

Procedure	Screening	Placebo Baseline Period			Triple-Blind Period										
	Prestudy <-365 days	Visit 1 Day -14	Visit 2 Day -7	Visit 3 Day 1	Visit 4 Month 1	Visit 5 Month 2	Visit 6 Month 4	Visit 7 Month 6	Visit 8 Year 1	Visit 9 Year 1.5	Visit 10 Year 2	Visit 11 Year 2.5	Visit 12 Year 3	Visit 13 Year 3.5	Visit 14 Year 4 ^a
Medical history		X													
Complete physical examination		X							X		X		X		X
Obtain informed consent	X ^b	X													
Sitting blood pressure and heart rate	(X)	X	X	X ^c	X	X	X	X	X	X	X	X	X	X	X
Standing blood pressure and heart rate				X		X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	
Laboratory safety tests ^e		X ^f		X	X ^g				X		X		X		X
Electrocardiogram (ECG) (12-lead)	X ^h	X ⁱ		X				X	X		X		X		X
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

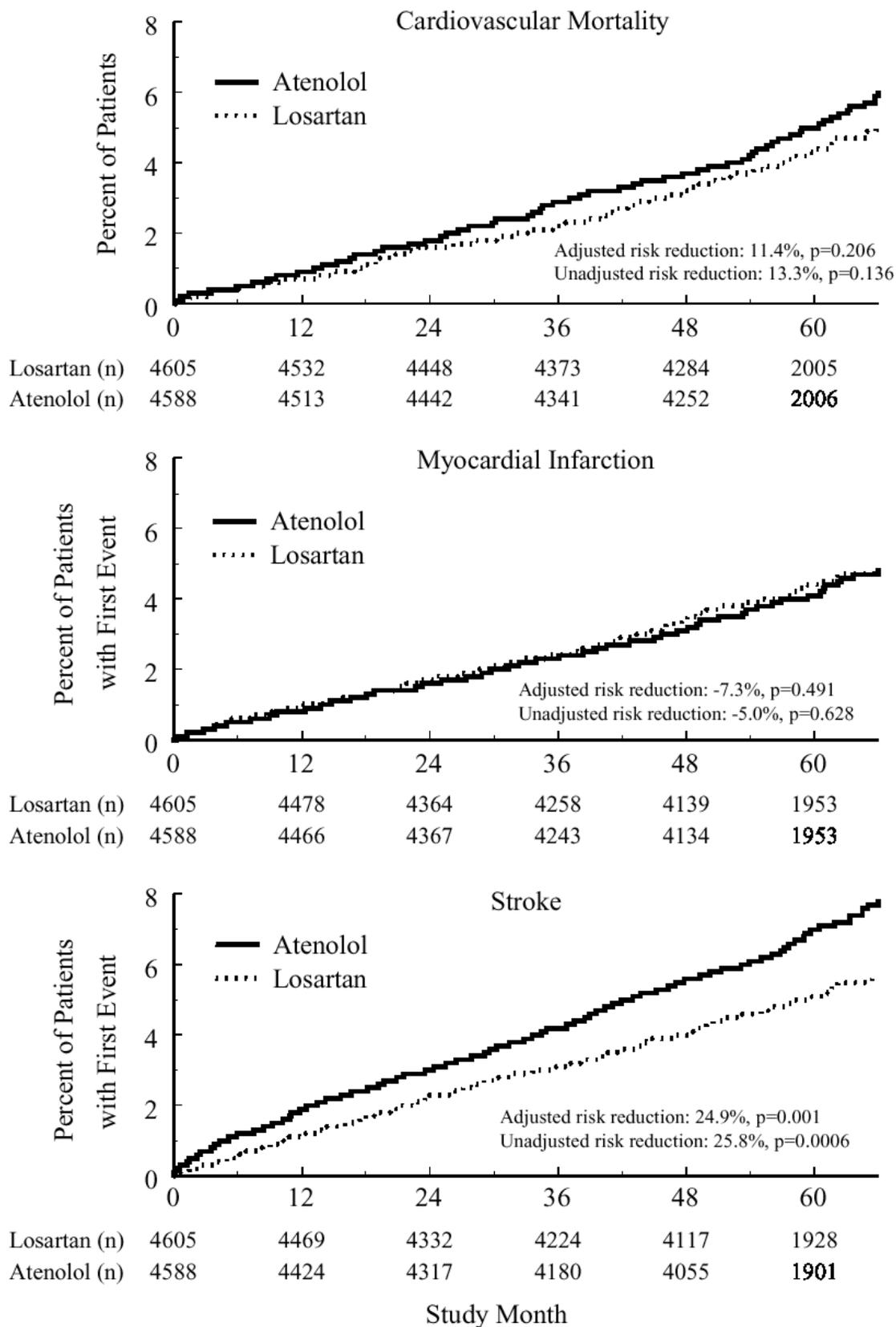


Figure 5: Sponsor's Kaplan-Meier Curves for Components of the Primary Composite Endpoint

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.

