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ORIGINAL RESEARCH

Insight into 144 patients with ocular vascular events during VEGF antagonist injections

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Aim: To record ocular vascular events following injections of vascular endothelium growth factor (VEGF) antagonists.

Methods: Collaborative multicenter case series (48 cases), literature reviews (32 cases), and reports to the FDA (64 cases) of patients that had vascular occlusions during anti-VEGF therapy were collected and analyzed.

Results: A total of 144 cases of ocular vascular events were identified, with these diagnosed a median of 15 days after anti-VEGF injection. The majority of patients had pre-existing risk factors for cardiovascular events and nine patients had a prior history of glaucoma. Mean visual acuity dropped by 6.4 lines with severe visual loss after injection to NLP (five eyes), LP (six eyes), and HM (two eyes). The overall risk of ocular vascular events following a VEGF antagonist injection was 0.108% in the general population and 2.61% in the diabetic population. Mean retinal arterial constriction after intravitreal bevacizumab in 13 eyes was 21% (standard deviation = 27%), and mean retinal venous constriction was 8% (standard deviation = 30%).

Conclusion: Ocular vascular events are rare during anti-VEGF therapy, but can lead to severe visual loss and may be caused by a number of factors including the vasoconstrictor effect of the drug, a post-injection rise of intraocular pressure, patient stress as a result of the procedure, and the patient's natural history of underlying ocular or systemic diseases. The diabetic population appears to have a tendency towards ocular vascular occlusions.

Keywords: Bevacizumab, retinal artery occlusion, retinal vein occlusion, retinal capillary occlusion, ranibizumab

Introduction

Vascular endothelial growth factor (VEGF) has vasodilatory effects so is used by vascular surgeons to treat ischemic diseases,[1] and intravitreal VEGF antagonists are now being used by ophthalmologists to treat various ischemic retinal disorders.[2,3] Several studies report that fluorescein angiographic findings are absent following the administration of intravitreal bevacizumab or ranibizumab.[4–9] Preliminary case series reported by some researchers suggest the possibility of a temporal link between these injections and subsequent retinal vascular events.[10–21] In the current study additional data that was contributed by various collaborators and supplemented by the literature[22–44] is presented to further analyze the possible relationship between anti-VEGF injections and ocular vascular accidents. Additionally, the current study provides information regarding the characterization of patients developing ocular vascular complications after intravitreal injections of anti-VEGF drugs.

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Methods

The current study is a retrospective survey among members of the American Society of Retinal Specialists who were invited to contribute a detailed protocol of cases that had vascular occlusions (central retinal artery occlusion [CRAO], branch retinal artery occlusion [BRAO], capillary occlusion, central retinal vein occlusion [CRVO], branch retinal vein occlusion [BRVO], anterior ischemic optic neuropathy [AION], and ocular ischemic syndrome) following anti-VEGF therapy. This research was approved by the Institutional Research Board (Rafic Hariri University Hospital, an affiliate of the American University of Beirut). Each center received Ethical Committee approval for the use of anti-VEGF for specific use and data analyses. The data collected included risk factors for vascular occlusion (carotid disease, coronary artery disease, systemic hypertension, diabetes mellitus, migraine, smoking, and glaucoma), the intraocular pressure on discharge, and the time period from intravitreal injection to detection of the vascular event. The total number of injections per investigator was also recorded.

A 14-month prospective study was also performed at Mansoura University using intravitreal bevacizumab. This included 42 patients, 33 of whom had proliferative diabetic retinopathy, seven with age-related macular degeneration, and two with central retinal vein occlusion. The study was approved by the Ethical Committee of Mansoura University.

Additionally, all studies in the literature regarding treatments with ranibizumab, bevacizumab, pegaptanib, and aflibercept as listed in PubMed and Scopus prior to August 2011 were searched for reports of adverse effects. As well as this, detailed reports of adverse effects of anti-VEGF medications sent to the FDA prior to April 2011 were retrieved via patientsville.com (for reports submitted from 2006 to 2009) and eHealthme.com (for reports submitted from 2010 to 2011), and retinal vascular events were selected for the current study.

Digital fundus photography and computerized determination of retinal trunk vessel diameters were performed using the previously described software.[3,45,46] For each case the pre- and post-anti-VEGF treatment fundus photographs were analyzed using custom computer software. For each case a grader (PKK) chose at least two artery segments and two vein segments that were deemed the most suitable for analysis based on image quality, contrast, straightness of the vessel, absence of branching, and absence of vessel crossings. Images of these vessel segments taken before and after anti-VEGF treatment were analyzed for each case. Images were considered non-gradable if the image was of poor quality (low contrast), as judged by the grader. When necessary, images were calibrated by scaling them so that they were of equal size. Results were presented as the relative change in vessel diameter following anti-VEGF treatment.

Results

A total of 144 cases were available for this study, which included 32 cases retrieved from the literature, 64 reports to the Food and Drug Administration (FDA), and 48 cases contributed from 22 centers across Africa, America, Asia, and Europe (Tables 1 and 2). Eight of these cases were part of a prospective study at Mansoura University (Mansoura City, Egypt) of 42 patients treated with intravitreal bevacizumab (33 patients with advanced proliferative diabetic retinopathy, seven with choroidal neovascularization, and two with central retinal vein occlusion). From 1665 reports of adverse effects following treatment with ranibizumab, 7167 reports of adverse effects following treatment with bevacizumab, 355 reports of adverse effects following treatment with pegaptanib, and 74 reports of adverse effects following treatment with aflibercept (VEGF Trap), the current study collected data on twelve ranibizumab-, 28 bevacizumab-, and six pegaptanib-related retinal vascular events.

Overall, 30 received ranibizumab, 9 pegaptanib and 106 bevacizumab (of which 13 received systemic bevacizumab, one received intracameral bevacizumab, one received 0.625 mg intravitreal bevacizumab, six received 2.5 mg intravitreal bevacizumab, and 55 received 1.25 mg intravitreal bevacizumab). The patient's gender was not always specified, but of those patients for whom this was specified there were 53 males and 55 females. In 95 patients, the median age was 67 (range = 0–95 years; mean = 64.5 years). Vascular events were diagnosed a median of 15 days after treatment (n = 56; range = 0–60 days). The median number of prior injections was one (range = 0–34). The right eye was involved in 30 patients, and the left eye in 28 patients (five patients had bilateral events, while the side was not specified for the remainder).

