

# Changes in Blood Pressure and Urine Albumin-Creatinine Ratio in a Randomized Clinical Trial Comparing Aflibercept, Bevacizumab, and Ranibizumab for Diabetic Macular Edema

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**PURPOSE.** To compare blood pressure and urine albumin-creatinine ratio over time for participants receiving aflibercept, bevacizumab, or ranibizumab.

**METHODS.** Preplanned secondary analyses from a randomized trial comparing aflibercept, bevacizumab, and ranibizumab for diabetic macular edema (DME). The Diabetic Retinopathy Clinical Research Network (DRCR.net) enrolled 660 participants with DME and visual acuity 20/32 or worse in at least one eye. Eyes received intravitreal injections of 2.0 mg aflibercept, 1.25 mg bevacizumab, or 0.3 mg ranibizumab based on a structured retreatment protocol over 2 years. Main outcome measures were (1) a change in blood pressure at 2 years, and (2) a change in urine albumin-creatinine ratio (UACR) at 1 year.

**RESULTS.** At baseline, 95 participants (14%) had normal blood pressure, 220 (33%) had borderline blood pressure elevation, 206 (31%) had mild blood pressure elevation, and 139 (21%) had moderate blood pressure elevation. Average change in mean arterial pressure from baseline to 2 years was  $-1.2 \pm 15$ ,  $-1.8 \pm 13.5$ ,  $-2.6 \pm 14.4$  mm Hg in the aflibercept, bevacizumab, and ranibizumab groups, respectively (global  $P = 0.69$ ). At baseline 247 participants (38%) had no albuminuria ( $<30$  mg/g), 195 (30%) had microalbuminuria (30–300 mg/g), and 212 (32%) had macroalbuminuria ( $>300$  mg/g). Changes in UACR category were not different among treatment groups at the 52-week visit (global  $P = 0.29$ ).

**CONCLUSIONS.** There do not appear to be treatment group differences for changes in blood pressure or UACR as a reflection of kidney function in patients with DME treated with aflibercept, bevacizumab, or ranibizumab.

**Keywords:** anti-VEGF, blood pressure, UACR, diabetic macular edema

Intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) agents have become standard treatment for central-involved diabetic macular edema (DME) based on results of several clinical trials.<sup>1–5</sup> The Diabetic Retinopathy Clinical Research Network (DRCR.net) conducted a randomized comparative effectiveness trial (Protocol T) evaluating the relative efficacy and safety of three anti-VEGF agents, aflibercept, bevacizumab, and ranibizumab, for treatment of central-involved DME with vision loss.<sup>1</sup>

When bevacizumab has been used systemically to treat certain types of cancers, systemic side effects have been reported including hypertension, proteinuria, thrombotic microangiopathy, and cardiovascular complications.<sup>6</sup> The majority of reports from ophthalmic studies have indicated that rates of thromboembolic events are similar in participants with and without anti-VEGF injections, at doses that are approximately 400 times smaller than the systemic dose. However, some reports have suggested that rates of cardiovascular and cerebrovascular events might be greater in participants who

received ocular anti-VEGF injections.<sup>7,8</sup> Even less is known about the relative effects of different anti-VEGF agents on systemic adverse events. Previous large scale studies have not demonstrated a difference between systemic adverse event rates among patients receiving different, intravitreally administered anti-VEGF agents, but these reports have focused on primarily nondiabetic populations.<sup>9,10</sup> In DRCR.net Protocol T, the rate of cardiovascular and cerebrovascular events as defined by the Anti-Platelet Trialists' Collaboration was slightly higher in the ranibizumab group as compared with the aflibercept and bevacizumab groups at 2 years, although this difference could be due to chance as it falls within the range of anti-VEGF associated adverse event rates consistent with other studies.<sup>11</sup>

Given the current gap in knowledge as to whether there is a difference in systemic adverse events among anti-VEGF agents when given for ophthalmic indications, an ancillary study to Protocol T was performed obtaining blood pressure measurements and urine samples to assess kidney function. This report compares blood pressure changes and albuminuria changes



over time for participants receiving aflibercept, bevacizumab, or ranibizumab for DME treatment.