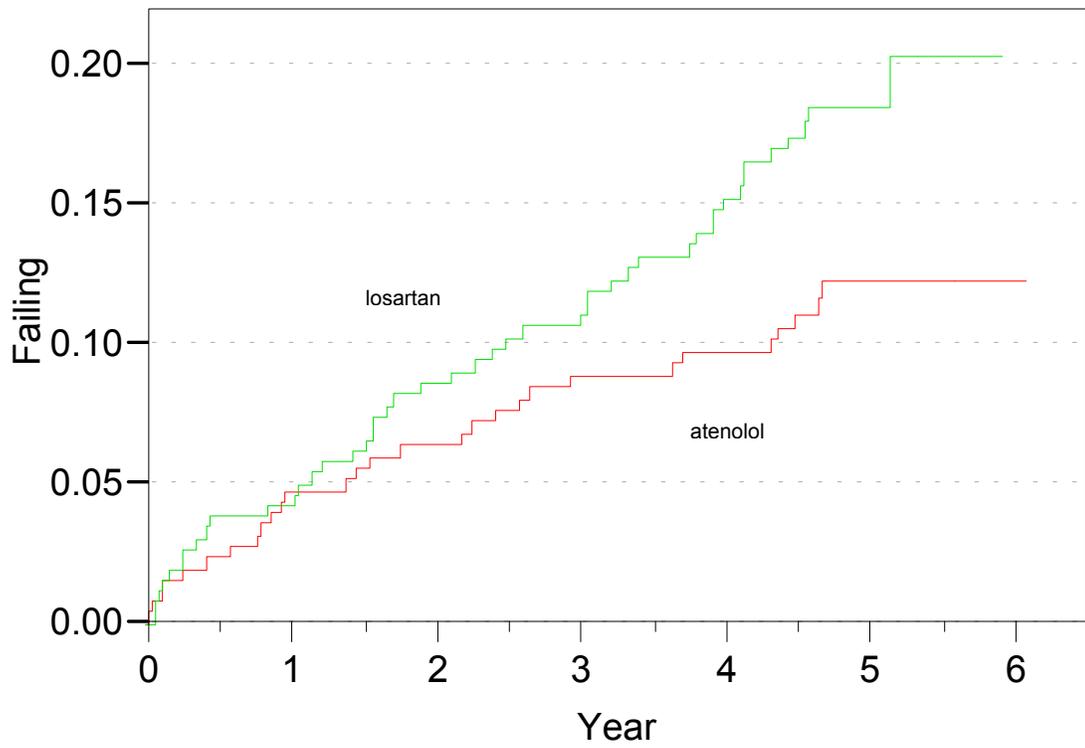


Figure 13: Reviewer’s Kaplan-Meier Plot of Primary Composite Endpoint in Blacks

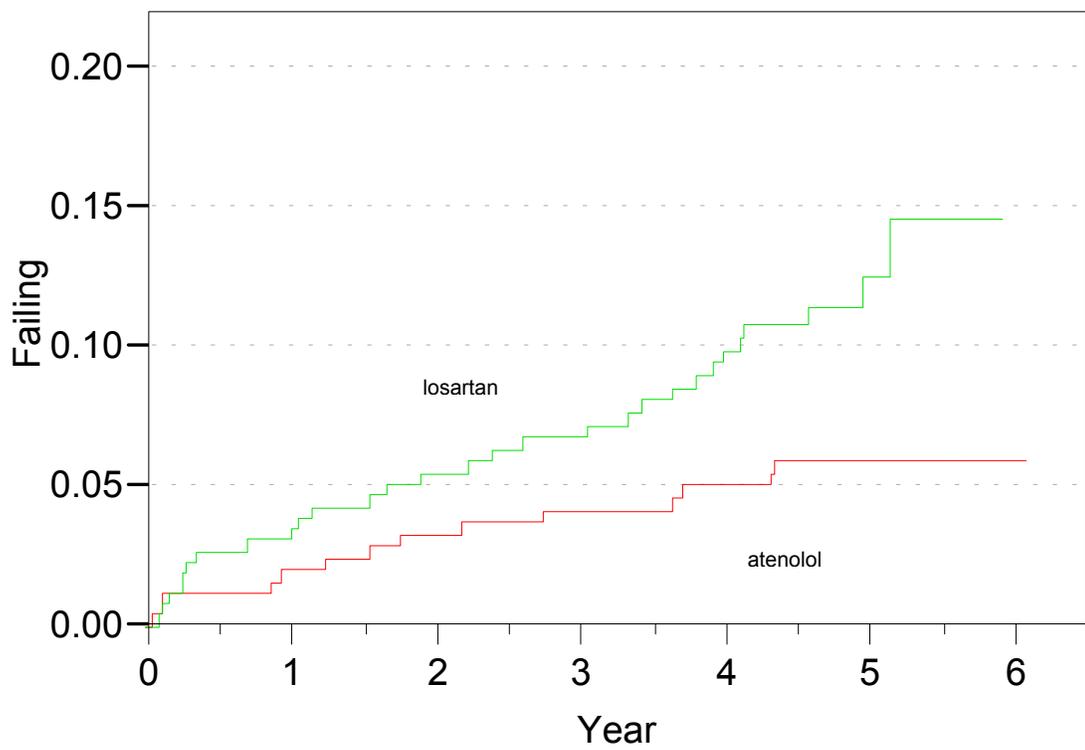


Figure 14: Reviewer’s Kaplan-Meier Plot of Strokes in Blacks

