

# Relationship of Blood Pressure to Retinal Vessel Diameter in Type 1 Diabetes Mellitus

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**Objective:** To examine the relationship of blood pressure (BP) and use of angiotensin-receptor blocker or angiotensin-converting enzyme inhibitor to retinal vessel diameter in normotensive, normoalbuminuric persons with type 1 diabetes mellitus.

**Methods:** In a randomized, controlled clinical trial, clinic and 24-hour ambulatory BPs were measured in persons with type 1 diabetes mellitus and gradable fundus photographs both at baseline (n=147) and at 5-year follow-up (n=124). Retinal arteriole and venule diameters were measured by a computer-assisted technique. Individual arteriole and venule measurements were combined into summary indexes that reflect the average retinal arteriole (central retinal arteriole equivalent [CRAE]) and venule (central retinal venule equivalent [CRVE]) diameter of an eye, respectively.

**Results:** While controlling for age, study site, glycosylated hemoglobin level, and ambulatory pulse rate, the daytime ambulatory systolic ( $-0.29\text{-}\mu\text{m}$  effect per 1 mm Hg;  $P=.02$ ), daytime ambulatory diastolic ( $-0.44\text{-}\mu\text{m}$

effect per 1 mm Hg;  $P=.04$ ), nighttime ambulatory systolic ( $-0.27\text{-}\mu\text{m}$  effect per 1 mm Hg;  $P=.03$ ), and 24-hour ambulatory systolic ( $-0.31\text{-}\mu\text{m}$  effect per 1 mm Hg;  $P=.03$ ) BPs were cross-sectionally associated with a smaller CRAE. While controlling for age, study site, glycosylated hemoglobin level, ambulatory pulse rate, and baseline CRAE, no BP measure was associated with a change in CRAE or CRVE during 5 years of follow-up. Treatment with losartan potassium or enalapril maleate was not associated with a statistically significant change in CRAE or CRVE.

**Conclusion:** Angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker therapy does not affect retinal arteriole or venule diameter in normotensive persons with type 1 diabetes mellitus.

**Trial Registration:** clinicaltrials.gov Identifier: NCT00143949

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**H**IGHER MEAN ARTERIAL blood pressure (MABP) has been consistently shown to be related to narrower retinal arterioles.<sup>1-6</sup> Most studies showing this relationship have been cross-sectional and involved general populations of middle aged to older persons and individuals with hypertension. Few studies have examined whether increases in blood pressure (BP) over time are related to a subsequent decrease in the retinal arteriole diameter and whether antihypertensive treatment affects retinal arteriole and venule diameters.<sup>7-11</sup> In a cross-sectional study in a general population, a history of use of an angiotensin-receptor-converting enzyme inhibitor (ACEI) was not related to retinal arteriole or venule caliber.<sup>7</sup> In the Anglo-Scandinavian Cardiac Outcomes Trial involving 712 hypertensive individuals, despite similar BP levels, persons randomized

to receive the calcium channel blocker amlodipine besylate had a smaller arteriole length to diameter ratio, a measure of retinal arteriole narrowing, than those randomized to receive the  $\beta$ -blocker atenolol.<sup>10</sup> Although the data suggest that BP lowering is associated with a decrease in retinal arteriole narrowing due to hypertension, it is not certain whether drugs such as amlodipine alter small-artery structure independent of BP reduction during antihypertensive treatment. There were no differences in venule measures between treatment groups in that study. In another study involving nondiabetic hypertensive patients, treatment with losartan potassium, an angiotensin-receptor blocker (ARB), led to an increase in the retinal arteriole diameter but did not affect the venule diameter.<sup>8</sup> In a randomized, controlled clinical trial in men with untreated hypertension, an ACEI (enalapril maleate), but not a diuretic (hydrochlorothiazide), was shown to

reduce narrowing of retinal arterioles.<sup>9</sup> In a small study of 25 men with untreated hypertension randomized to treatment with amlodipine or lisinopril during a 1-year period, BP reductions with both treatments were associated with a reduction in arteriole narrowing but had no effect on venule diameter.<sup>11</sup>

There are no comparable data on the effect of ACEI or ARB on retinal arteriole diameter in normotensive persons with type 1 diabetes mellitus (T1DM). Understanding the relationship of these drugs to retinal arteriole narrowing and venule widening is important because the latter are thought to be markers of microvascular changes in the cerebral, coronary, peripheral, and renal circulations, and possibly of pathogenetic processes damaging to other targets of diabetic microvascular injury.<sup>4,5,12-20</sup> In this report, we examine the relationship of ACEI or ARB treatment and BP to changes in retinal vessel caliber in a randomized, controlled clinical trial of normotensive, normoalbuminuric persons with T1DM.<sup>21</sup>