## METHODS

The study protocol is available in the public domain at [www.drccr.net](http://www.drccr.net). The study adhered to the tenets of the Declaration of Helsinki and was approved by multiple institutional review boards. Study participants provided written informed consent. All participants were at least 18-years old and had type 1 or 2 diabetes. Detailed descriptions of study eligibility criteria and the structured anti-VEGF retreatment algorithm were specified in the study protocol. At the baseline visit, 660 participants were randomly assigned 1:1:1 to one of the three treatment groups for management of DME: 2.0 mg intravitreal aflibercept, 1.25 mg intravitreal bevacizumab, or 0.3 mg intravitreal ranibizumab. Retreatment with the assigned anti-VEGF agent could occur as frequently as monthly through 2 years, but was deferred once study eyes met prespecified sustained stability or success criteria related to changes in visual acuity and central retinal thickness on optical coherence tomography. If indicated, the same anti-VEGF was given in the nonstudy eye as in study eye, but treatment frequency was at investigator discretion.

Systolic and diastolic blood pressure were measured three times using the same automated blood pressure monitor (Omron 10 Series Plus; Omron Healthcare, Inc., Kyoto, Japan) after participants had been sitting for 10 minutes at the following visits: baseline, 4, 8, 12, 52, and 104 weeks. Using the average of the three measurements, blood pressure was categorized into four groups: normal (systolic <120 mm Hg and diastolic <80 mm Hg), borderline elevation (systolic 120–139 mm Hg or diastolic 80–89 mm Hg), mild elevation (systolic 140–159 mm Hg or diastolic 90–99 mm Hg), and moderate elevation (systolic  $\geq$ 160 mm Hg or diastolic  $\geq$ 100 mm Hg).<sup>12</sup> Mean arterial pressure (MAP) was also calculated.

At the baseline and 52-week protocol visits, urine samples were collected to assess kidney function. The samples were frozen at  $-20^{\circ}\text{C}$  and shipped within 7 days of collection to the Advanced Research and Diagnostic Laboratory at the University of Minnesota for measurement of urinary albumin and creatinine. Urine albumin-creatinine ratio (UACR) was calculated and categorized into three levels: no albuminuria (<30 mg/g), microalbuminuria (30–300 mg/g), or macroalbuminuria (>300 mg/g).<sup>13</sup> In addition, participants were asked to return 2 to 3 days after one of the first three injections for an optional visit to obtain a blood pressure and urine sample.

The MAP treatment group comparison was performed using analysis of covariance (ANCOVA) with adjustment for baseline level. Fisher's exact test was used to compare categorical UACR among treatment groups. Ordinal logistic regression was used to assess the association between urine albumin-creatinine ratio category and characteristics of interest at baseline. All *P* values are two-sided. SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA) was used for all statistical analyses.

## RESULTS

### Blood Pressure

At baseline, 535 (81%) of all 660 participants reported a pre-existing condition of hypertension. Nearly 70% of the participants (*N* = 456) were on treatment with angiotensin-converting enzyme inhibitor (ACE inhibitor) or angiotensin receptor blockers (ARB) at the time of enrollment, while an additional 74 (11%) participants (24 [11%] in aflibercept group, 23 [11%] in bevacizumab group, and 27 [12%] in ranibizumab

group) started an ACE inhibitor or ARB after enrollment. The average duration of diabetes was  $17 \pm 11$  years. Baseline average systolic blood pressure, diastolic blood pressure, and MAP were similar across the treatment groups (Table 1). Combining all treatment groups, 95 (14%) participants had normal blood pressure, 220 (33%) had borderline elevation, 206 (31%) had mild elevation, and 139 (21%) had moderate elevation. Average baseline systolic blood pressure, diastolic blood pressure, and MAP were  $139 \pm 20$ ,  $83 \pm 11$ , and  $102 \pm 13$  mm Hg, respectively. Table 1 shows the changes in blood pressure at each follow-up visit by treatment group. Mean change in MAP at 2 years from baseline was  $-1.2 \pm 15$ ,  $-1.8 \pm 13.5$ ,  $-2.6 \pm 14.4$  mm Hg in the aflibercept, bevacizumab, and ranibizumab groups, respectively (global *P* = 0.69). At 2 years, 63 (32%), 59 (33%), and 67 (37%) of participants in the aflibercept, bevacizumab, and ranibizumab groups, respectively, improved from their baseline category, while 59 (30%), 65 (36%), and 42 (23%) worsened. The mean systolic and diastolic blood pressure over time is shown in the Figure.