A majority of patients had preexisting risk factors for cardiovascular events. More specifically, diabetes mellitus was documented in a total of 44 patients. There were 37 diabetic patients in the combined group of 80 patients from the collaborative study and the literature review, ie, 46.3% of the combined group had diabetes mellitus. Other systemic disorders of the whole series included systemic hypertension

in 31 patients, coronary heart disease in 16, and carotid artery disease in eight. Moreover, nine patients had a prior history of glaucoma. Mean initial intraocular pressure was 15.5 mm Hg (range = 7–24 mm Hg), and on discharge this was 21.5 mm Hg (range = 11–50 mm Hg) (n = 32). Paracentesis was performed in only three cases after the injection to reverse post-injection ocular hypertension and to facilitate retinal perfusion as assessed by indirect ophthalmoscopy (two eyes had neovascular glaucoma, and one eye had central retinal artery occlusion at a post-injection pressure of 21 mm Hg).

The major ocular conditions under therapy included diabetic retinopathy in 39 patients (21 with proliferative retinopathy and twelve with background retinopathy), wet age-related macular degeneration in 25, and retinal venous occlusion in 18 (13 central and five branch varieties). The ocular vascular events registered were ocular vascular occlusions (of an unspecified type in 30 cases), ipsilateral central retinal artery occlusion (19 cases), contralateral central retinal artery occlusion (one case), branch retinal artery occlusion (four cases), unspecified retinal artery occlusion (14 cases), ophthalmic artery occlusion (two cases), choroidal ischemia (one case), retinal capillary occlusion (31 cases, 19 of which were causing macular ischemia), central retinal vein occlusion (three cases), branch retinal vein occlusion (four cases), unspecified retinal vein occlusion (twelve cases), retinal artery spasm (two cases), anterior ischemic optic neuropathy (16 cases), ischemic optic neuropathy (four cases), and one case of vision loss of unspecified origin (Tables 1 and 2).

The median follow-up time in 48 patients was 3 months (average = 8 months; range = 1–36 months). Mean visual acuity (log Mar) dropped by 6.4 lines from 0.85 (20/142; median = 0.7) to 1.49 (20/618; median = 1.0) (Student's *t*-test n = 62; $P = 0.0002$). 40 eyes lost vision, ten eyes maintained vision, and 15 eyes gained vision at the last carried examination. Severe visual loss after injection to no light perception (NLP) occurred in five eyes, light perception (LP) in six eyes, and hand motion (HM) in three eyes.

Ocular vascular events occurred during anti-VEGF therapy in eight of 42 of patients (19.0%) in this selective prospective study. Overall in 26 centers, 55 ocular vascular events were reported among a total of 51,152 patients (0.108%) that received intravitreal anti-VEGF therapy (Tables 1 and 2). Eight ocular vascular events were reported in five centers among a total of 5340 patients (0.149%) that received intravitreal bevacizumab therapy. In the subset of the population who were diabetic, 15 ocular vascular events were reported in four centers from a total of 575 patients (2.61%; Tables 1 and 2). In one center, two cases of retinal vascular occlusions followed intravitreal VEGF antagonists from a total of 300 retinovascular occlusion cases examined. In a double blind randomized prospective study, two patients (2%) developed retinovascular events among 102 diabetics with macular edema treated with intravitreal ranibizumab, while there were no events reported in the control group.[30] Terui et al[37] described the occurrence of capillary nonperfusion in four out of 58 eyes (6.9%) with branch retinal vein occlusion 1 month after intravitreal bevacizumab (note that this was minimal in three eyes and marked in one); it is unknown if this is related to the injection or part of the natural history of the ocular disease.

Retinal vasoconstriction was observed after both bevacizumab and ranibizumab injections. More specifically, vasoconstriction analyses were available in 13 of the submitted 20 eyes (seven eyes did not meet the requirements for a paired comparison; Table 3). Vasoconstriction was measured between 7 and 30 days (median = 14 days) after injection of bevacizumab (1.25 mg) in 13 eyes. Mean retinal arterial constriction was 21% (standard deviation = 27%) and mean venous constriction was 8% (standard deviation = 30%). Four cases had prominent retinal arterial vasoconstriction of 78%, 57%, 54%, and 28%, while a fifth eye had 33% retinal venous constriction. Vasoconstriction was also measured in one eye that had intravitreal ranibizumab (0.5 mg), with 42% retinal arterial constriction and 16% retinal venous constriction reported.

Discussion

The adverse events associated with systemic bevacizumab include hypertension, proteinuria, and thromboembolism.[44,47] Mourad et al used intravital video microscopy to measure dermal capillary densities in the dorsum of the fingers of patients receiving systemic bevacizumab and showed endothelial dysfunction and rarefaction by laser Doppler flowmetry.[48] The ocular vascular effects of VEGF antagonists are still unclear. Costa et al evaluated the safety of intravitreal bevacizumab injections for the management of macular edema due to ischemic central or hemicentral retinal vein occlusion, with no complications noted at the 25-week follow-up in seven patients.[49] Neubauer et al tried to assess peripheral perfusion before and after intravitreal bevacizumab and described a significant improvement in retinal perfusion post injection in 19 patients with nonproliferative diabetic macular edema.[9] Chung et al found no visual improvement in eyes with diabetic macular ischemia after intravitreal bevacizumab, and

Table 1 Collaborative and literature review of 106 cases of ocular vascular complications of the VEGF antagonist bevacizumab: clinical profile

