

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Mauer M, Zinman B, Gardiner R, et al. Renal and retinal effects of enalapril and losartan in type 1 diabetes. *N Engl J Med* 2009;361:40-51.

TABLE 1 - APPENDIX

**Baseline Characteristics of the 285 Randomized Subjects vs.
the 707 Who Declined the Study**

	Randomized (285)	Declined (707)
Age (years)	29.7±9.7	30.1±9.9
Age at onset (years)	18.5±10.0	19.3±9.9
Duration of diabetes (years)	11.2±4.7	10.8±9.9
Gender (% male)	46	50
Ethnicity (% Caucasian)	98	92

*Values are mean ± the standard deviation

ETDRS SEVERITY SCALE - APPENDIX

- Level 10: No retinopathy.
- Level 21: Microaneurysms only or retinal hemorrhages or soft exudates in the absence of microaneurysms.
- Level 31: Microaneurysms and one or more of the following: venous loops 31 μ m or greater; questionable soft exudate, intra-retinal microvascular abnormalities or venous beading; and retinal hemorrhages.
- Level 37: Microaneurysms and one or more of the following: hard exudate and soft exudate.
- Level 43: Microaneurysms and one or more of the following: Hemorrhages/Microaneurysms equaling or exceeding those in standard photo 1 in four or five fields; Hemorrhages/Microaneurysms equaling or exceeding those in standard photo 2A in one field; and intra-retinal microvascular abnormalities in one to three fields.
- Level 47: Microaneurysms and one or more of the following: both intra-retinal microvascular abnormalities and Hemorrhages/Microaneurysms characteristics from level 43; intra-retinal microvascular abnormalities in four or five fields; Hemorrhages/Microaneurysms equaling or exceeding those in standard photo 2A in two or three fields; and venous beading in one field.
- Level 53: Microaneurysms and one or more of the following: any two or three characteristics from level 47; Hemorrhages/Microaneurysms equaling or exceeding those in standard photo 2A in four or five fields; intra-retinal microvascular abnormalities equaling or exceeding those in standard photo 8A; venous beading in two or more fields.

- Level 61: No evidence of levels 60 or 65, but scars of photocoagulation either in "scatter" or confluent patches, presumably directed at new vessels.
- Level 60: Fibrous proliferations only.
- Level 71: Diabetic Retinopathy Study high-risk characteristics. Lesions as follows: vitreous hemorrhage and/or pre-retinal hemorrhage equaling or exceeding 1 disc area; new vessels elsewhere equaling or exceeding one-half disc area with vitreous hemorrhage and/or pre-retinal hemorrhage; new vessels on or within 1 disc diameter less than standard photo 10A with vitreous hemorrhage and/or pre-retinal hemorrhage; and new vessels on or within 1 disc diameter equaling or exceeding standard photo 10A.
- Level 75: Advanced proliferative diabetic retinopathy, lesions as follows: new vessels on or within 1 disc diameter equaling or exceeding standard photo 10A with vitreous hemorrhage and/or pre-retinal hemorrhage.
- Level 85: End-stage proliferative diabetic retinopathy, lesions as follows: macular obscured by vitreous hemorrhage and/or pre-retinal hemorrhage; retinal detachment at center of macula; phthisis bulbi; and enucleation secondary to complications of diabetic retinopathy.

TABLE 2 - APPENDIX**Baseline Characteristics for Participants with Two Renal Biopsies**

	Placebo	Enalapril	Losartan
	(85)	(86)	(85)
Age (years)	29.0±9.3	30.6±9.8	29.0±9.7
Diabetes duration (years)	11.2±4.6	11.8±4.9	10.8±4.9
Body Mass Index (kg/m ²)	25.5±3.7	25.5±3.3	26.0±4.0
Gender (% male)	46	48	48
Ethnicity (% Caucasian)	100	98	95
Glycosylated hemoglobin (%)	8.3±1.4	8.7±1.6	8.6±1.6
Systolic Blood Pressure (mmHg)	119±11	120±13	120±11
Diastolic Blood Pressure (mmHg)	70±8	70±8	70±8
Albumin Excretion Rate (µg/min)*	4.7(1.0 – 28.8)	5.2 (0.5 – 27.5)	5.3 (0.5 – 57.8)
Glomerular Filtration Rate† (ml/min/1.73m ²)	127±22	129±20	130±17

*Albumin Excretion Rate is median (range); all other values are mean ± the standard deviation

† Glomerular Filtration Rate corrected up to 1.73m².