## METHODS

### DESCRIPTION OF COHORT

The Renin-Angiotensin System Study (RASS) was a parallel, double-blind, placebo-controlled, multicenter clinical trial of primary prevention of diabetic nephropathy conducted at 3 clinical centers in Minneapolis, Minnesota; Montreal, Quebec, Canada; and Toronto, Ontario, Canada. The study design and cohort description have been detailed elsewhere.<sup>21,22</sup> The study was conducted and data were collected with institutional review board approval in conformity with all federal, state, and provincial laws, and the study adhered to the tenets of the Declaration of Helsinki as revised in 1983. The study was overseen by a data and safety monitoring board of the National Institutes of Health. Informed consent was obtained. Subjects were 15 years or older with 2 to 20 years of T1DM and onset before their 45th birthday. All were normotensive and normoalbuminuric (albumin excretion rate, <20 µg/min on at least 2 of 3 timed overnight urine collections) and had a normal or increased glomerular filtration rate ( $\geq 90$  mL/min per 1.73 m<sup>2</sup>). Two hundred eighty-five subjects were randomly assigned to 1 of the following 3 treatment groups: losartan (an ARB), enalapril, or placebo.<sup>22</sup> We limited our analyses to the 147 who had fundus photography before randomization into the trial and whose retinal vessels were measurable. Those included were older, but, after controlling for age, there were no statistically significant differences ( $P < .05$ ) in glycosylated hemoglobin level, BP, retinopathy severity, and other characteristics in those included in and excluded from the analyses (**Table 1**).

### BLOOD PRESSURE, WEIGHT, AND HEIGHT

The baseline and follow-up examinations included clinic measurement of BP and pulse rate, with the participant in the seated position after resting for 5 minutes, and with the use of an automated BP device (DinaMap Vital Signs Monitor 18465X; GE Healthcare, Chalfont St Giles, England). Three readings of the systolic BP (SBP) and fifth-phase diastolic BP (DBP) were recorded 1 minute apart, and the average of the second and third readings was used as the mean for each visit. This was labeled "clinic BP."

Annual 24-hour ambulatory BP and ambulatory pulse rate (APR) monitoring were performed with an ambulatory monitor (SpaceLabs 90207; SpaceLabs Medical Inc, Redmond, Washington). The BP was recorded at 20-minute intervals day and

night for a period of 24 hours, and individual measurement values were analyzed on a computer (Macintosh; Apple Computers, Cupertino, California) using the Mathematica 3.0 program (Wolfram Research, Champaign, Illinois). Individual BP and pulse rate values were excluded if any of the following criteria were met: DBP greater than SBP; DBP less than 49 or greater than 150 mm Hg; SBP less than 60 or greater than 250 mm Hg; SBP-DBP difference less than 10 mm Hg; or pulse rate less than 50 or greater than 175 beats/min. Individual records were discarded if more than 20% of measurements had been excluded or if a recording gap of more than 4 hours was present. Mean ambulatory SBP and DBP and intraindividual standard deviation were calculated for the entire 24-hour record. Daytime values were calculated for the hours 10 AM to 8 PM; nighttime values were calculated for the hours midnight to 6 AM.<sup>23</sup> Participants were defined as "nondippers" if the night to day ratios for both ambulatory SBP and ambulatory DBP were greater than 0.9.<sup>23,24</sup>

Height and weight were measured according to standard anthropometric procedures.

### RETINAL MEASUREMENTS

Pupils were dilated and 30° color stereoscopic fundus photographs were taken of the 7 standard fields as defined in the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol.<sup>25</sup> The photographs were graded in a masked fashion by the University of Wisconsin Ocular Epidemiology Reading Center by means of the modified Airlie House classification scheme and the ETDRS retinopathy severity scale. Grading protocols have been described in detail elsewhere.<sup>25,26</sup> For each eye, the maximum grade in any of the 7 standard photographic fields was determined for each of the lesions and used to define the "retinopathy levels." For purposes of classification, if the retinopathy severity could not be graded in an eye, it was considered to have a score equivalent to that in the other eye. Diabetic retinopathy (DR) severity, based on the more severe eye, was grouped as follows: none (level 10), mild nonproliferative (levels 20-43), moderate to severe nonproliferative (levels 47-53), and proliferative (levels  $\geq 60$ ).