Case N./ sex/age	Ocular vascular event after	Dose used (mL)	Paracentesis	IOP at discharge post injection	Prior IOP	Glaucoma	Primary eye disease
Arterial occlusion							
1/F/60	CRAO	Bevacizumab 2.5 mg	No	30	15	No	Ischemic CRVO/ PDR/serous macular elevation
2/F/74	CRAO	Bevacizumab 1.25 mg	No	NA	10	No	Ischemic CRVO/ serous macular elevation
3/F/95	CRAO	Bevacizumab 1.25 mg	No	NA	7	No	AMD
4/M/49	CRAO	Bevacizumab 1.25 mg	Yes	21 before tap	14	No	PDR/DM
5/F/47	CRAO	Bevacizumab 1.25 mg	No	14	16	No	PDR/vitreous hemorrhage
6/M/70	CRAO	Bevacizumab 1.25 mg	No	NI	NI	No	CRVO
7/F/56	CRAO	Bevacizumab 1.25 mg	No	NI	NI	No	CRVO
8/F/60	CRAO	Bevacizumab 2.5 mg	No	NA	12	Yes	CRVO
9/M/73	CRAO	Bevacizumab 1.25 mg	No	16	17	No	AMD
10/F/72	CRAO	Bevacizumab 1.25 mg	No	19	20	No	AMD
11/74/F	CRAO	Bevacizumab 1.25 mg	No	<25	<25	No	DM
12/52/F	CRAO	Bevacizumab 1.25 mg	No	20 mmHg	20 mmHg	Yes	NVG
13[31]	CRAO	Bevacizumab	NA	NA	NA	NA	NA
14/F/60[22]	CRAO	Bevacizumab1.25 mg intracameral	Yes	50	20	Yes	PDR/NVG
15[27]	CRAO	Bevacizumab	NA	NA	NA	NA	NA
16/M/78	Contralateral CRAO	Bevacizumab 1.25 mg	NA	NA	NA	NA	AMD
17/M/44	BRAO	Bevacizumab 1.25 mg	No	NI	NA	No	Ischemic CRVO
18/M/76	BRAO	Bevacizumab 1.25 mg	No	28	12	No	AMD
19/M/45	BRAO	Bevacizumab systemic	No	16	16	No	None
20/F/53[32]	BRAO	Bevacizumab 1.25 mg	NA	NA	NA	NA	PDR
21/M/65	Retinal artery occlusion	Bevacizumab					
22/M/80	Retinal artery occlusion	Bevacizumab 2.5 mg					DR
23/F/60	Retinal artery occlusion	Bevacizumab				Yes	
24/F/x	Retinal artery occlusion	Bevacizumab 15mg/kg q 3wk					

Interval injection to detection of vascular occlusion (days)	N. prior injections	OD or OS	Visual acuity prior to vascular event (log MAR)	Visual acuity after vascular event (log MAR)	Follow up after ocular event (months)	Systemic disease and risk of the vascular event per submitting author (new cases per total number of injected patients)
5	1	OD	CF3m (1.6)	20/60 (0.5)	4	HTN DM carotid stenosis 1/19,158
14	1	OD	CF0.3m (2.5)	CF0.3m (2.5)	1	Smoker 1/19,158
28	4	OD	20/50 (0.4)	LP (3.3)	5	HTN CAD 1/19,158
0	1	OS	20/160 (0.9)	NLP (3.6)		DM 1/19,158
45	1	OD	20/200 (1)	HM (3)		DM 1/2,000
30	1	NA	20/200 (1)	CF0.3m (2.5)		HTN 1/2,400 bevacizumab
30	1	NA	20/80 (0.6)	HM (3)		None 1/2,400 bevacizumab
14	0	OD	20/20 (0.0)	HM (3)	6	
15	1	OD	20/100 (0.7)	20/400 (1.3)	15	HTN Smoker 1/6,478 anti-VEGF
10	1	OD	20/160 (0.9)	20/250 (1.1)	18	HTN Smoker CAD 1/6,478 anti-VEGF
2	3	NA	CF (1.6)	NLP (3.6)		DM/CAD
1	1	NA	20/200 (1)	NLP (3.6)		DM/HTN
NA	NA		20/1000 (1.7)	LP (3.3)		1/400 bevacizumab
30	1	OD	20/200 (1)	20/200 (1)	12r	DM
7	NA	NA	NA	NA		1/5,228
21	0	NA	CF0.3m (2.5)	CF1m (2)	3	Hypercholesterolemia, CAD post coronary bypass 3/2,400 bevacizumab
2	1	OD	20/125 (0.8)	CF2m (1.8)	9	HTN 1/2,400 anti-VEGF
NA	13	OD	20/400 (1.3)	20/50 (0.4)	24	HTN DM CAD Smoker 1/19,158
1	1	OS	20/100 (0.7)	20/50 (0.4)	3	HTN cancer
14	1	OS	20/50 (0.4)	20/600 (1.5)	1	DM 1/12 PDR patients Avastin Side Effects Report: 5096382-0 DM Avastin Side Effects Report: 5105228-35105228-3 Avastin Side Effects Report: 5536025-2 Lung cancer on Navelbine Avastin Side Effects Report: 5593981-4

(*Continued*)

Table 1 (*Continued*)

Case N./ sex/age	Ocular vascular event after	Dose used (mL)	Paracentesis	IOP at discharge post injection	Prior IOP	Glaucoma	Primary eye disease
25/M/x	Retinal artery occlusion	Bevacizumab 1.25 mg					CME
26/M/44	Retinal artery occlusion	Bevacizumab 1.25 mg					Retinal vein occlusion
Venous occlusion							
27/M/93	CRVO	Bevacizumab 1.25 mg	No	29	15	Yes	AMD
28/M/50[34]	CRVO	Bevacizumab systemic	NA	NA	NA	NA	None
29/F/65[36]	CRVO-like picture	Bevacizumab 1.25 mg	No	NA	NA	No	PDR
30/F/79	BRVO	Bevacizumab 1.25 mg	No	32	11	No	AMD
31/M/65	BRVO	Bevacizumab 1.25 mg	No	22	16	No	PDR/ischemic DM/ vitreous hemorrhage
32/M/63	BRVO	Bevacizumab 1.25 mg	No	24	16	No	PDR/ischemic DM
33/premature baby[28]	Inferior retinal vein sheathing (nonperfusion)	Bevacizumab 0.625 mg	NA	NA	NA	No	Retinopathy of prematurity
34[39]	Retinal vein occlusion	Bevacizumab 1.25 mg	NA	NA	NA	NA	AMD
35[39]	Retinal vein occlusion	Bevacizumab 1.2 mg	NA	NA	NA	NA	AMD
36/M/90	Retinal vein occlusion (ischemic)	Bevacizumab 1.25 mg					
37/F/x	Retinal vein occlusion (ischemic)	Bevacizumab 1.25 mg					
38/F/x	Retinal vein occlusion	Bevacizumab 1.25 mg					DR
39/F/27	Retinal vein occlusion	Bevacizumab					Retinal neovascularization
40/F/73	Retinal vein occlusion	Bevacizumab 350 mg q2wk					
41/F/x	Retinal vein occlusion	Bevacizumab 1000 mg q3wk					
42/M/69	Retinal vein occlusion	Bevacizumab					CME
43/M/72	Retinal vein occlusion	Bevacizumab					CME