### Urine Albumin-Creatinine Ratio

Among the 654 participants who had an available urine sample at the baseline visit, 82 (13%) participants reported pre-existing kidney disease. Combining all treatment groups, 247 (38%) participants had no albuminuria, 195 (30%) had microalbuminuria, and 212 (32%) had macroalbuminuria. The median baseline UACR level was 67 mg/g. The relationship between baseline demographic factors and baseline UACR is presented in Table 2.

Higher baseline HbA1c and higher blood pressure were both significantly associated with higher UACR levels (*P* = 0.005 and *P* < 0.001, respectively). With the adjustment for these two baseline factors, non-Hispanic whites appeared less likely to have macroalbuminuria (28%) compared with Hispanics (44%, *P* = 0.003), but not with African Americans (38%, *P* = 0.14).

Kidney function as assessed by UACR also was associated with baseline ocular characteristics in multivariable models controlling for baseline HbA1c and hypertensive status. Among 644 participants who had an available urine sample and a gradable fundus photograph at baseline, the distribution of UACR categories was different across baseline diabetic retinopathy subgroups: 40%, 31%, and 28% had no albuminuria, microalbuminuria, or macroalbuminuria, respectively, in nonproliferative diabetic retinopathy (NPDR) group (diabetic retinopathy [DR] severity of level 53 or better, *N* = 490), and 30%, 24%, and 46%, respectively, in the PDR group (DR severity level of 60 or worse, *N* = 154), respectively (*P* < 0.001). On average, individuals with macroalbuminuria also had worse baseline study eye visual acuity (*P* = 0.002).

The distribution of UACR categories was similar across anti-VEGF treatment groups when obtained at the optional 2- to 3-day postinjection visit (*P* = 0.55) and required 52-week protocol visit (*P* = 0.44; Table 3). At the 52-week visit, microalbuminuria was present in 68 (34%) and macroalbuminuria in 58 (29%) participants treated with aflibercept, 64 (33%) and 63 (32%), respectively, treated with bevacizumab, and 56 (28%) and 74 (38%), respectively, treated with ranibizumab. Changes in UACR categories were not different among treatment groups at the postinjection (*P* = 0.18) or 52-week visit (*P* = 0.29; Table 3). While 77% to 78% in each group maintained their baseline UACR category at 52 weeks, improvement in UACR category was seen in 23 (11%), 14 (7%), and 14 (7%) of the aflibercept, bevacizumab, and ranibizumab groups, respectively, and worsening was present in 21 (10%), 28 (14%), and 31 (16%), respectively. On average, participants received 9 to 10 intravitreal injections through 52 weeks regardless of treatment group assignment and baseline UACR category (Table 3).