Retinal vessel diameters were measured at the baseline and 5-year follow-up examinations by a computer-assisted technique based on the following standard protocol: retinal photographs of field 1 (centered at the optic nerve head) were converted to digital images by a high-resolution scanner using identical settings for all photographs.<sup>1</sup> Retinal vessel measurements were made independently for each examination and each eye. Trained graders masked to participant characteristics measured the diameters of all arterioles and venules coursing through a specified area one-half to 1 disc diameter surrounding the optic disc by means of a computer software program. On average, between 7 and 14 arterioles and between 7 and 14 venules were measured per eye. Individual arteriole and venule measurements were combined into summary indexes that reflect the average retinal arteriole (central retinal arteriole equivalent [CRAE]) and venule (central retinal venule equivalent [CRVE]) diameter of an eye, respectively, on the basis of the Parr-Hubbard-Knudtson formula.<sup>27</sup> Graders regularly participated in quality control exercises; the intergrader and intragrader variability was small (interclass and intraclass correlations, >0.90 for CRAE and CRVE).

### STATISTICAL ANALYSES

Statistical analyses were conducted in SAS software, version 9 (SAS Institute Inc, Cary, North Carolina). Means were compared for statistically significant differences by the unpaired, 2-tailed *t* test and analysis of variance when 2 or more than 2

**Table 1. Difference in Baseline Characteristics Between Those Included in and Excluded From Analyses in the Renin-Angiotensin System Study**

Characteristic	Included Group (n=147) <sup>a</sup>	Excluded Group (n=138) <sup>b</sup>	P Value <sup>c</sup>	Age-Adjusted P Value <sup>d</sup>
Age, mean (SD), y	31.3 (9.3)	27.9 (9.9)	.003	...
Male sex, No. (%)	67 (45.6)	65 (47.1)	.80	.15
Glycosylated hemoglobin, mean (SD), % <sup>b</sup>	8.49 (1.55)	8.65 (1.59)	.39	.67
BMI, mean (SD)	26.11 (3.92)	25.28 (3.39)	.06	.09
Clinic measurements, mean (SD)				
SBP, mm Hg	119.78 (12.04)	119.54 (10.99)	.87	.51
DBP, mm Hg	70.57 (8.20)	69.76 (8.56)	.41	.74
MABP, mm Hg	86.98 (8.58)	86.36 (8.45)	.54	.60
Pulse pressure, mm Hg	49.20 (9.38)	49.78 (8.92)	.59	.61
Ambulatory measurements, mean (SD) <sup>a,b</sup>				
Pulse, beats/min	77.38 (9.30)	80.52 (8.68)	.01	.06
24-h SBP, mm Hg	117.84 (8.77)	118.92 (8.87)	.37	.20
24-h DBP, mm Hg	71.41 (5.41)	72.22 (5.95)	.30	.09
Daytime SBP, mm Hg	121.95 (9.66)	122.94 (9.82)	.46	.18
Daytime DBP, mm Hg	75.44 (6.16)	76.39 (7.12)	.30	.08
Nighttime SBP, mm Hg	111.17 (9.66)	111.65 (8.85)	.71	.60
Nighttime DBP, mm Hg	65.34 (6.94)	65.13 (7.11)	.83	.81
CRAE, mean (SD), $\mu\text{m}^b$	158.43 (13.58)	159.71 (12.59)	.44	.83
CRVE, mean (SD), $\mu\text{m}^b$	227.03 (21.22)	229.47 (23.29)	.38	.81
Current smoker, No. (%)	37 (25.2)	35 (25.4)	.97	.87
Nondipper status, No. (%) <sup>e</sup>	32 (21.8)	25 (18.1)	.44	.33
Treatment, No. (%)				
Placebo	48 (32.7)	44 (31.9)	.87	.56
Enalapril maleate	48 (32.7)	46 (33.3)		
Losartan potassium	51 (34.7)	48 (34.8)		
Diabetic retinopathy, No. (%) <sup>b</sup>				
None	54 (36.7)	35 (31.8)	.37	.75
Mild nonproliferative	75 (51.0)	67 (60.9)		
Moderate to severe nonproliferative	15 (10.2)	7 (6.4)		
Proliferative	3 (2.0)	1 (0.9)		

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CRAE, central retinal arteriole equivalent; CRVE, central retinal venule equivalent; DBP, diastolic blood pressure; ellipses, not applicable; MABP, mean arterial blood pressure; SBP, systolic blood pressure. SI conversion factor: To convert glycosylated hemoglobin to a proportion of total hemoglobin, multiply by 0.01.

<sup>a</sup>There were 147 patients in the included group; the ambulatory measurements were available in 115 of them.

<sup>b</sup>There were 138 patients in the excluded group; the ambulatory measurements were available in 100, glycosylated hemoglobin in 137, CRAE and CRVE in 110, and diabetic retinopathy information in 110.