Interval injection to detection of vascular occlusion (days)	N. prior injections	OD or OS	Visual acuity prior to vascular event (log MAR)	Visual acuity after vascular event (log MAR)	Follow up after ocular event (months)	Systemic disease and risk of the vascular event per submitting author (new cases per total number of injected patients)
						Avastin Side Effects Report: 5736856-X, 5746319-3 Avastin Side Effects Report: 6237313-7, 6237504-5, 6253539-0, 6253542-0, 6341872-3; 6358564-7
10	1	OD	20/60 (0.5)	20/400 (1.3)	18	HTN CAD (stent; pacemaker) Left carotid artery disease 1/19,158
1 day after each cycle	NA	OD	20/120 (0.8)	NA		Metastatic adenocarcinoma of colon after 2 cycles of capecitabine, oxaliplatin and bevacizumab
7	0	OD	20/400 (1.3)	20/200 (1)	9	DM
55	1	OS	20/30 (0.2)	20/30 (0.2)	18	HTN CAD Migraine CVA 1/19,158
7	0	OS	CF2m (1.8)	20/200 (1)	3	HTN DM 1/42 prospective study
7	0	OD	CF4m (1.5)	20/80 (0.6)	3	HTN DM 1/42 prospective study
3	0	OU	NA	NA		Retinopathy of prematurity 1/40 patients with retinopathy of prematurity
NA	NA	NA	NA	NA		1/300 of wet AMD
NA	NA	NA	NA	NA		1/300 of wet AMD
						HTN, CAD, dyslipidemia Avastin Side Effects Report: 5197845-X, 5197968-5 Avastin Side Effects Report: 5508336-8, 5532270-0 DM Avastin Side Effects Report: 5706126-4 Side Effects Report: 6054515-3 Colon cancer on capecitabine, oxaliplatin Avastin Side Effects Report: 4839872-5, 4865570-8 Lung cancer Avastin Side Effects Report: 6209258-X Avastin Side Effects Report: 6440612-7 Avastin Side Effects Report: 6440613-9

(*Continued*)

Table 1 (*Continued*)

Case N./ sex/age	Ocular vascular event after	Dose used (mL)	Paracentesis	IOP at discharge post injection	Prior IOP	Glaucoma	Primary eye disease
Retinal vascular occlusion (unspecified)							
44/M/43	Retinal vascular disorder	Bevacizumab 1 mg					DR
45/M/41	Retinal vascular disorder	Bevacizumab 1 mg					DR
46/F/x	Retinal vascular disorder	Bevacizumab 1 mg					DR
47/M/x	Retinal vascular disorder	Bevacizumab 1 mg					maculopathy
48/F/x	Retinal vascular disorder	Bevacizumab 1 mg					
49/M/75	Retinal vascular disorder	Bevacizumab 1 mg					DM
50/F/33	Retinal vascular disorder	Bevacizumab					Vitreous hemorrhage
51-59/9 cases above 40 years	Retinal vascular disorder	Bevacizumab					mixed
Optic neuropathy							
60/F/72	AION	Bevacizumab 1.25 mg	No	NA	12	No	AMD; fellow eye AION
61/F/71	AION	Bevacizumab 1.25 mg	No	16	20	No	AMD
62/M/51	AION	Bevacizumab 1.25 mg	No	NA	NA	No	AMD
63/F/38	AION	Bevacizumab 1.25 mg	No	21	23	Yes	DM
64/F/70	AION	Bevacizumab 1.25 mg	No	NI	NI	No	AMD
65/M/86	AION	Bevacizumab 2.5 mg	No			No	AMD
66/F/92	AION	Bevacizumab 2.5 mg					AMD
67/M/70	AION	Bevacizumab 1.25 mg					AMD
68/M/x	AION	Bevacizumab 10 mg/kg					
69/F/x	AION	Bevacizumab 394 mg days 1 and 15					
70/F/x	AION	Bevacizumab 1.25 mg					DR
71/F/72	AION	Bevacizumab					
72/F/47	Optic neuropathy	Bevacizumab systemic monthly	NA	NA	NA	NA	Glioblastoma right frontotemporal
73/M[42]	Optic neuropathy	Bevacizumab systemic	NA	NA	NA	NA	Glioblastoma
74/F/67[42]	Optic neuropathy	Bevacizumab systemic	NA	NA	NA	NA	Glioblastoma
75/F/59[42]	Optic neuropathy	Bevacizumab systemic	NA	NA	NA	NA	Glioblastoma
Capillary occlusion							
76/F/58	Macular ischemia	1.25 mg Bevacizumab	No	NI	NI	No	Background DR
77/F/73	Macular ischemia	Bevacizumab 1.25 mg	No	NA	NA	No	Pre-PDR

Interval injection to detection of vascular occlusion (days)	N. prior injections	OD or OS	Visual acuity prior to vascular event (log MAR)	Visual acuity after vascular event (log MAR)	Follow up after ocular event (months)	Systemic disease and risk of the vascular event per submitting author (new cases per total number of injected patients)
						DM Avastin Side Effects Report: 5959710-7 DM Avastin Side Effects Report: 5961890-4 DM Avastin Side Effects Report: 6033375-0 HTN Avastin Side Effects Report: 6159169-3 CAD, unstable angina Avastin Side Effects Report: 6291768-0 DM Avastin Side Effects Report: 6438164-01[i] Avastin Side Effects Report: 5724031-4 2010 events from eHealthMe drug outcomes from FDA and community
7	1	OS	CF2m (1.8)	LP (3.3)	0.5	none 1/2,100 bevacizumab
60	1	OS	20/70 (0.55)	20/70 (0.55)	6	HTN 1/333
15	1	OD	20/25 (0.1)	20/25 (0.1)	12r	Pseudoxanthoma elasticum
21	0	OS	20/40 (0.3)	20/25 (0.1)	14	DM 1/150 bevacizumab
28	3	OD	20/60 (0.5)	20/120 (0.8)	6	None 1/500 bevacizumab
30	14	OD	20/70 (0.55)	20/100 (0.7)	12	HTN, prostate cancer, esophageal cancer, on amlodipine 1/6000 injection anti-VEGF
	8	OS	20/70 (0.55)	20/100 (0.7)	48	No significant past medical history, on no medications
	34	OS	20/70 (0.55)	20/200 (1.0) Visual acuity reduced	6	No significant past medical history, on aspirin Renal cancer on interferon Avastin Side Effects Report: 5863726-9, 5872556-3 Breast cancer on capecitabine Avastin Side Effects Report: 5927943-1 DM Avastin Side Effects Report: 6155052-8 Avastin Side Effects Report: 6367854-3
2 years after initial injection	>20 (monthly)	OU	20/200 (1) (amblyopia) OD 20/70 (0.55) OS	LP OD (3.3) NLP (3.6) OS	30	
NA	8	OU	NA	NA		
NA	6	OS	NA	NA		
NA	7	OU	NA	NA		
2	1	OD	20/60 (0.5)	20/400 (1.3)	12	DM 1/2,350 anti-VEGF
42	0	OS	20/80 (0.6)	20/80 (0.6)	3	DM HTN 1/53 retrospective study of BRVO and diabetic maculopathy