TABLE 1. Blood Pressure (mm Hg) by Visit and Treatment Group

	Aflibercept	Bevacizumab	Ranibizumab	P Value*
Baseline, <i>N</i>	224	218	218	
MAP, mean ± SD	101 ± 14	101 ± 12	103 ± 12	
Normal blood pressure, <i>N</i> (%)	41 (18)	33 (15)	21 (10)	
Borderline elevation, <i>N</i> (%)	68 (30)	71 (33)	81 (37)	
Mild elevation, <i>N</i> (%)	65 (29)	73 (33)	68 (31)	
Moderate elevation, <i>N</i> (%)	50 (22)	41 (19)	48 (22)	
2-3 d postinjection, <i>N</i> †	175	169	152	0.62
MAP, mean ± SD	102 ± 14	103 ± 13	103 ± 13	
Change from baseline, mean ± SD	+1.5 ± 12.3	+1.7 ± 10.5	+0.2 ± 11.3	
Normal blood pressure, <i>N</i> (%)	26 (15)	17 (10)	22 (14)	
Borderline elevation, <i>N</i> (%)	57 (33)	60 (36)	52 (34)	
Mild elevation, <i>N</i> (%)	54 (31)	56 (33)	44 (29)	
Moderate elevation, <i>N</i> (%)	38 (22)	36 (21)	34 (22)	
4 wk, <i>N</i>	218	216	215	0.76
MAP, mean ± SD	101 ± 14	101 ± 13	102 ± 14	
Change from baseline, mean ± SD	0 ± 11.2	+0.1 ± 11.1	-1.0 ± 11.3	
Normal blood pressure, <i>N</i> (%)	41 (19)	31 (14)	32 (15)	
Borderline elevation, <i>N</i> (%)	62 (28)	74 (34)	72 (33)	
Mild elevation, <i>N</i> (%)	67 (31)	70 (32)	73 (34)	
Moderate elevation, <i>N</i> (%)	48 (22)	41 (19)	38 (18)	
8 wk, <i>N</i>	210	211	207	0.20
MAP, mean ± SD	101 ± 14	101 ± 13	101 ± 14	
Change from baseline, mean ± SD	-0.8 ± 11.5	+0.3 ± 11.9	-2.0 ± 10.7	
Normal blood pressure, <i>N</i> (%)	39 (19)	27 (13)	38 (18)	
Borderline elevation, <i>N</i> (%)	76 (36)	74 (35)	73 (35)	
Mild elevation, <i>N</i> (%)	53 (25)	65 (31)	60 (29)	
Moderate elevation, <i>N</i> (%)	42 (20)	45 (21)	36 (17)	
12 wk, <i>N</i>	209	206	201	0.52
MAP, mean ± SD	100 ± 13	101 ± 13	101 ± 13	
Change from baseline, mean ± SD	-1.4 ± 11.7	-0.1 ± 12.8	-1.9 ± 12.3	
Normal blood pressure, <i>N</i> (%)	36 (17)	31 (15)	34 (17)	
Borderline elevation, <i>N</i> (%)	76 (36)	63 (31)	72 (36)	
Mild elevation, <i>N</i> (%)	67 (32)	71 (34)	60 (30)	
Moderate elevation, <i>N</i> (%)	30 (14)	41 (20)	35 (17)	
52 wk, <i>N</i>	208	204	203	0.80
MAP, mean ± SD	100 ± 14	101 ± 14	102 ± 15	
Change from baseline, mean ± SD	-0.8 ± 13.6	-0.1 ± 13.4	-0.7 ± 14.8	
Normal blood pressure, <i>N</i> (%)	39 (19)	26 (13)	30 (15)	
Borderline elevation, <i>N</i> (%)	75 (36)	83 (41)	71 (35)	
Mild elevation, <i>N</i> (%)	55 (26)	55 (27)	65 (32)	
Moderate elevation, <i>N</i> (%)	39 (19)	40 (20)	37 (18)	
104 wk, <i>N</i>	197	179	182	0.69
MAP, mean ± SD	100 ± 14	99 ± 13	100 ± 13	
Change from baseline, mean ± SD	-1.2 ± 15	-1.8 ± 13.5	-2.6 ± 14.4	
Normal blood pressure, <i>N</i> (%)	32 (16)	26 (15)	32 (18)	
Borderline elevation, <i>N</i> (%)	68 (35)	71 (40)	71 (39)	
Mild elevation, <i>N</i> (%)	63 (32)	50 (28)	49 (27)	
Moderate elevation, <i>N</i> (%)	34 (17)	32 (18)	30 (16)	

The average of the 3 MAPs calculated from each of three blood pressure measurements (diastolic + 1/3 [systolic - diastolic]). Blood pressure was defined into four categories based on systolic and diastolic pressure (in mm Hg): normal (systolic <120 and diastolic <80), borderline elevation (systolic 120-139 or diastolic 80-89), mild elevation (systolic 140-159 or diastolic 90-99), and moderate elevation (systolic ≥160 or diastolic ≥100). MAP, mean arterial pressure (mm Hg).

\* Global *P* value to compare mean changes in mean arterial pressure (mm Hg) from baseline, using analysis of covariance (ANCOVA) with adjustment for baseline MAP.