<sup>c</sup>P value is for unpaired, 2-tailed *t* test for difference in means between continuous variables and  $\chi^2$  test for categorical variables.

<sup>d</sup>P value is for unpaired, 2-tailed *t* test for differences in means between continuous variables, adjusted for age, and for the Cochran-Mantel-Haenszel test of general association for categorical variables.

<sup>e</sup>Nondippers were patients in whom the nighttime to daytime ratios for both arterial SBP and arterial DBP were greater than 0.9.

groups, respectively, were involved. Multivariate associations between clinic BP, ambulatory BP, and APR (and changes in these measures) and ACEI, ARB, or control placebo status with changes in CRAE and CRVE were explored by multiple linear regression controlling for age, site, glycosylated hemoglobin level, and APR. In additional analyses, baseline CRAE was controlled for in models involving changes in CRAE, and baseline CRVE was controlled for in models involving changes in CRVE.

and mean CRVE was 227.0 (21.2)  $\mu\text{m}$  with a range of 178.9 to 289.1  $\mu\text{m}$  in the 147 RASS participants in whom retinal photography was done before randomization into the RASS. Eighty-eight percent of the cohort (129 subjects) had no or mild DR (ETDRS severity score of 37/37 or less). Twenty-two percent of the cohort (32 subjects) were nondippers.

## RESULTS

### DESCRIPTION OF COHORT

At baseline, the mean (SD) age was 31.3 (9.3) years; mean duration of T1DM was 11.2 (4.7) years; mean clinic SBP, DBP, MABP, and 24-hour ambulatory SBP and ambulatory DBP were 119.8 (12.0), 70.6 (8.2), 87.0 (8.6), 117.8 (8.8), and 71.4 (5.4) mm Hg, respectively; mean glycosylated hemoglobin level was 8.5% (1.6%); mean CRAE was 158.4 (13.6)  $\mu\text{m}$  with a range of 123.8 to 194.4  $\mu\text{m}$ ;

### CROSS-SECTIONAL RELATIONSHIPS WITH CRAE AND CRVE

At baseline, greater age and higher clinic SBP, DBP, and MABP; 24-hour ambulatory SBP and DBP; and daytime ambulatory SBP and DBP were inversely associated with CRAE (**Table 2**). Sex, glycosylated hemoglobin level, body mass index, clinic pulse pressure, ambulatory pulse, nighttime ambulatory SBP and DBP, smoking status, dipper status, DR severity, and treatment group were not statistically significantly associated with CRAE.