TABLE 3 - APPENDIX**Baseline Characteristics for Participants with Two Biopsies vs. One Biopsy**

	2 biopsies (256)	1 biopsy (29)
Age (years)	29.5±9.6	30.9±11.1
Diabetes duration (years)	11.3±4.8	10.6±4.5
Body Mass Index (kg/m ²)	25.7±3.7	25.9±3.7
Gender (% male)	47	38
Ethnicity (% Caucasian)	98	100
Glycosylated hemoglobin (%)	8.5±1.5	8.8±1.9
Systolic Blood Pressure (mmHg)	120±11	118±13
Diastolic Blood Pressure (mmHg)	70±8	71±10
Albumin Excretion Rate (µg/min)*	5.1(0.5 – 57.8)	4.7(1.2 – 48.1)
Glomerular Filtration Rate† (ml/min/1.73m ²)	129±20	129±21

*Albumin Excretion Rate is median (range); all other values are mean ± the standard deviation

† Glomerular Filtration Rate corrected up to 1.73m².

FIGURE 1 - APPENDIX

Average HbA1c over Time

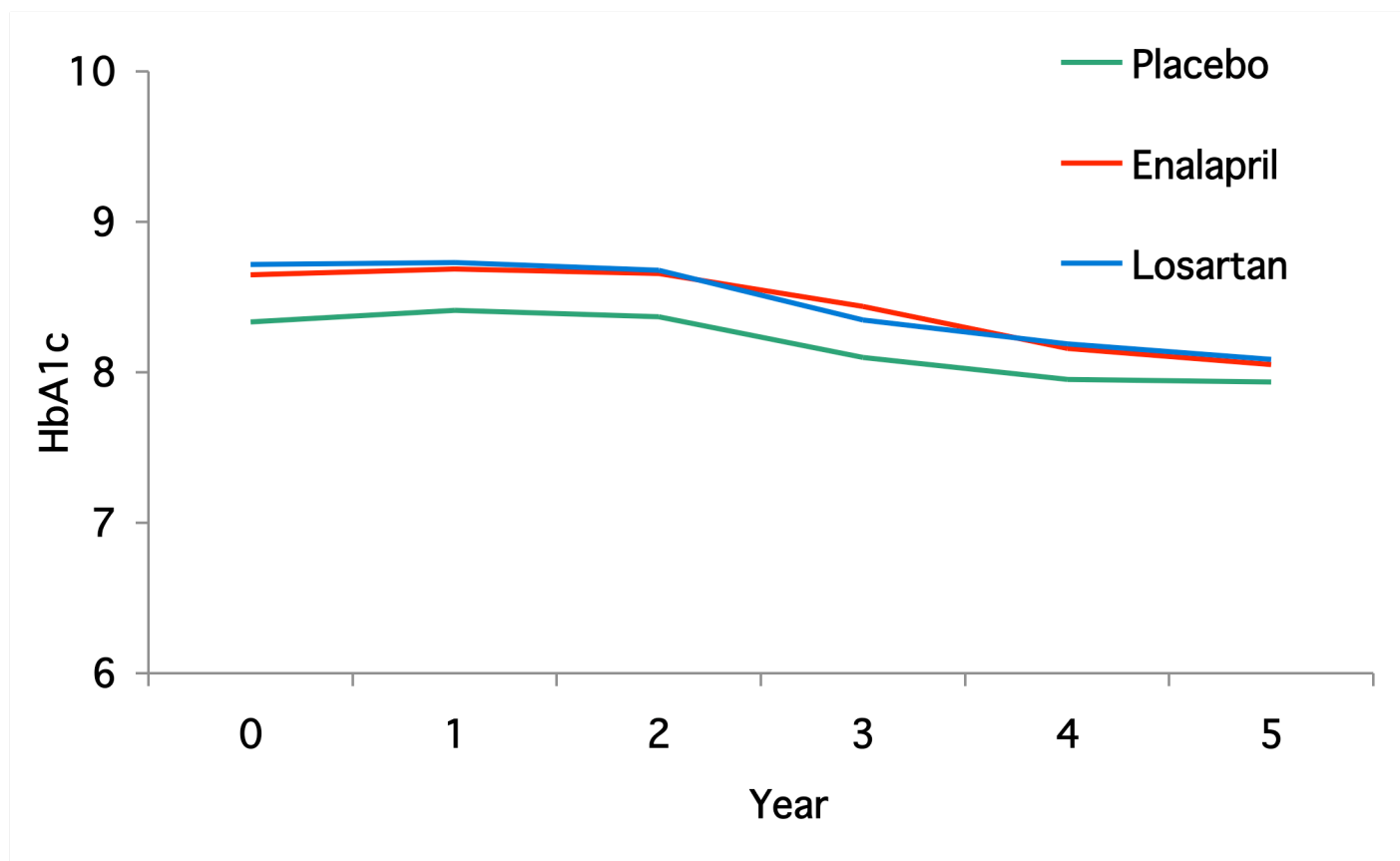


TABLE 4 - APPENDIX**Clinic Blood Pressure Studies**

Clinic Systolic Blood Pressure (mmHg)	Placebo	Enalapril	Losartan
Mean at baseline	119±11	120±13	120±11
Mean over 5 yrs of follow-up	117±8	113±9	115±8
Mean at exit	116±10	113±13	115±11
p-values			
Each treatment vs. placebo over 5 years*		<0.001	0.02
Each treatment vs. placebo at exit*		0.06	0.37
Clinic Diastolic Blood Pressure (mmHg)	Placebo	Enalapril	Losartan
Mean at baseline	70±8	71±8	70±8
Mean over 5 yrs of follow-up	68±5	66±6	66±6
Mean at exit	66±7	65±9	66±8
p-values			
Each treatment vs. placebo over 5 years*		<0.001	0.01
Each treatment vs. placebo at exit*		0.32	0.83

*Adjusted for baseline systolic/diastolic blood pressure

TABLE 5 - APPENDIX

Renal Structural Studies

Structural Variables	Placebo (N=85)		Enalapril (N=86)		Losartan (N=85)		p value for change from baseline*	