† For the total 496 blood pressure measurements taken 2- to 3-days poststudy treatment injection, 350 were taken after the randomization injection (124/122/104 in aflibercept/bevacizumab/ranibizumab group), 100 were taken after the 4-week injection (34/35/31 in aflibercept/bevacizumab/ranibizumab group), and 46 were taken after the 8-week injection (17/12/17 in aflibercept/bevacizumab/ranibizumab group).

## DISCUSSION

Based on results of this study, changes in blood pressure and UACR measurements appear similar with intravitreal treatment with aflibercept, bevacizumab, or ranibizumab for DME. Substantial changes in UACR were uncommon across all three

treatment groups. Approximately equal percentages of participants had improvement or worsening in blood pressure at 2 years. Previously published results from this trial stated that 7% to 12% of participants in each treatment group developed hypertension and 11% to 12% experienced renal events based participant self-reporting through 1 year of follow-up.<sup>1</sup> By

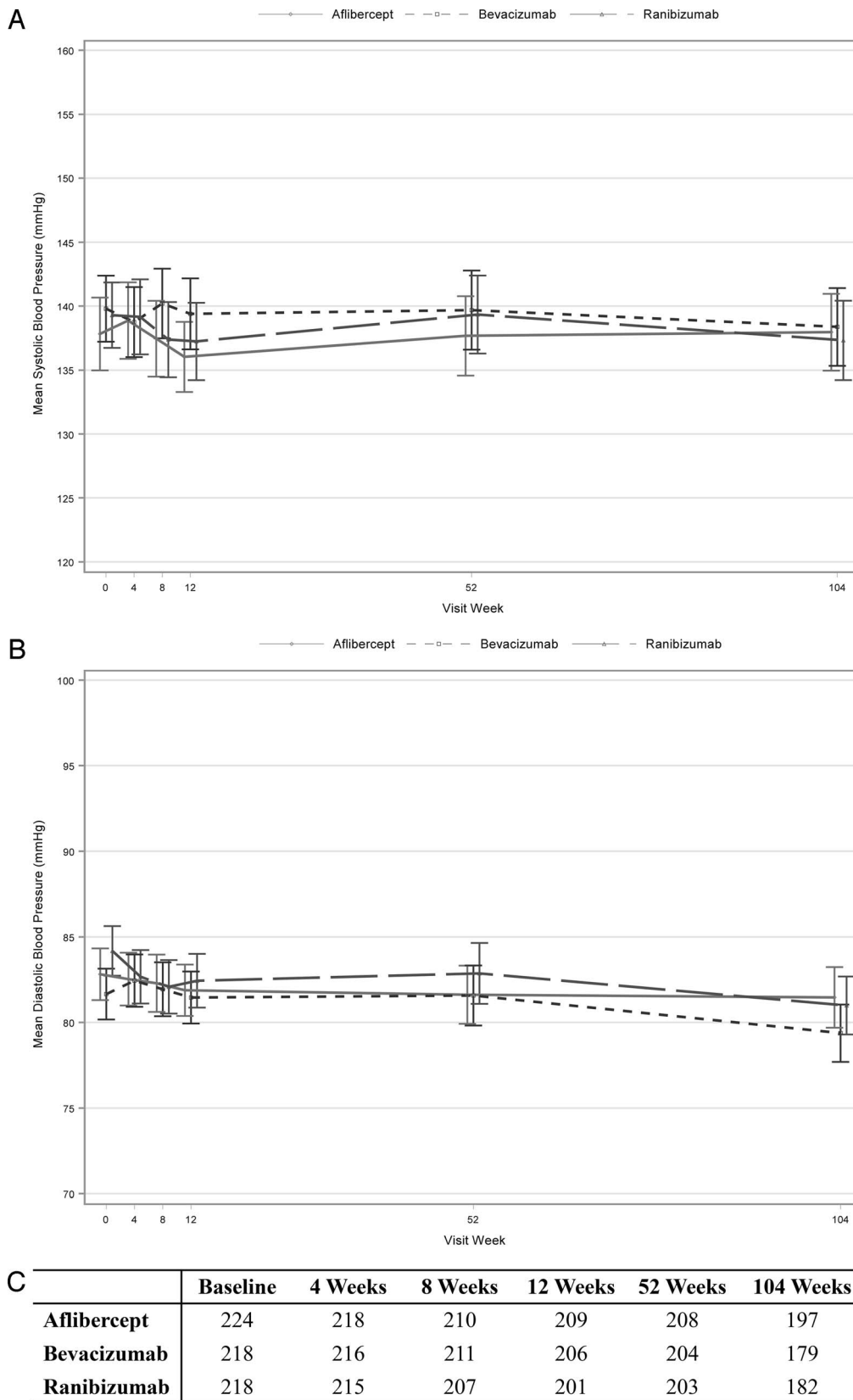


FIGURE. Mean systolic and diastolic blood pressure over time (mm Hg). Mean systolic blood pressure (*top*). Mean diastolic blood pressure (*bottom*). Error bars indicate 95% confidence limits.

TABLE 2. Baseline Characteristics by Urine Albumin-Creatinine Ratio Category

	Baseline Urine Albumin-Creatinine Ratio Subgroups*			P Value†	P Value‡
	No Albuminuria	Microalbuminuria	Macroalbuminuria		
N	247	195	212		
Age, y					
Mean ± SD	61 ± 10	62 ± 10	59 ± 11	0.04	0.05
Median (25th, 75th percentile)	61 (54, 67)	62 (56, 68)	59 (52, 65)		
Sex, N (%)					
Female	120 (39)	99 (32)	87 (28)	0.13	0.34
Male	127 (36)	96 (28)	125 (36)		
Race/ethnicity, N (%)					
White	182 (43)	126 (30)	117 (28)	<0.001	0.004
Black/African American	35 (34)	29 (28)	40 (38)		