**Table 2. Relationship of Characteristics to CRAE and CRVE at Baseline in the Renin-Angiotensin System Study**

Characteristic	No.	CRAE, $\mu\text{m}$		CRVE, $\mu\text{m}$	
		Mean (SD)	P Value <sup>a</sup>	Mean (SD)	P Value <sup>a</sup>
Sex					
Male	67	156.86 (13.08)	.20	226.38 (20.74)	.74
Female	80	159.74 (13.93)		227.57 (21.72)	
Age, y					
15-29	64	163.31 (13.27)	<.001	236.78 (19.82)	<.001
30-58	83	154.66 (12.65)		219.51 (19.19)	
Glycosylated hemoglobin, %					
5.5-7.8	46	157.43 (14.19)	.10	225.48 (18.18)	.32
7.9-8.8	57	158.57 (14.52)		228.42 (24.28)	
8.9-15.3	44	159.30 (11.80)		226.85 (20.23)	
BMI					
20.0-23.9	45	159.95 (12.07)	.78	224.78 (21.00)	.19
24.0-26.9	51	156.70 (14.78)		226.61 (22.55)	
27.0-43.9	51	158.82 (13.66)		229.43 (20.18)	
Clinic measurements					
SBP, mm Hg					
90-113	47	161.45 (12.49)	.001	230.95 (18.00)	.03
114-124	51	160.11 (14.39)		226.32 (24.88)	
125-152	49	153.79 (12.73)		224.00 (19.71)	
DBP, mm Hg					
42-66	46	162.73 (12.55)	<.001	229.93 (18.14)	.005
67-73	53	157.86 (12.44)		229.66 (20.61)	
74-97	48	154.94 (14.84)		221.33 (23.76)	
MABP, mm Hg					
63-81	47	163.58 (12.08)	<.001	231.76 (16.41)	.005
82-90	50	157.30 (13.21)		225.89 (24.32)	
91-115	50	154.72 (14.04)		223.71 (21.51)	
Pulse pressure, mm Hg					
30-46	52	158.97 (14.44)	.21	227.28 (24.17)	.80
47-54	52	158.64 (13.20)		226.08 (18.90)	
55-81	43	157.52 (13.24)		227.86 (20.49)	
Ambulatory measurements <sup>b</sup>					
Pulse, beats/min					
59-74	44	154.39 (14.45)	.10	222.23 (20.98)	.03
75-82	42	158.95 (11.44)		224.15 (20.93)	
83-103	29	160.27 (15.20)		233.16 (21.27)	
24-h SBP, mm Hg					
97-112	40	161.44 (14.51)	.005	223.29 (22.19)	.93
113-121	38	157.62 (13.70)		227.94 (22.37)	
122-151	37	153.23 (11.90)		225.97 (19.49)	
24-h DBP, mm Hg					
59-68	40	161.99 (14.27)	.04	227.44 (22.44)	.62
69-72	43	156.34 (11.99)		225.23 (20.10)	
73-96	32	153.59 (14.15)		224.11 (21.99)	
Daytime SBP, mm Hg					
98-116	44	162.20 (13.76)	.001	225.43 (21.60)	.48
117-125	39	157.03 (13.76)		227.36 (22.54)	
126-164	32	151.74 (11.61)		224.00 (19.86)	
Daytime DBP, mm Hg					
62-72	39	162.65 (11.71)	.002	230.44 (19.46)	.14
73-77	43	157.06 (14.24)		225.47 (22.63)	
78-98	33	152.13 (13.49)		220.35 (20.99)	
Nighttime SBP, mm Hg					
90-106	42	159.88 (15.11)	.06	224.42 (22.67)	.58
107-116	43	158.33 (12.76)		226.56 (20.52)	
117-152	30	153.12 (12.46)		226.22 (21.12)	
Nighttime DBP, mm Hg					
51-61	37	160.88 (12.67)	.25	226.82 (21.76)	.75
62-68	53	156.08 (14.03)		224.20 (19.54)	
69-97	25	155.69 (14.33)		227.18 (24.74)	
Smoking status					
Nonsmoker	110	157.95 (13.79)	.46	226.29 (20.71)	.47
Smoker	37	159.85 (13.02)		229.21 (22.82)	
Dipping status <sup>c</sup>					
Dipper	115	158.08 (14.21)	.55	226.30 (22.33)	.43
Nondipper	32	159.70 (11.13)		229.64 (16.64)	
Treatment					
Placebo	51	158.93 (14.65)	.24	225.43 (23.38)	.50
Enalapril maleate	48	155.87 (14.08)		225.74 (19.33)	
Losartan potassium	48	160.47 (11.64)		230.01 (20.73)	
Diabetic retinopathy					
None	54	154.72 (13.11)	.15	223.42 (19.49)	.22
Mild nonproliferative	75	161.41 (13.42)		229.09 (22.24)	
Moderate to severe nonproliferative	15	157.43 (12.81)		230.39 (18.09)	
Proliferative	3	155.71 (19.25)		223.65 (39.78)	

Abbreviations: See Table 1.

SI conversion factor: To convert glycosylated hemoglobin to a proportion of total hemoglobin, multiply by 0.01.

<sup>a</sup> P value is for correlation between each continuous variable and CRAE or CRVE or for analysis of variance test for difference between mean CRAE and CRVE for categorical variables.

<sup>b</sup> Ambulatory measurements were available in 115 patients.

<sup>c</sup> Nondippers were patients in whom the nighttime to daytime ratios for both arterial SBP and arterial DBP were greater than 0.9.

**Table 3. Multivariate Models of Association of Blood Pressure Measures With Baseline CRAE Adjusting for Site, Baseline Age, Glycosylated Hemoglobin Level, and Ambulatory Pulse Rate**

Variable	CRAE, $\mu\text{m}$		CRVE, $\mu\text{m}$	
	Effect (SE)	P Value	Effect (SE)	P Value
Clinic measurements				
SBP	-0.18 (0.10)	.09	-0.003 (0.16)	.99
DBP	-0.25 (0.16)	.12	-0.26 (0.24)	.29
MABP	-0.28 (0.15)	.07	-0.15 (0.23)	.49
Ambulatory measurements				
24-h SBP	-0.31 (0.14)	.03	0.24 (0.21)	.26
24-h DBP	-0.35 (0.25)	.17	0.33 (0.37)	.37
Daytime SBP	-0.29 (0.13)	.02	0.17 (0.20)	.38
Daytime DBP	-0.44 (0.21)	.04	0.03 (0.32)	.93
Nighttime SBP	-0.27 (0.13)	.03	0.16 (0.19)	.39
Nighttime DBP	-0.23 (0.19)	.21	0.23 (0.28)	.40
Dipper status <sup>a</sup>	0.33 (2.71)	.90	1.53 (4.03)	.71

Abbreviations: See Table 1.