(*Continued*)

Table 1 (*Continued*)

Case N./ sex/age	Ocular vascular event after	Dose used (mL)	Paracentesis	IOP at discharge post injection	Prior IOP	Glaucoma	Primary eye disease
78/F/72	Macular ischemia	Bevacizumab 1.25 mg	No	NA	NA	No	BRVO
79/M/66	Macular ischemia	Bevacizumab 1.25 mg	No	16	10	Yes	CRVO/pre-PDR
80/F/37[26]	Macular ischemia	Bevacizumab 1.25 mg	NA	NA	NA	No	Vasculitis
81/M/40[35]	Macular ischemia	Bevacizumab 2.5 mg	NA	NA	NA	No	PDR
82/F/76[25]	Macular ischemia	Bevacizumab 1.25 mg	NA	NA	NA	NA	CRVO ischemic
83/M/74[25]	Macular ischemia	Bevacizumab 1.25 mg	NA	NA	NA	NA	CRVO ischemic
84/M/58[29]	Macular ischemia	Bevacizumab 1.25 mg	No	NA	NA	No	DM
85/ F/58	Macular ischemia	Bevacizumab 1.25 mg	No	20	14	No	PDR/diffuse DM
86/F/60	Macular ischemia	Bevacizumab 1.25 mg	No	18	14	No	PDR/diffuse DM
87/M/64	Macular ischemia	Bevacizumab 1.25 mg	No	20	16	No	PDR/diffuse DM/ vitreous hemorrhage
88/F/65	Macular ischemia	Bevacizumab 1.25 mg	No	22	14	No	PDR/diffuse DM
89/M/64	Macular ischemia	Bevacizumab 1.25 mg	No	18	14	No	PDR/ischemic DM
90/M/52	Macular ischemia	Bevacizumab 1.25 mg	No	24	18	No	PDR/diffuse DM
91/M/70	Hemorrhagic macular infarction; worsening CRVO	Bevacizumab 1.25 mg	NA	NA	15	No	CRVO
92/M/65[23]	Conversion of nonischemic CRVO into ischemic CRVO	Bevacizumab 1.25 mg	NA	NA	NA	NA	CRVO
93[44]	Capillary occlusion Cotton wool spot	Bevacizumab intravitreal					
94[37]	Capillary ischemia	Bevacizumab 1.25 mg	No	NA	NA	No	Nonischemic BRVO
95[37]	Capillary ischemia	Bevacizumab 1.25 mg	No	NA	NA	No	Nonischemic BRVO
96[37]	Capillary ischemia	Bevacizumab 1.25 mg	No	NA	NA	No	Nonischemic BRVO
97/F/62[37]	Capillary ischemia	Bevacizumab 1.25 mg	No	NA	NA	No	Ischemic BRVO
98[41]	Retinal ischemia	Bevacizumab 1.25 mg	NA	NA	NA	NA	CRVO
99/M/66	Capillary occlusion Cotton wool spot	Bevacizumab 1.25 mg	No	14	24	No	AMD
100/F/74	Capillary occlusion Cotton wool spot	Bevacizumab 1.25 mg	No	11	23	No	Idiopathic foveal telangiectasia
101/F/27	Capillary occlusion	Bevacizumab 1.25 mg	No	NA	NA	No	Retinal vasculitis

Interval injection to detection of vascular occlusion (days)	N. prior injections	OD or OS	Visual acuity prior to vascular event (log MAR)	Visual acuity after vascular event (log MAR)	Follow up after ocular event (months)	Systemic disease and risk of the vascular event per submitting author (new cases per total number of injected patients)
28	0	OS	20/60 (0.5)	20/80 (0.6)	2	DM HTN 1/53 retrospective study of BRVO and diabetic maculopathy
4	1	OS	20/100 (0.7)	20/220 (1.04)	30	DM 1 of 1,500 anti-VEGF
7	1	OS	20/50 (0.4)	20/125 (0.8)	1	None
NA	0	OS	20/400 (1.3)	20/400 (1.3)		DM
28	1	OD	20/200 (1)	20/200 (1)	1	DM CVA 1/300 of retinal vascular occlusion cases
28	2	OS	20/100 (0.7)	20/200 (1)	1	DM MI 1/300 of retinal vascular occlusion cases
21	0	OD	20/80 (0.6)	20/200 (1)	6	DM
7	0	OD	20/200 (1)	20/80 (0.6)	3	HTN DM 1/42 prospective study
7	0	OS	20/200 (1)	20/120 (0.8)	3	HTN DM 1/42 prospective study
7	0	OD	CF3m (1.6)	20/80 (0.6)	3	HTN DM Hepatic disease 1/42 prospective study
7	0	OD	20/120 (0.8)	20/80 (0.6)	3	DM 1/42 prospective study
7	0	OS	20/200 (1)	20/80 (0.6)	3	HTN DM 1/42 prospective study
7	0	OD	20/200 (1)	20/120 (0.8)	3	DM 1/42 prospective study
21	0	OS	20/100 (0.7)	20/320 (1.2)	1	None 1/2,000
21	1	OD	20/50 (0.4)	20/800 (1.6)	6	DM
1 month	0	NA	NA	NA	1	1/37 nonischemic branch retinal vein occlusion
1 month	0	NA	NA	NA	1	1/37 nonischemic branch retinal vein occlusion
1 month	0	NA	NA	NA	1	1/37 nonischemic branch retinal vein occlusion
1 month	0	OS	20/120 (0.8)	20/200 (1.0)	1	1 of 21 with ischemic BVO
NA	NA	NA	NA	NA		1/186 total patients in 1 center (1/9 eyes with CRVO, 0/173 eyes with AMD)
30	1	OS	20/200 (1)	20/200 (1)	36	Gout 1/2,500
60	1	OS	20/80 (0.6)	20/70 (0.55)	36	HTN 1/2,500
14	1	OU	20/20 (0)	20/20 (0)	1	No 1/19,158

(*Continued*)

Table 1 (*Continued*)

Case N./ sex/age	Ocular vascular event after	Dose used (mL)	Paracentesis	IOP at discharge post injection	Prior IOP	Glaucoma	Primary eye disease
Miscellaneous							
102/M/55	Ophthalmic artery occlusion	Bevacizumab 1.25 mg	Yes	NA	NA	Yes	PDR/NVG
103/F/40	Choroidal infarction, HTN retinopathy	Bevacizumab 15 mg/kg q3wk					
104[24]	Visual loss	Bevacizumab	NA	NA	NA	NA	PDR
105/M/78	Retinal artery spasm	Bevacizumab 5 mg/kg q2wk					
106/M/x	Retinal artery spasm	Bevacizumab 5 mg/kg q2wk					

Notes: Red, prospective study data; blue, literature data; black, retrospective collaborative case series; black underlined, data reported to FDA till 2009 and eHealthMe from FDA and community for 2010 and late 2009.