Hispanic or Latino	25 (24)	33 (32)	45 (44)		
Other	5 (23)	7 (32)	10 (45)		
Diabetes type, N (%)					
Type 1	26 (53)	9 (18)	14 (29)	0.07§	0.37§
Type 2	215 (36)	184 (31)	193 (33)		
Uncertain	6 (46)	2 (15)	5 (38)		
Duration of diabetes, y					
Mean ± SD	18 ± 12	16 ± 10	18 ± 9	0.79	0.43
Median (25th, 75th percentile)	16 (10, 24)	15 (9, 21)	17 (12, 23)		
Use of insulin, N (%)					
No	77 (37)	69 (33)	61 (29)	0.65	0.51
Yes	170 (38)	126 (28)	151 (34)		
Hemoglobin A1c (%)					
Mean ± SD	7.8 ± 1.5	8.2 ± 1.9	8.3 ± 1.8	0.005	N/A
Median (25th, 75th percentile)	7.6 (6.7, 8.7)	7.7 (6.8, 9.1)	7.8 (7.2, 9.2)		
Body mass index, kg/m <sup>2</sup> ¶					
Mean ± SD	33 ± 8	34 ± 9	34 ± 7	0.34	0.40
Median (25th, 75th percentile)	32 (28, 36)	33 (28, 39)	33 (29, 38)		
Smoking status, N (%)					
Never	166 (40)	128 (31)	122 (29)	0.11	0.04
Prior	65 (34)	54 (28)	72 (38)		
Current	16 (34)	13 (28)	18 (38)		
Blood pressure, mm Hg, N (%)#					
Normal blood pressure	58 (62)	23 (24)	13 (14)	<0.001	N/A
Borderline elevation	116 (53)	65 (30)	38 (17)		
Mild elevation	55 (27)	69 (34)	78 (39)		
Moderate elevation	18 (13)	38 (27)	83 (60)		
On treatment of ACE-I or ARB at enrollment, N (%)					
No	85 (42)	54 (27)	64 (32)	0.29	0.89
Yes	162 (36)	141 (31)	148 (33)		
Visual acuity letter score					
Mean ± SD	67 ± 9	64 ± 12	63 ± 13	<0.001	0.002
Median (25th, 75th percentile)	70 (63, 74)	67 (57, 73)	67 (57, 73)		
OCT central subfield thickness (μm, stratus equivalent)**					
Mean ± SD	404 ± 125	401 ± 121	432 ± 142	0.02	0.02
Median (25th, 75th percentile)	373 (304, 470)	374 (308, 457)	407 (315, 510)		
Lens status, N (%)					
PC IOL	60 (38)	49 (31)	49 (31)	0.79	0.21
Phakic	187 (38)	146 (29)	163 (33)		
Diabetic retinopathy severity (ETDRS level), N (%)††					
NPDR or better (level 53 or better)	198 (40)	153 (31)	139 (28%)	<0.001	<0.001
PDR (level 60 or worse)	46 (30)	37 (24)	71 (46)		