<sup>a</sup>Non-dippers were patients in whom the nighttime to daytime ratios for both arterial SBP and arterial DBP were greater than 0.9.

Age and clinic SBP, DBP, and MABP were inversely associated with CRVE, whereas APR was directly associated with CRVE (Table 2). Sex, glycosylated hemoglobin level, body mass index, clinic pulse pressure, 24-hour ambulatory SBP and DBP, daytime or nighttime ambulatory SBP or DBP, dipper status, smoking status, DR severity, and treatment group were not statistically significantly associated with CRVE.

Multivariate analyses controlling for age, study site, glycosylated hemoglobin level, and APR showed that higher baseline levels of 24-hour ambulatory SBP, daytime ambulatory SBP and DBP, and nighttime ambulatory SBP were associated with smaller CRAE (Table 3). While controlling for the same factors, there were no statistically significant associations of clinic SBP, clinic DBP, clinic MABP, 24-hour ambulatory DBP, nighttime ambulatory DBP, or dipper status with CRAE and no relationship of any BP measure with CRVE (Table 3).

#### RELATIONSHIPS OF BP, TREATMENT STATUS, AND OTHER FACTORS AT BASELINE TO CHANGE IN CRAE AND CRVE DURING 5 YEARS

Of the 147 subjects, 124 had both baseline and 5-year follow-up photographs gradable for retinal vessel measurements. The mean (SD) increase in CRAE during the 5-year period was 1.61 (8.14)  $\mu\text{m}$  with a range of -14.53 to 36.62  $\mu\text{m}$ , and for CRVE it was 4.08 (15.83)  $\mu\text{m}$  with a range of -29.28 to 63.60  $\mu\text{m}$ .

The relationships of baseline characteristics to changes in retinal vessel measures are presented in Table 4. Higher baseline daytime ambulatory DBP was significantly associated with a 5-year increase in CRAE. Daytime ambulatory DBP remained significantly associated with an increase in CRAE while adjusting for age, study site, glycosylated hemoglobin level, and APR (data not shown). However, when baseline CRAE ( $P=.08$ ) was controlled for in the multivariate model,

the association was no longer statistically significant (data not shown). Baseline age, sex, glycosylated hemoglobin level, smoking status, body mass index, clinic SBP, clinic DBP, clinic MABP, 24-hour ambulatory DBP, daytime ambulatory SBP, nighttime ambulatory SBP and DBP, dipper status, and DR severity were not related to change in CRAE. When the analyses were limited to the placebo group, none of the BP measures was associated with an increase in CRAE.

Clinic SBP, DBP, and MABP at baseline were the only factors related to larger increase in the CRVE (Table 4). Age, sex, and none of the other baseline BP measures were associated with a change in CRVE. Clinic SBP and MABP remained significantly associated with an increase in CRVE while adjusting for age, study site, glycosylated hemoglobin level, and APR (data not shown). When baseline CRVE was also controlled for in the model, the association of clinic SBP with change in CRVE remained statistically significant ( $P=.05$ ), whereas clinic MABP ( $P=.08$ ) was no longer associated with change in CRVE (data not shown). Clinic DBP ( $P=.14$ ) was no longer associated with CRVE after controlling for age, study site, glycosylated hemoglobin level, and APR (data not shown). Similar relationships were found when percentage instead of absolute change in CRAE or CRVE was used as the end point (data not shown).

There were no differences in the changes in the mean CRAE among the 3 treatment groups. The mean (SD) difference in the change in CRAE between the enalapril and placebo groups was 1.49 (1.80)  $\mu\text{m}$  ( $P=.99$ ) and that between the losartan and placebo groups was 1.15 (1.81)  $\mu\text{m}$  ( $P=.99$ ). Adjusting for age, site, and daytime ambulatory DBP did not change these relationships (data not shown).

While controlling for age and site, there were no statistically significant interactions of any of the BP medications by treatment status for change in CRAE (data not shown).

#### RELATIONSHIPS OF AVERAGE BP TO CHANGE IN CRAE AND CRVE

While controlling for age, study site, glycosylated hemoglobin level, and APR, none of the 5-year average BP variables was significantly associated with change in CRAE or CRVE (data not shown). There was no change after further controlling for baseline CRAE or CRVE in the models (data not shown).

