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Journal of Ophthalmic Studies

Open Access

RESEARCH ARTICLE

Volume 1 - Issue 1 | DOI: http://dx.doi.org/10.16966/jos.107

The Clinical History of Central Retinal Vein Occlusion: A Cohort Study in Routine Clinical Practice

Hasan Chichan*

Charité, Center for Stroke Research Berlin, Dessau Eye Hospital, Germany

***Corresponding author:** Hasan Chichan, Charité, Center for Stroke Research Berlin, Dessau Eye Hospital, Germany **E-mail:** hasan.t.chichan@gmail.com

Received: 13 Mar, 2018 | **Accepted:** 09 Apr, 2018 | **Published:** 16 Apr, 2018

Citation: Chichan H (2018) The Clinical History of Central Retinal Vein Occlusion: A Cohort Study in Routine Clinical Practice. J Ophthalmic Stud 1(1): dx.doi.org/10.16966/jos.107

Abstract

Aim: This study aims to evaluate the clinical development of symptoms and complications of the central retinal vein occlusions (CRVO) in patients receiving anti-vascular endothelial growth factor (VEGF) therapy, dexamethasone intravitreal implant, laser photocoagulation or a combination of therapies.

Methods: A cohort study was performed at a single academic institution. 378 patients were identified (based on International Classification of Disease (ICD)-10 codes) with retinal vein occlusion (RVO), between 2009 and 2015. The evaluation of the clinical development of symptoms and complications due to central retinal vein occlusions was done. The primary outcome was the change in the mean visual acuityafter 1st, 3rd and 6th month. To be eligible, patients should have no prior other ocular conditions that could affect the outcomes of interest, such as diabetic retinopathy, age-related macular degeneration, Cataract, severe glaucoma or treatment during the study for CRVO.

Results: Visual acuity was affected most in patients between 60-80 years old with CRVO, with a visual acuity of 0.4 (decimal) or less. Significant associations with visual deterioration with time due to CRVO were found with age and history of the development of Myocardial Infarct.

Conclusion: This study highlights CRVO as an important cause of unilateral visual loss in the older population. CRVO was found significantly associated with cardiovascular disorders. We firmly suggest treating the chronic comorbidities that could lead to cardiovascular disorders like diabetes and hypertension, and the referral of the newly diagnosed CRVO patients who are not already being managed by a primary care physician. The present study provides new evidence that patients with CRVO with combination of IVEGF therapies have worse visual outcome compared to individual IVEGF therapy with bevacizumab. The patients who only treated with bevacizumab alone had 0.4 visual acuity (VA) gain compared to 0.15 VA gain in the combination of bevacizumab and ranibizumab.

Introduction

Central retinal vein occlusion (CRVO) is a common retinal vascular disease and a frequent cause of painless blindness in elderly and middle-aged population [1]. An implemented pooled analysis suggested that approximately 16 million people are affected by retinal vein occlusion (RVO) globally 2.5 million of them are CRVO [2]. The incidence and associated burden of RVO is expected to increase globally since the incidence increases exponentially with age, nevertheless, one of 6 CRVO patients are younger than 55 years [3]. Central retinal vein occlusion results in a visual loss because of hypoxia and macular edema. Vascular endothelial growth factor (VEGF) is a cytokine produced by the hypoxic retina that increases vascular permeability leading to macular edema [4]. VEGF work to stimulate endothelial cell hypertrophy, which reduces the capillary lumen and causes more ischemia and thus tends to perpetuate edema. Anti-VEGF treatment could reverse this cycle and facilitate resolution of macular edema. The edema may cause an additional reduction in visual acuity that often exceeds the primary ischemic damage; which is the most frequent complication of vein occlusions [5]. It has been already established that intravitreal levels of VEGF are significantly increased after retinal vein occlusions and that the degree of macular edema is correlated with VEGF levels