OCT, optical coherence tomography; PC IOL, posterior chamber intraocular lens; ETDRS, Early Treatment Diabetic Retinopathy Study; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

\* Urine albumin-creatinine ratio was defined into three categories (in mg/g): no albuminuria (<30), microalbuminuria (30–300), and macroalbuminuria (>300).

† Global P values were obtained from ordinal logistic regression to assess the association between baseline characteristics and baseline urine albumin-creatinine ratio subgroup.

‡ Global P values were obtained from ordinal logistic regression to assess the association between baseline characteristics and baseline urine albumin-creatinine ratio subgroup, with adjustment for hemoglobin A1c level and blood pressure category.

§ Excluding participants with uncertain diabetes type.

TABLE 2. Continued

|| Hemoglobin A1c data were missing for four no albuminuria participants, one microalbuminuria participant, and one macroalbuminuria participant.

¶ BMI data were missing for 30 no albuminuria participants, 15 microalbuminuria participants, and 17 macroalbuminuria participants.

\* Blood pressure was defined into four categories based on systolic and diastolic pressure (in mm Hg): normal (systolic <120 and diastolic <80), borderline elevation (systolic 120–139 or diastolic 80–89), mild elevation (systolic 140–159 or diastolic 90–99), and moderate elevation (systolic ≥160 or diastolic ≥100).

\*\* OCT central subfield thickness data were missing for three no albuminuria participants, three microalbuminuria participants, and two macroalbuminuria participants.

†† Diabetic retinopathy severity data were missing for three no albuminuria participants, five microalbuminuria participants, and two in macroalbuminuria participants.

systemically evaluating changes in blood pressure and UACR measurements over time, this study provided additional quantitative information on systemic side effects when ocular anti-VEGF agents were administered over 2 years of follow-up.

In the current era, approximately 27% of United States adults with diabetes have albuminuria, of whom approximately 75% have microalbuminuria and 25% have macroalbuminuria.<sup>14</sup> However, in this trial, at baseline, approximately two-thirds of participants had albuminuria, among whom approximately half had microalbuminuria and half macroalbuminuria; interestingly, only 13% of participants self-reported a history of kidney disease. Multiple studies have reported associations between diabetic nephropathy and DR.<sup>15,16</sup> As a result, one might expect that kidney disease in this cohort of participants

with DME to be more prevalent than among patients with diabetes with earlier or no retinopathy.

To our knowledge, there are no published reports providing baseline levels of UACR in a large cohort of patients with DME to determine prevalence of kidney disease in similar cohorts. However, unpublished data (Karen Chu, personal communications, 2017) from the VISTA trial that measured urine protein and creatinine ratio (UPCR) at baseline among 461 participants with similar characteristics as Protocol T, showed that approximately 70% of participants had a normal UPCR (<1 g).<sup>17</sup> In the VISTA trials, approximately 54% of participants were on ACE inhibitors and 29% of participants were on receptor blockers compared with 50% and 21% (including 2% on both) in the DRCR.net trial. Given the substantial