#### COMMENT

We had hypothesized that higher BP at baseline would be associated with narrower retinal arteriole diameters as measured by CRAE and that renin-angiotensin system blockade would result in larger CRAE and smaller CRVE than for those assigned to placebo independent of BP level. The hypothesized relationship of renin-angiotensin system blockade with retinal arteriole diameter was based on observations that ACEIs and ARBs block the local renin system in the eye. The expected relationship with retinal venule diameter was based on observations that ACEIs and

**Table 4. Relationship of Various Characteristics to 5-Year Change in CRAE and CRVE in the Renin-Angiotensin System Study**

Characteristic	No.	5-y Change in CRAE, $\mu\text{m}$		5-y Change in CRVE, $\mu\text{m}$	
		Mean (SD)	P Value <sup>a</sup>	Mean (SD)	P Value <sup>a</sup>
Sex					
Male	56	1.60 (8.22)	.99	3.70 (14.58)	.81
Female	68	1.62 (8.13)		4.39 (16.90)	
Age, y					
15-29	53	0.47 (6.72)	.12	1.76 (12.21)	.17
30-58	71	2.46 (9.01)		5.81 (17.97)	
Glycosylated hemoglobin, %					
5.5-7.8	38	0.95 (6.36)	.89	1.71 (17.09)	.06
7.9-8.8	48	2.66 (9.33)		3.47 (16.16)	
8.9-15.3	38	0.95 (8.17)		7.21 (13.91)	
BMI					
20.0-23.9	37	2.61 (8.44)	.62	5.18 (15.11)	.44
24.0-26.9	45	2.06 (7.75)		4.80 (16.64)	
27.0-43.9	42	0.25 (8.28)		2.34 (15.81)	
Clinic measurements					
SBP, mm Hg					
90-113	39	0.44 (6.04)	.23	-1.77 (10.59)	.01
114-124	44	1.71 (7.86)		4.81 (15.48)	
125-152	41	2.62 (10.01)		8.86 (18.69)	
DBP, mm Hg					
42-66	38	0.77 (7.71)	.08	1.94 (16.29)	.02
67-73	47	2.08 (8.34)		2.72 (13.52)	
74-97	39	1.87 (8.45)		7.81 (17.63)	
MABP, mm Hg					
63-81	37	0.72 (5.72)	.09	1.14 (14.52)	.01
82-90	45	0.94 (8.83)		2.55 (14.68)	
91-115	42	3.11 (9.10)		8.31 (17.52)	
Pulse pressure, mm Hg					
30-46	43	1.54 (6.17)	.99	2.33 (13.08)	.25
47-54	44	1.45 (8.64)		2.45 (16.06)	
55-81	37	1.88 (9.62)		8.05 (18.05)	
Ambulatory measurements <sup>b</sup>					
Pulse, beats/min					
59-74	38	4.25 (10.17)	.29	6.78 (18.41)	.49
75-82	35	0.46 (7.51)		2.92 (17.25)	
83-103	24	0.28 (7.82)		5.01 (14.65)	
24 h SBP, mm Hg					
97-112	34	1.03 (8.10)	.22	4.35 (17.04)	.86
113-121	31	0.88 (7.95)		3.58 (17.41)	
122-151	32	3.81 (10.25)		6.91 (17.05)	
24 h DBP, mm Hg					
59-68	33	-0.29 (6.74)	.10	4.14 (14.48)	.25
69-72	38	2.13 (8.53)		2.06 (13.85)	
73-96	26	4.34 (11.01)		10.20 (22.81)	
Daytime SBP, mm Hg					
98-116	36	0.47 (7.59)	.28	4.75 (16.73)	.98
117-125	33	0.95 (8.28)		3.88 (16.69)	
126-164	28	4.85 (10.42)		6.47 (18.32)	
Daytime DBP, mm Hg					
62-72	31	0.19 (6.04)	.03	3.34 (11.19)	.18
73-77	39	1.47 (8.89)		2.40 (17.10)	
78-98	27	4.48 (10.95)		10.48 (21.34)	
Nighttime SBP, mm Hg					
90-106	37	1.56 (8.10)	.15	2.99 (16.62)	.56
107-116	33	0.58 (8.77)		5.42 (19.02)	
117-152	27	3.97 (9.78)		7.06 (15.29)	
Nighttime DBP, mm Hg					
51-61	32	1.21 (8.79)	.14	1.92 (14.28)	.20
62-68	43	1.78 (8.24)		6.10 (19.73)	
69-97	22	3.14 (10.23)		7.11 (15.03)	
Smoking status					
Nonsmoker	94	1.40 (8.23)	.60	4.08 (16.81)	.99
Smoker	30	2.28 (7.92)		4.07 (12.52)	
Dipping status <sup>c</sup>					
Dipper	99	1.56 (8.14)	.90	3.95 (16.48)	.85
Nondipper	25	1.79 (8.28)		4.61 (13.26)	
Diabetic retinopathy					
None	44	3.03 (9.20)	.17	4.08 (18.35)	.88
Mild nonproliferative	64	0.87 (7.27)		3.77 (13.37)	
Moderate to severe nonproliferative	14	1.28 (8.72)		5.51 (19.54)	
Proliferative	2	-3.44 (2.92)		3.85 (9.73)	

Abbreviations: See Table 1.