Abbreviations: AMD, wet age-related macular degeneration; DR, diabetic retinopathy; PDR, proliferative diabetic retinopathy; DM, diabetic maculopathy (in column of eye disease); NA, not assessed; NI, normal; DM, diabetes mellitus (in column of systemic disease); HTN, systemic hypertension; CAD, coronary artery disease; CRAO, central retinal artery occlusion; BRAO, branch retinal artery occlusion; CRVO, central retinal vein occlusion; BRVO, branch retinal vein occlusion; AION, anterior ischemic optic neuropathy; CME, cystoid macular edema; NVG, neovascular glaucoma; IOP, intraocular pressure; OD, right eye; OS, left eye; OU, bilateral; HM, hand motion; LP, light perception; NLP, no light perception.

no worsening of macular ischemia was found (pers comm; Koh HJ, March 2010).[50]

Evidence suggests that vessel diameter is influenced by the drug.[51–53] Retinal arteriolar diameter decreased by 4.6% ± 4.6% at day 7 and by 8.1% ± 3.2% at day 30 in eleven eyes with neovascular macular degeneration after treatment with intravitreal ranibizumab.[51] Similarly, 1 month after ranibizumab was injected into ten eyes with macular degeneration, Mendrinos et al found a mean arterial vasoconstriction of 8.4% ± 3.2%.[52] Sacu et al found significant retinal arterial and venous vasoconstriction with a significant reduction in retinal perfusion in 27 patients with retinal branch vein occlusion.[53] Soliman et al used bevacizumab to treat ten eyes with diffuse diabetic macular edema, and found that the most pronounced changes in vessel diameter occurred in two patients with proliferative diabetic retinopathy.[3] We measured a higher vasoconstrictor effect and some eyes had marked vasoconstriction. It is also possible that there is a shift from vessel dilation driven by ischemia to constriction induced by VEGF antagonists, hence the large constrictive response which is reported.

Treatment with intravitreal VEGF antagonists is accompanied by exacerbation of systemic hypertension[54] and attenuation of systemic VEGF levels.[55] This effect on the vascular tone may last for 3 weeks following intravitreal injections,[54–56] but Lee et al found that only 30-minute systolic values were significantly higher than baseline blood pressure after bevacizumab injection.[56] It is possible that this acute rise in blood pressure may be related to the stress of the intravitreal injection. Some patients have a panic attack during the injection, others get hyperglycemia,[57] while a few may develop a dendritic corneal ulcer following treatment.[58]

Transient ocular hypertension after intravitreal injection of VEGF antagonists has been emphasized in many studies.[59–62] Persistent ocular hypertension is of recent concern and occurs in around 3.4% of eyes, usually following multiple injections.[62] This may relate to the presence of silicone oil or other large particulate matter in the syringe, such as high molecular weight aggregates in repackaged bevacizumab. A considerable short-term rise in intraocular pressure occurs preferentially in hyperopic eyes[60,62] and eyes with known glaucoma, so there is a need to monitor intraocular pressure and retinal perfusion especially in eyes with poor retinal circulation.[18] Acute angle closure glaucoma may also be precipitated by intravitreal injections.[62]

The risk of ocular vascular events during anti-VEGF therapy was 0.108% in the treatments considered in the current study. The low rate and the large variation in the occurrence of such events among the collaborating centers may be related to several factors including the retrospective nature of the study, the ocular pathology bias, the natural history of ocular disease, and the absence of precisely scheduled fluorescein angiographic studies. Performing detailed eye examinations with fundus photography and fluorescein angiography initially, at 1 week,

Interval injection to detection of vascular occlusion (days)	N. prior injections	OD or OS	Visual acuity prior to vascular event (log MAR)	Visual acuity after vascular event (log MAR)	Follow up after ocular event (months)	Systemic disease and risk of the vascular event per submitting author (new cases per total number of injected patients)
3	1	OS	20/200 (1)	NLP (3.6)	3	DM, carotid artery occlusion 1/256 bevacizumab Glioma, HTN Avastin Side Effects Report: 4969093-7
21	NA	NA	NA	NA		DM Colon cancer on oxaliplatin avastin Side Effects Report: 5407594-8
			Tunnel vision			Colon cancer; obesity on oxaliplatin Avastin Side Effects Report: 5442353-1

and 1 month post-injection in a prospective setting (such as in the prospective study from Mansoura University) yielded higher rates of ocular events than were reported following retrospective quick screening examinations at the time of repeated injections. Many of the reported events were asymptomatic, such as capillary occlusion outside the fovea, and minor branch retinal artery or vein occlusion. In the RESOLVE study, a total of 102 cases having ranibizumab injections for diabetic maculopathy resulted in two cases with retinal vascular events (capillary and arterial occlusions).[30] In the ROCC study, one of the 16 patients with central retinal vein occlusion developed central retinal artery occlusion.[63] Branch retinal artery occurred in one out of twelve consecutive patients with proliferative diabetic retinopathy following intravitreal bevacizumab.[32] In the ANCHOR[64] and MARINA[65] studies (280 and 477 patients, respectively), no retinal vascular events were noted after 2 years of repeated intravitreal ranibizumab for the wet form of age-related macular degeneration. Prior prospective studies and the current survey found that eyes with wet age-related macular degeneration had the lowest frequencies of vascular events (0%–0.3%)[5,65] while eyes with a greater number of ischemic vascular diseases such as proliferative diabetic retinopathy yielded a higher frequency of retinal vascular events (2%–19%, as in the current prospective study).[30] The occurrence of ocular vascular occlusions after anti-VEGF medications was 2.61% in the diabetic population (Tables 1 and 2), almost 24 times the occurrence in the general population receiving VEGF antagonists (Tables 1 and 2).