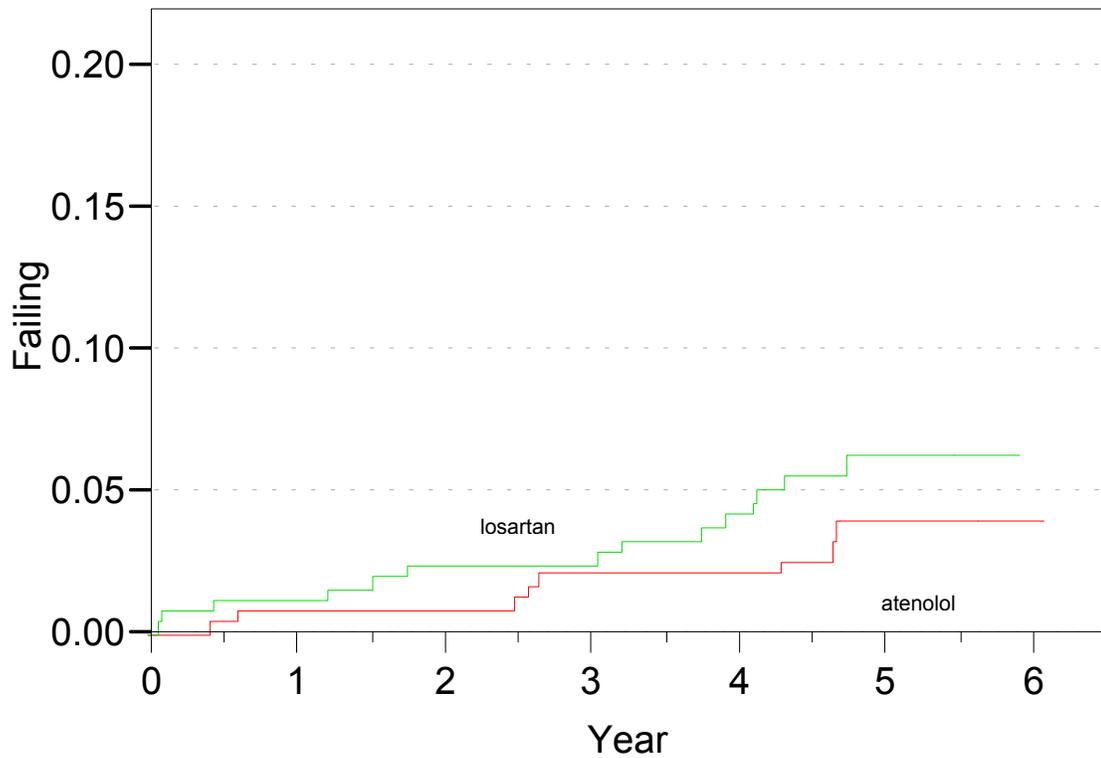


Figure 15: Reviewer's Kaplan-Meier Plot of Myocardial Infarctions in Blacks

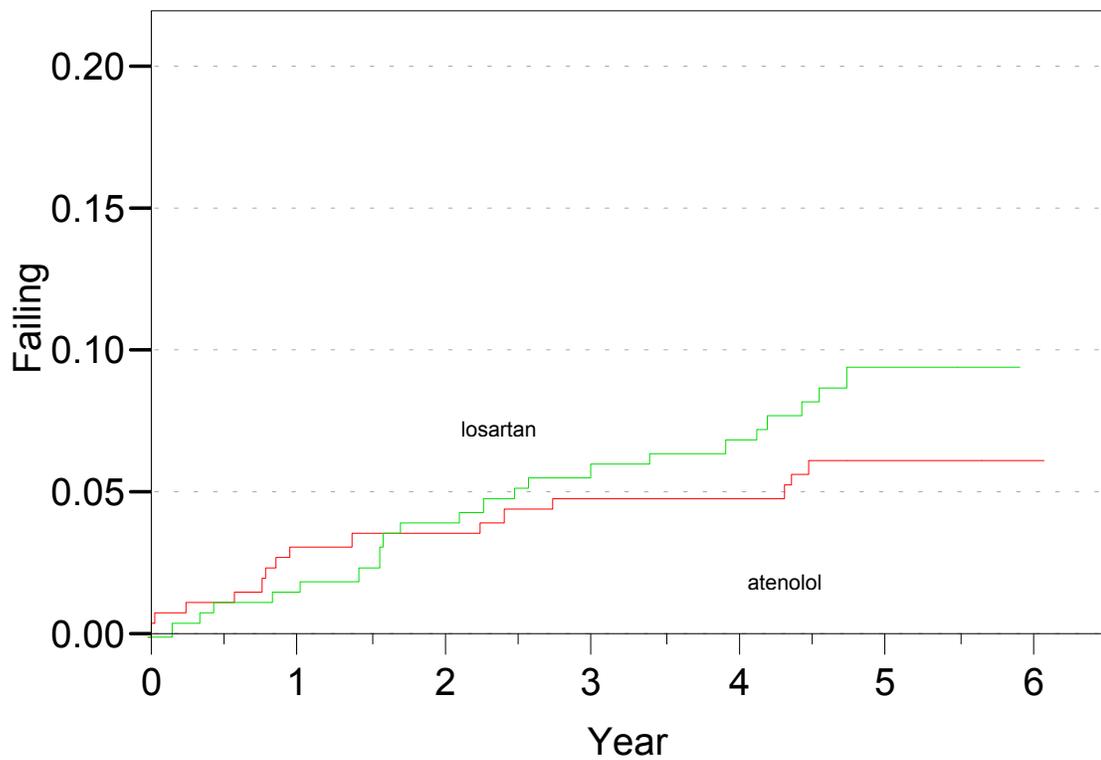


