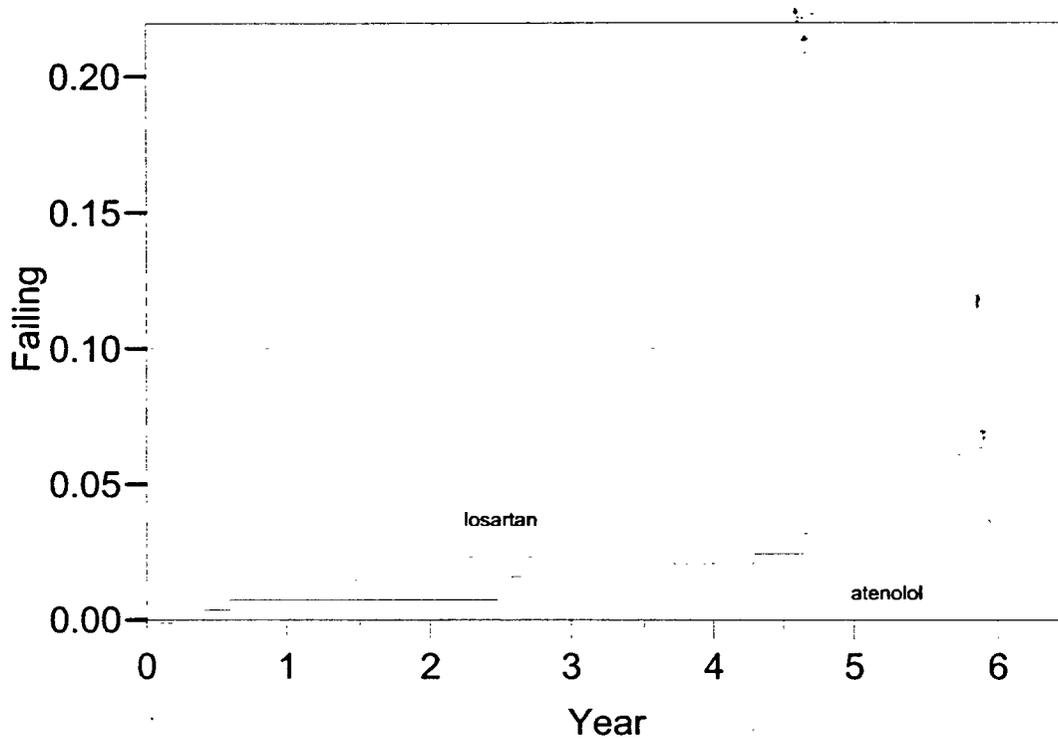


Figure 15: Reviewer's Kaplan-Meier Plot of Myocardial Infarctions in Blacks

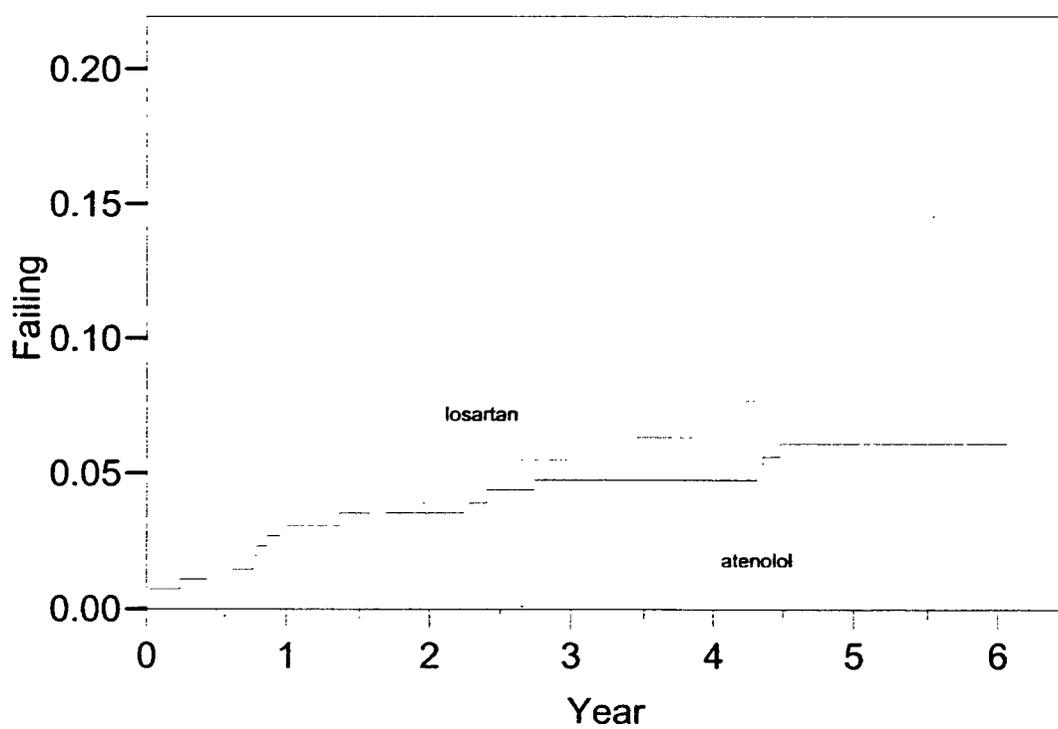


Figure 16: Reviewer's Kaplan-Meier Plot of CV Mortality in Blacks

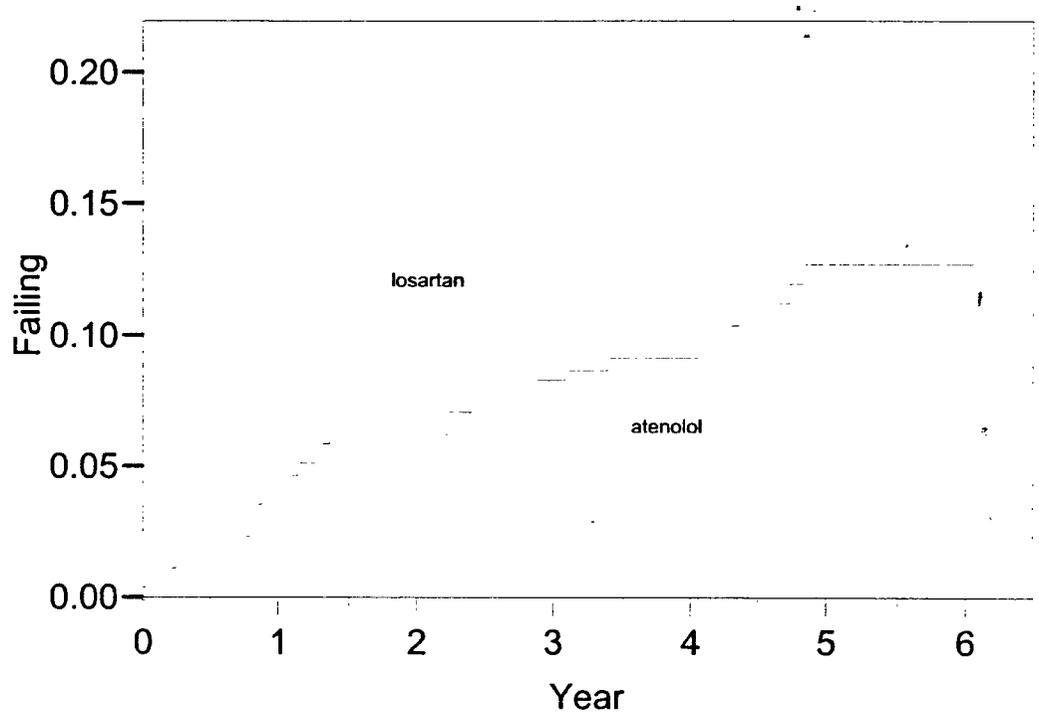


Figure 17: Reviewer's Kaplan-Meier Plot of Total Mortality in Blacks

Table 69: Sponsor's Endpoint Results for Baseline Diabetics

	Crude Rate						Kaplan-Meier Rates								Hazard [†] Ratio	95% CI		p-Value [‡]
	Losartan (N= 586)			Atenolol (N= 609)			Losartan				Atenolol					Lower	Upper	
	Rate [§]	n	(%)	Rate [§]	n	(%)	1-Yr	2-Yr	3-Yr	4-Yr	1-Yr	2-Yr	3-Yr	4-Yr				
Composite	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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/s/

Thomas Marciniak
1/15/03 09:42:49 AM
MEDICAL OFFICER
See amended clinical review