SI conversion factor: To convert glycosylated hemoglobin to a proportion of total hemoglobin, multiply by 0.01.

<sup>a</sup>P value is for correlation between each continuous variable and CRAE or CRVE or for analysis of variance test for difference between mean CRAE and CRVE for categorical variables.

<sup>b</sup>Ambulatory measurements were available in 97 patients.

<sup>c</sup>Nondippers were patients in whom the nighttime to daytime ratios for both arterial SBP and arterial DBP were greater than 0.90.

ARBs may reduce inflammation and endothelial dysfunction, both previously shown to be related to larger CRAE.<sup>18,28-37</sup> While controlling for age and other factors, we found an inverse cross-sectional association of daytime ambulatory SBP and DBP, nighttime ambulatory SBP, and 24-hour ambulatory SBP at baseline with CRAE; no relationship of any BP measure with change in CRAE; and no relationship of the 5-year average of any BP measure with change in CRAE. There was no statistically significant effect of enalapril or losartan compared with placebo on changes in CRAE or CRVE in the normotensive, normoalbuminuric patients with T1DM in our study.

Higher BP has been consistently found to be associated with smaller CRAE.<sup>1-5</sup> In the Wisconsin Epidemiologic Study of Diabetic Retinopathy, in persons with type 1 and 2 diabetes mellitus including those with hypertension, an increase in BP was cross-sectionally associated with a smaller CRAE.<sup>2,6</sup> It has been hypothesized that this was due to the damaging effect of higher levels of BP on arteriole structure. In the RASS, higher 24-hour ambulatory SBP and daytime ambulatory SBP were all related to smaller CRAE at baseline, but no BP measure at baseline or averaged over the study was related to change in CRAE during the 5-year period. Thus, in normotensive, normoalbuminuric patients with T1DM, higher baseline BP does not appear to be associated with a decrease in retinal arteriole narrowing during a 5-year period.

Treatment with enalapril and losartan reduced the rate of 2-step or more progression of DR by approximately 65% in the RASS but had no effect on CRAE and CRVE.<sup>21</sup> The lack of an effect on CRAE and CRVE in our study is not consistent with findings of earlier studies that showed that ACEI or ARB treatment either reduced the amount of narrowing or increased the width of retinal arterioles.<sup>8,9</sup> These studies involved treatment in older hypertensive patients, and the effect of such treatment would be expected to be weaker and less apparent in younger normotensive individuals in whom the retinal arterioles would be unlikely to be narrowed at baseline.<sup>8-11</sup>

Severity of DR was unrelated to CRAE or CRVE in the RASS. This was unexpected on the basis of earlier observations in the Wisconsin Epidemiologic Study of Diabetic Retinopathy.<sup>2</sup> In that study, increasing severity of retinopathy was associated with a gradual decrease in mean arteriole diameter and an increase in venule diameter in people with T1DM. Differences in factors associated with CRAE and CRVE, such as higher BP, glycosylated hemoglobin levels, and lipid levels, and the frequency of renal disease in the Wisconsin Epidemiologic Study of Diabetic Retinopathy compared with the RASS may, in part, explain the differences between the studies.

Strengths of our study included the objective determination of retinal vessel caliber using standardized protocols for photography and grading, the research protocol clinic measurements of SBP and DBP 4 times per year, and the annual measurement of ambulatory BP during a 5-year period. However, caution must be used in interpreting the findings described herein. Factors associated with variability of measurements of CRAE and CRVE, eg, variation in photograph quality, the time in the pulse cycle at which the photographs were taken, and grader

variability in measuring retinal vessels, may have limited the ability to find associations with retinal vessel measurements in this cohort. Second, there was limited variability of change in BP in this normotensive cohort. Third, the sample sizes were relatively small. Fourth, other measures of arteriole changes, eg, tortuosity, bifurcation angle, and optimality, that might be affected by BP were not measured in this study.<sup>10</sup>

In summary, use of ACEIs or ARBs, despite their beneficial effect in reducing the progression of DR, were not statistically significantly associated with changes in retinal blood vessel caliber in younger, normotensive, normoalbuminuric patients with T1DM.

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