	Baseline	Exit	Baseline	Exit	Baseline	Exit	Enalapril vs. Placebo	Losartan vs. Placebo
Mesangial fractional volume	0.187±0.045	0.203±0.050	0.201±0.044	0.206±0.038	0.189±0.041	0.215±0.058	0.38	0.26
Mesangial matrix fractional volume	0.100±0.030	0.108±0.034	0.108±0.030	0.111±0.028	0.103±0.028	0.115±0.038	0.48	0.54
Mesangial cell fractional volume	0.072±0.020	0.076±0.021	0.076±0.020	0.077±0.016	0.069±0.018	0.082±0.024	0.45	0.07
Peripheral glomerular basement membrane surface density	0.130±0.022	0.115±0.020	0.128±0.018	0.112±0.016	0.128±0.023	0.110±0.019	0.55	0.20
Glomerular basement membrane width (nm)	473±99	490±109	476±94	483±90	490±92	499±101	0.17	0.32
Fractional volume of cortex which is interstitium ‡	0.11±0.04	0.17±0.05	0.11±0.04	0.18±0.06	0.11±0.04	0.18±0.04	0.51	0.19
Index of arteriolar hyalinosis §	1.06±0.12	1.20±0.31	1.11±0.24	1.17±0.21	1.10±0.18	1.15±0.19	0.25	0.11
Fractional volume of cortical tubules which are atropic	0.0018±0.0053	0.0065±0.0146	0.0059±0.0307	0.0118±0.0557	0.0040±0.0136	0.0122±0.0192	0.70	0.17

*Adjusted for baseline morphometric value (e.g., change in mesangial fractional volume is adjusted for the baseline value for mesangial fractional volume), systolic/diastolic blood pressure, glycosylated hemoglobin, glomerular filtration rate, albumin excretion rate, age at onset, diabetes duration and sex.

‡ N's for fractional volume of cortex which is interstitium were: placebo, 68; enalapril, 68; losartan, 62

§ N's for index of arteriolar hyalinosis were placebo, 68; enalapril, 69; losartan, 66

|| N's for fractional volume of cortical tubules which were atropic are placebo, 59; enalapril, 62; losartan 59