TABLE 3. Urine Albumin-Creatinine Ratio (mg/g) by Visit and Treatment Group

	Aflibercept	Bevacizumab	Ranibizumab	P Value*
Baseline, N	221	217	216	
Median (25th, 75th percentile)	69 (14, 548)	68 (16, 660)	61 (13, 777)	
No albuminuria, N (%)	82 (37)	79 (36)	86 (40)	
Microalbuminuria, N (%)	72 (33)	70 (32)	53 (25)	
Macroalbuminuria, N (%)	67 (30)	68 (31)	77 (36)	
2–3 d postinjection, N†‡	172	167	150	
Median (25th, 75th percentile)	72 (12, 484)	84 (18, 677)	75 (17, 858)	0.55
No albuminuria, N (%)	70 (41)	54 (32)	55 (37)	
Microalbuminuria, N (%)	50 (29)	58 (35)	44 (29)	
Macroalbuminuria, N (%)	52 (30)	55 (33)	51 (34)	
Change in UACR from baseline, median (25th, 75th percentile)§	0 (–32, +10)	+2 (–32, +35)	–1 (–47, +11)	0.18
Improved in UACR category, N (%)	10 (6)	13 (8)	10 (7)	
Sustained in UACR category, N (%)	156 (91)	138 (83)	132 (88)	
Worsened in UACR category, N (%)	6 (3)	16 (10)	8 (5)	
52 wk, N†	202	195	197	
Median (25th, 75th percentile)	75 (13, 407)	74 (17, 637)	109 (18, 822)	0.44
No albuminuria, N (%)	76 (38)	68 (35)	67 (34)	
Microalbuminuria, N (%)	68 (34)	64 (33)	56 (28)	
Macroalbuminuria, N (%)	58 (29)	63 (32)	74 (38)	
Change in UACR from baseline, median (25th, 75th percentile)§	+2 (–36, +54)	+4 (–12, +107)	+5 (–16, +137)	0.29
Improved in UACR category, N (%)	23 (11)	14 (7)	14 (7)	
Sustained in UACR category, N (%)	158 (78)	153 (78)	152 (77)	
Worsened in UACR category, N (%)	21 (10)	28 (14)	31 (16)	
Number of injections from baseline to 52 wk by baseline UACR category, mean ± SD				
No albuminuria	9.1 ± 1.9	9.4 ± 2.3	9.2 ± 2.2	
Microalbuminuria	9.4 ± 2.2	10.2 ± 2.5	9.4 ± 2.2	
Macroalbuminuria	8.9 ± 2.1	9.7 ± 2.1	9.7 ± 1.9	

\* Urine albumin-creatinine ratio was defined into three categories (in mg/g): no albuminuria (<30), microalbuminuria (30–300), and macroalbuminuria (>300). Global P value to compare urine albumin-creatinine ratio category or change in UACR category among treatment groups using Fisher's exact test.

† Only including participants who had available urine albumin-creatinine ratio at both baseline and the corresponding follow-up visit

‡ For the total 489 changes in urine albumin-creatinine ratio category 2- to 3-days poststudy treatment injection, 343 were from postrandomization injection (121/121/101 in aflibercept/bevacizumab/ranibizumab group), 100 were from post 4-week injection (34/34/32 in aflibercept/bevacizumab/ranibizumab group), and 46 were from post 8-week injection (17/12/17 in aflibercept/bevacizumab/ranibizumab group).

§ Global P value = 0.51 at postinjection visit and 0.32 at 52 weeks, respectively, for comparing changes in UACR as a continuous variable on the logarithm scale (base 10) between treatment groups, using ANCOVA with adjustment for baseline UACR on log scale (base 10).

differences between baseline measures indicative of potential kidney disease between the two studies, the true rate in patients with DME remains to be determined.

There are several limitations of the study. First, all participants received an anti-VEGF drug and there was not a control group for comparison. Therefore, no assessments can be made with respect to whether anti-VEGF treatment has an effect on UACR or blood pressure. Second, over 80% of participants were on blood pressure lowering medications at the time of study entry, which could impact the ability to assess the effect of anti-VEGF treatments on blood pressure changes. In addition, at each time point blood pressure was only measured on 1 day and could be affected by changes in or compliance with antihypertensive medications. Although it is presumed that this would not bias treatment group comparisons, the incidence of blood pressure worsening cannot be readily determined from the study data. Finally, this study did not measure estimated glomerular filtration rate, which could indicate diabetic nephropathy without micro- or macroalbuminuria.

## CONCLUSIONS

In conclusion, there do not appear to be differences in changes in blood pressure over 2 years or kidney function as assessed by UACR through 1 year based upon treatment with aflibercept, bevacizumab, or ranibizumab. In addition, anti-VEGF treatment with any of these agents does not appear to substantially increase the risk of developing or worsening hypertension or proteinuria during this follow-up period.

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