Figure 16: Reviewer's Kaplan-Meier Plot of CV Mortality in Blacks

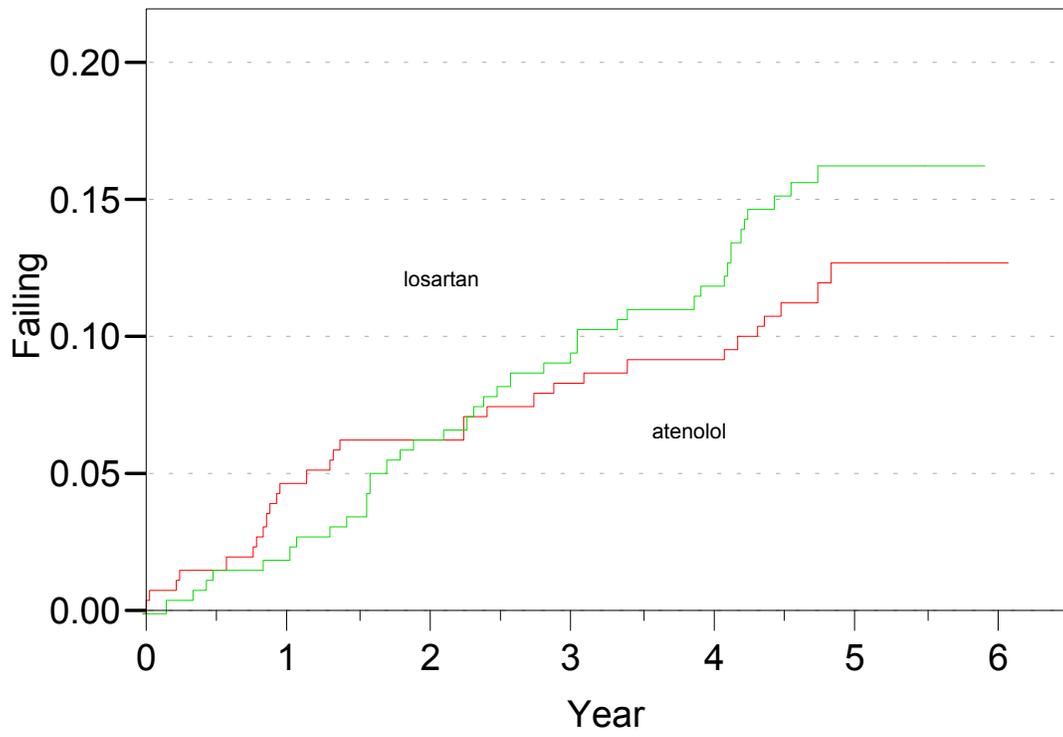


Figure 17: Reviewer's Kaplan-Meier Plot of Total Mortality in Blacks

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.