FIGURE 2 - APPENDIX

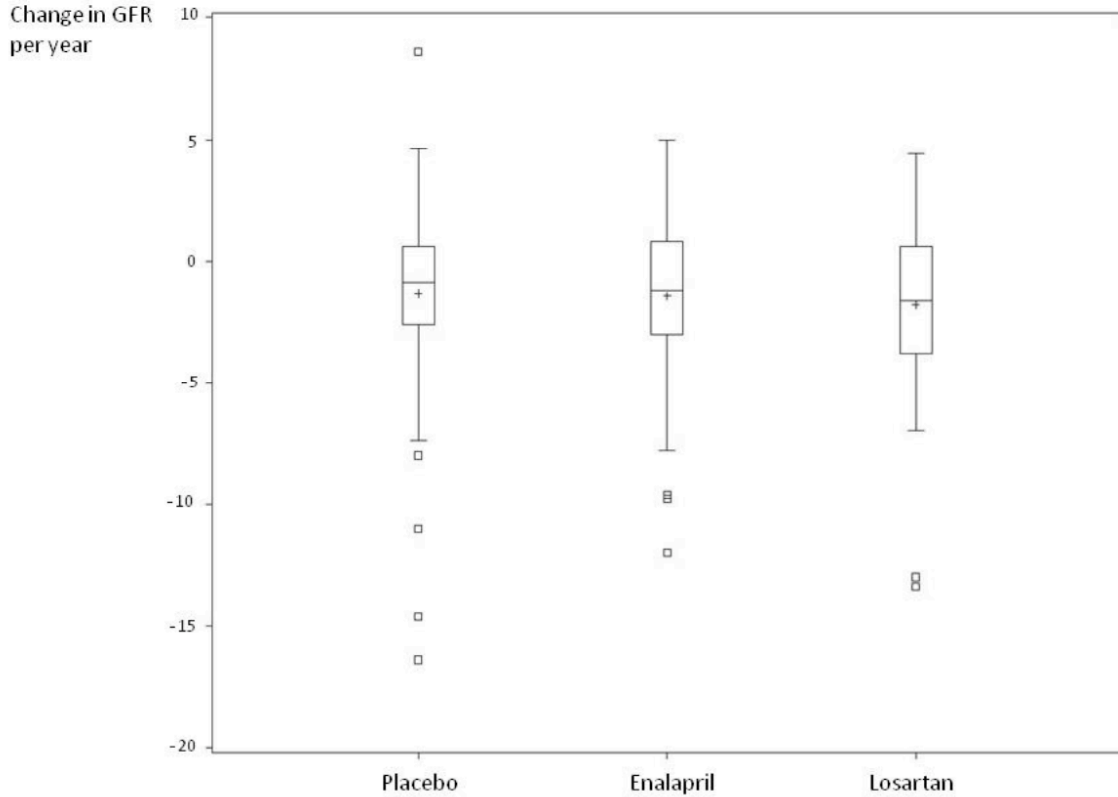


FIGURE LEGEND

Distribution of the annual change in glomerular filtration rate (GFR), for the placebo, enalapril and losartan groups. The annual change was computed using the difference between the baseline and 5-year GFR, divided by the follow-up time. The box plots provide the mean, median and interquartile range, while the whiskers represent the distance from the interquartile limits to the value closest to within 1.5 times the interquartile size, with data points outside these limits plotted individually.

TABLE 6 - APPENDIX**Baseline Characteristics for Participants with Two Fundus Photos vs.
Those without Two Fundus Photos**

	2 photos (223)	1 photo (62)
Age (years)	29.9±9.7	28.8±9.9
Diabetes duration (years)	11.3±4.7	10.8±5.0
Body Mass Index (kg/m ²)	25.7±3.8	25.8±3.4
Gender (% male)	47	45
Ethnicity (% Caucasian)	98	97
Glycosylated hemoglobin (%)	8.5±1.6	8.7±1.6
Systolic Blood Pressure (mmHg)	120±12	118±11
Diastolic Blood Pressure (mmHg)	70±8	70±9
Albumin Excretion Rate (µg/min)*	5.2 (0.5 – 27.5)	4.7 (0.7 – 57.8)
Glomerular Filtration Rate† (ml/min/1.73m ²)	129±21	128±18

* Albumin Excretion Rate is median (range); all other values are mean ± the standard deviation

† Glomerular Filtration Rate corrected up to 1.73m²

TABLE 7 - APPENDIX

	Placebo (74)	Enalapril (77)	Losartan (72)
Age (years)	28.9±9.2	30.9±10.2	29.9±9.7
Diabetes duration (years)	10.9±4.6	12.0±4.7	11.0±4.6
Body Mass Index (kg/m ²)	25.7±3.8	25.4±3.3	25.9±4.1
Gender (% male)	47	45	47
Ethnicity (% Caucasian)	100	99	96
Glycosylated hemoglobin (%)	8.3±1.4	8.7±1.7	8.6±1.6
Systolic Blood Pressure (mmHg)	120±11	120±13	121±11
Diastolic Blood Pressure (mmHg)	70±8	71±8	70±8
Albumin Excretion Rate (µg/min)*	4.8 (1.0 – 19.3)	5.2 (0.5 – 27.5)	5.5 (0.5 – 22.1)
Glomerular Filtration Rate† (ml/min/1.73m ²)	128±23	129±21	129±19

*Albumin Excretion Rate is median (range); all other values are mean ± the standard deviation

† Glomerular Filtration Rate corrected up to 1.73m².

FIGURE 3 - APPENDIX

15-Step Retinopathy Severity Scale