Three studies show choroidal or retinal vaso-occlusion after intravitreal bevacizumab injections in experimental animals. Peters et al analyzed the acute intravitreal effects of bevacizumab in four cynomolgus monkeys and found that choriocapillaris endothelial cell fenestrations were significantly reduced, and that densely packed thrombocytes and leukocytes regionally occluded the choriocapillaris lumen of treated eyes.[66] Schraermeyer et al found that bevacizumab immune complexes activate platelets and cause thrombosis in choroidal vessels of primate eyes.[67,68] Ameri et al evaluated the effects of intravitreal bevacizumab in a rabbit retinal neovascularization model. An intravitreal VEGF injection was administered and intravitreal bevacizumab was then injected at day 2 and at week 1, and it was found that administration of intravitreal bevacizumab at week 1 resulted in severe capillary nonperfusion at week 2.[69] Bonnin et al demonstrated ocular hypoperfusion after intravitreal bevacizumab in humans. In 15 patients with wet age-related macular degeneration, mean blood flow velocities were measured by ultrasound imaging before, and 4 weeks after, a single intravitreal injection of bevacizumab. Velocities decreased significantly in the central retinal, temporal posterior ciliary, and ophthalmic arteries by 10%, 20%, and 20% respectively.[60,70] Sacu et al found significant vasoconstriction of retinal arteries and veins outside the area of nonischemic retinal branch vein occlusions as well as a

Table 2 Collaborative and literature review of 38 cases of ocular vascular complications of VEGF antagonists excluding bevacizumab (ranibizumab and pegaptanib): clinical profile

Case N./ sex/age	Ocular vascular event after	Dose used (mL)	Paracentesis	IOP at discharge post injection	Prior IOP	Glaucoma	Primary eye disease
Arterial occlusion							
1/M/75	CRAO	Ranibizumab 0.5 mg	No	NI	NA	No	Ischemic CRVO
2/M/67	CRAO	Ranibizumab 0.5 mg	No	15	15	No	DM
3[30]	CRAO	Ranibizumab	NA	NA	NA	NA	DM
4/M/85 (Reimao*)	CRAO	Ranibizumab 0.5 mg	No	38 mmHg	NA	Yes	NVG
5/F/81	Retinal artery occlusion	Ranibizumab					
6/F/x	Retinal artery occlusion	Ranibizumab 0.5 mg					
7/M/84	Retinal artery occlusion	Ranibizumab 0.5 mg		High IOP			AMD
8/F/70	Retinal artery occlusion	Ranibizumab					
9/F/70	Retinal artery occlusion	Ranibizumab 0.5 mg					
10/F/86	Retinal artery occlusion	Pegaptanib					
11/M/67	Retinal artery occlusion	Pegaptanib					
12/F/above 60 years	Retinal artery occlusion	Ranibizumab					AMD
Venous occlusion							
13/M/84	Retinal vein occlusion	Ranibizumab 0.5 mg					
14/M/74	Retinal vein occlusion	Ranibizumab					
Retinal vascular occlusion (unspecified)							
15[37c]	Ocular vascular occlusion	Ranibizumab 0.5 mg	NA	NA	NA	NA	DM
16[37c]	Ocular vascular occlusion	Ranibizumab 0.5 mg	NA	NA	NA	NA	DM
17[37c]	Ocular vascular occlusion	Ranibizumab 0.5 mg	NA	NA	NA	NA	DM
18/M/47	Retinal vascular disorder	Ranibizumab 0.3 mg					CME
19/M/x	Retinal vascular disorder	Ranibizumab					
20/F/66	Retinal vascular disorder	Pegaptanib					AMD

Interval injection to detection of vascular occlusion (days)	N. prior injections	OD or OS	Visual acuity prior to vascular event (log MAR)	Visual acuity after vascular event (log MAR)	Follow up after ocular event (months)	Systemic disease and risk of the vascular event per submitting author (new cases per total number of injected patients)
30	1	OS	20/400 (1.3)	LP (3.3)	2	DM CAD 1/2,400 anti-VEGF 1/16 ROCC study[63]
30	4	OS	20/100 (0.7)	20/400 (1.3)	12	DM HTN 1/6,478 anti-VEGF
NA	NA	NA	NA	NA	12	DM 1/102 eyes prospective study (RESOLVE)
2d	0	OD	20/25 (0.1)	20/80 (0.6)		HTN COPD ex-smoker bilateral carotid stenosis Lucentis Side Effects Report: 6109626-0 HTN, CAD Lucentis Side Effects Report: 6184843-2 Lucentis Side Effects Report: 6210113-X Lucentis Side Effects Report: 6480905-0, 6496635-5 Lucentis Side Effects Report: 6207699-8 HTN, dyslipidemia Macugen Side Effects Report: 5248582-4, 5224175-X Macugen Side Effects Report: 6108967-0
<1 month						2010 events from eHealthMe drug outcomes from FDA and community Lucentis Side Effects Report: 5216324-4/5889807-1 Lucentis Side Effects Report: 5253885-3/5259058-2
NA	NA	NA	NA	NA		DM 1/375 for diabetic CME
NA	NA	NA	NA	NA		DM 1/375 for diabetic CME
NA	NA	NA	NA	NA		DM 1/375 for diabetic CME Lucentis Side Effects Report: 5896098-4 Lucentis Side Effects Report: 6180863-2 Macugen Side Effects Report: 6409650-4

(*Continued*)

Table 2 (*Continued*)

Case N./ sex/age	Ocular vascular event after	Dose used (mL)	Paracentesis	IOP at discharge post injection	Prior IOP	Glaucoma	Primary eye disease
21/M/60	Retinal vascular disorder	Pegaptanib 0.3 mg					AMD
22/Above 60 years	Retinal vascular disorder	Pegaptanib					AMD
23–28/6 cases above 60 years	Retinal vascular disorder	Ranibizumab					mixed
Optic neuropathy							
29/M/75	AION	Ranibizumab 0.5 mg					AMD
30/F/70[37a]	AION OU	Pegaptanib	No	NA	NA	No	AMD OD Diabetic prophylaxis for cataract surgery OS
31/M/93	AION	0.3 mg Pegaptanib					
32/M/72	AION	Pegaptanib					AMD
Capillary occlusion							
33/F/x	Retinal ischemia (macular)	Ranibizumab					
34/F/x	Retinal ischemia (macular)	Ranibizumab 0.5 mg					
35[30]	Capillary occlusion (peripheral)	Ranibizumab	NA	NA	NA	NA	DM
36/F/x	Retinal ischemia (peripheral)	Ranibizumab 0.5 mg					
37/above 60 years	Retinal ischemia	Ranibizumab					Unspecified
Miscellaneous							
38/M/85	Diffuse vascular occlusion	Ranibizumab 0.5 mg	No	NA	15	No	Ocular ischemic syndrome

Notes: Red, prospective study data; blue, literature data; black, retrospective collaborative case series; black underlined, data reported to FDA till 2009 and eHealthMe from FDA and community for 2010 and late 2009; *Reimao reference refers to eposter EP-GLA-405 SOE 2011 Geneve presented by Reimao P, Macedo M, Gomes M, Maia S, Santos M, Meneres MJ, from Portugal.

Abbreviations: AMD, wet age-related macular degeneration; DR, diabetic retinopathy; PDR, proliferative diabetic retinopathy; DM, diabetic maculopathy (in column of eye disease); NA, not assessed; NI, normal; DM, diabetes mellitus; HTN, systemic hypertension; CAD, coronary artery disease; CRAO, central retinal artery occlusion; BRAO, branch retinal artery occlusion; CRVO, central retinal vein occlusion; BRVO, branch retinal vein occlusion; AION, anterior ischemic optic neuropathy; IOP, intraocular pressure; OD, right eye; OS, left eye; CME, cystoid macular edema; NVG, neovascular glaucoma.

significant reduction in the flow velocity of the retrobulbar central retinal artery.[53]

The vascular events reported during VEGF antagonist therapies could be part of the natural history of the underlying ocular disease. A rise in blood pressure, stress of the procedure, the underlying systemic disease, and a sharp rise in intraocular pressure are variables that can be involved in some cases of ocular vascular events, and these variables can be detected and treated. A majority of the patients discussed in the current study had systemic diseases, particularly diabetes mellitus. VEGF antagonism could play a leader role in some cases that demonstrated vasoconstriction by analysis of vessel caliber. VEGF acts as a vessel dilator by stimulating nitric oxide synthesis, and influences the autoregulation

Interval injection to detection of vascular occlusion (days)	N. prior injections	OD or OS	Visual acuity prior to vascular event (log MAR)	Visual acuity after vascular event (log MAR)	Follow up after ocular event (months)	Systemic disease and risk of the vascular event per submitting author (new cases per total number of injected patients)
						Macugen Side Effects Report: 6463543-5 Late 2009 events from eHealthMe drug outcomes from FDA and community 2010 events from eHealthMe drug outcomes from FDA and community
	4	OS	20/40	20/60	1	HTN, hypothyroidism, BPH, angina, on amlodipine, levothyroxine, temazepam, nitroglycerin 1/4500 antiVEGF injection
7d OD 4d OS	0	OD OS	20/40 (0.3) NA	20/4000 (2.2) 20/200 (1)	3 3	DM HTN
				Visual acuity reduced		Macugen Side Effects Report: 4825003-4 Macugen Side Effects Report: 4982605-2 Lucentis Side Effects Report: 5889807-1 Lucentis Side Effects Report: 6454819-6
NA	NA	NA	NA	NA	12	DM 1/102 eyes prospective study (RESOLVE)
					9	Lucentis Side Effects Report: 6037721-3; patient died 9 months after injection 2010 events from eHealthMe drug outcomes from FDA and community
14	1	OD	20/100 (0.7)	LP (3.3)	10	Carotid stenosis

in the microcirculation. If we block this rescuer, the retina may be damaged due to decreased retinal perfusion in the presence of a low ophthalmic systolic pressure. Because retinal vessel diameter is a useful surrogate for retinal perfusion, changes in the diameter of the retinal arterioles may indicate changes in retinal capillary blood flow. Thus, these findings suggest that VEGF antagonists may reduce retinal capillary blood flow, and caution should be exercised in the use of intravitreal VEGF inhibitors in eyes with severe ocular ischemia such as ocular ischemic syndrome with low ophthalmic systolic pressure or severe proliferative diabetic retinopathy.[11,15] Further studies are needed to evaluate the incidence of vascular events during VEGF antagonist therapy in such high-risk patients.[11]

Table 3 Retinal vasoconstriction values in subjects with ocular vascular events during bevacizumab therapy in 13 eyes, and intravitreal ranibizumab therapy in one eye

Case/sex/age	Ocular vascular event after	Bevacizumab (mg)	Primary eye disease	Interval injection to last fluorescein angiography (days)	N. prior injections	Systemic disease	Arterial vasoconstriction from baseline 1.0	Venous vasoconstriction from baseline 1.0
1/F/74	CRAO	1.25	Ischemic CRVO	14	1	Smoker (heavy)	0.93	0.68*
2/F/27	Capillary occlusion	1.25	Retinal vasculitis	14	1	No	0.46*	0.73
3/M/93	CRVO	1.25	CNV	10	1	HTN CAD carotid artery disease	0.90	1.35+
4/M/66	Capillary occlusion CWS	1.25	CNV	30	1	Gout	0.96	0.84
5/M/51	AION	1.25	CNV	15	1	Pseudoxanthoma elasticum	0.72*	0.88
6/F/76	Macular ischemia	1.25	CRVO ischemic	28	1	DM CVA	1.03	0.95
7/M/74	Macular ischemia	1.25	CRVO ischemic	28	2	DM MI	1.03	0.93
8/M/65	BRVO	1.25	PDR	7	0	HTN DM	0.22*	0.67*
9/M/63	BRVO	1.25	PDR	7	0	HTN DM	0.43*	0.85
10/F/ 60	Macular ischemia	1.25	PDR	7	0	HTN DM	0.83	1.82
11/M/64	Macular ischemia	1.25	PDR	7	0	HTN DM Hepatic disease	1.01	0.88
12/M/ 64	Macular ischemia	1.25	PDR	7	0	HTN DM	0.95	0.85
13/M/52	Macular ischemia	1.25	PDR	7	0	DM	Not measurable	0.97
14/M/85	Diffuse vascular occlusion	Lucentis 0.5 mg	Ocular ischemic syndrome	14	1	Carotid stenosis complete	0.58*	0.84

Notes: Red, intravitreal ranibizumab; *refers to marked constriction; +indicates that this value not counted because it was part of CRVO.

Abbreviations: PDR, proliferative diabetic retinopathy; NA, not assessed; CNV, choroidal neovascularization; DM, diabetes mellitus; HTN, systemic hypertension; CAD, coronary artery disease; MI, myocardial infarction; CVA, cerebrovascular accident; CRAO, central retinal artery occlusion; BRAO, branch retinal artery occlusion; CRVO, central retinal vein occlusion; BRVO, branch retinal vein occlusion; AION, anterior ischemic optic neuropathy.

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