in aqueous humour [6]. It has been found that the preservation of the foveal inner/outer segment photoreceptor line after resolution of macular edema was significantly correlated with good visual function [7]. The most common cause of vision loss in CRVO patients is macular edema [8]. Which resolves spontaneously in only 30% of nonischemic type and may not resolve in ischemic cases [9]. Previous Studies showed that vascular endothelial growth factor (VEGF) could take part in the formation of macular edema secondary to CRVO. VEGF is released as a result of retinal hypoxia, which occurs in CRVO due to impaired capillary blood flow [9]. VEGF stimulates angiogenesis and may lead to a neovascularization of the retina, the anterior segment or some cases both, in addition to vascular leakage resulting in macular edema [9]. In CRVO patients, the vitreous level of VEGF correlates with the severity of macular edema [10]. Furthermore, the injections of the anti-VEGF medications in the vitreous body ranibizumab or aflibercept significantly improve visual and anatomic outcomes in patients with macular edema secondary to CRVO [5,10]. Nevertheless, the treatment remains controversial. There are several published studies done to determine the effectiveness of intravitreal injections of bevacizumab in CRVO. Some studies have found no correlation between retinal thickness and visual acuity in patients with CRVO. In a retrospective study with intravitreal bevacizumab for non-ischaemic CRVO, in which they obtained a significant decrease in central retinal thickness, without significant improvement of visual acuity after 12 months of follow-up [11]. In another prospective study of ranibizumab for macular edema due to CRVO, visual acuity and central retinal thickness were not correlated [6].

The impairment of vision is not the only a health issue related to CRVO but also cerebrovascular and cardiovascular diseases, which are a leading cause of morbidity and mortality [12]. Furthermore, the retinal vasculature has gained attention because the retinal blood vessels display notably similar physiologic, embryologic and anatomic characteristics as the cerebral vessels in the brain [13]. Provided that the vasculature of the retina is unique in that the retinal vessel can be visualized without any invasive intervention *via* indirect ophthalmoscopy. Retinal vein occlusion (RVO) related hemodynamic changes and thrombi formation with RVO are due to compression of the adjacent retinal vein by the thickened retinal artery; that is to say, RVO is a type of arterial disease [3]. Nevertheless, reported associations between RVO and Stroke are not compelling. However, there have been some clinical and population based studies in Taiwan that did not report a significant association [14]. On the otherhand, a large population-based study in the United States has found that the event rate for cerebral vascular accidents in patients with RVO was associated with an approximate increase by 2-fold compared to a control group [2].

Despite the introduction of new interventions, the natural history of CRVO is unclear [15]. A major limitation in the current literature is the lack of data of the natural history of CRVO, the long-term visual outcomes, the therapy and risk of developing neovascularization. A better understanding is needed in advising patients regarding prognosis, assessing new treatment options and providing evidence-based interventions. The objective of our study is to evaluate the clinical development of symptoms and complications due to central retinal vein occlusions in patients receiving intravitreal therapies.

Materials and Methods

Study design

This Study performed at department of ophthalmology, städtisches Klinikum Dessau, Sachsen-Anhalt, Germany, was designed as a cohort study and performed in accordance with good clinical practice (International Conference on Harmonization of Technical Requirements of Pharmaceuticals for Human Use (ICH) E6), the Declaration of Helsinki II. According to Danish law, no ethical approval was required for this register study of encrypted personal information.

Participants

This study was designed as a cohort study at a single academic hospital. Patients were included between January 2009, and December 2015, inclusion criteria were as followed:a new diagnosis based on International Classification of Disease (ICD-10) codes of CRVO (H34.8), age 18 years or older, follow-up of at least 6 months after the first anti-VEGF injection, patients who had no laser treatment prior to study inclusion. Exclusion criteria were the following: patients should have no previous other ocular conditions that could affect the outcomes of interest, such as diabetic retinopathy, cataract, amblyopia, age-related macular degeneration, severe glaucoma, other treatment during the study for CRVO, history of pars plana vitrectomy or any prior intravitreal injection treatment.

A total number of 378 patients were identified based on Classification of Disease (ICD)-10 codes with retinal vein occlusion (RVO) between 2009 and 2015. Of the 378 patients 162 patients have had branch retinal vein occlusion, 8 have had hemi central retinal vein occlusion, and 23 have had no adequate documentation. 185 had CRVO with adequate documentation for this study. Of 185 patients 55 who had been diagnosed as having CRVO during the previous 5-year period with intravitreal injection (IVI) therapy relative to the diagnosis with available 6 months follow-up (Figure 1). From the hospital records, we identified the date of presentation, age of the patients, change in visual acuity before and after intravitreal Injection, development of macular edema, the side of the involved eye, number and type of injection, development of neovascular complications (secondary glaucoma and the need of laser photocoagulation therapy, table 2), the development of vision after the first, third and sixth month, continuation of the treatment, present of comorbidities (hypertension, diabetes, cardiac diseases, hypercholesterolemia, glaucoma, history of stroke and number of developed strokes during follow up, Table 1). Code H 34.8 of the International Classification of Disease Tenth Revision [ICD-10] was reviewed using the following criteria for CRVO: swelling of the whole or part of the optic nerve head, dilated retinal veins, intraretinal hemorrhages in all 4 fundus quadrants, macular edema (occasional), and cotton

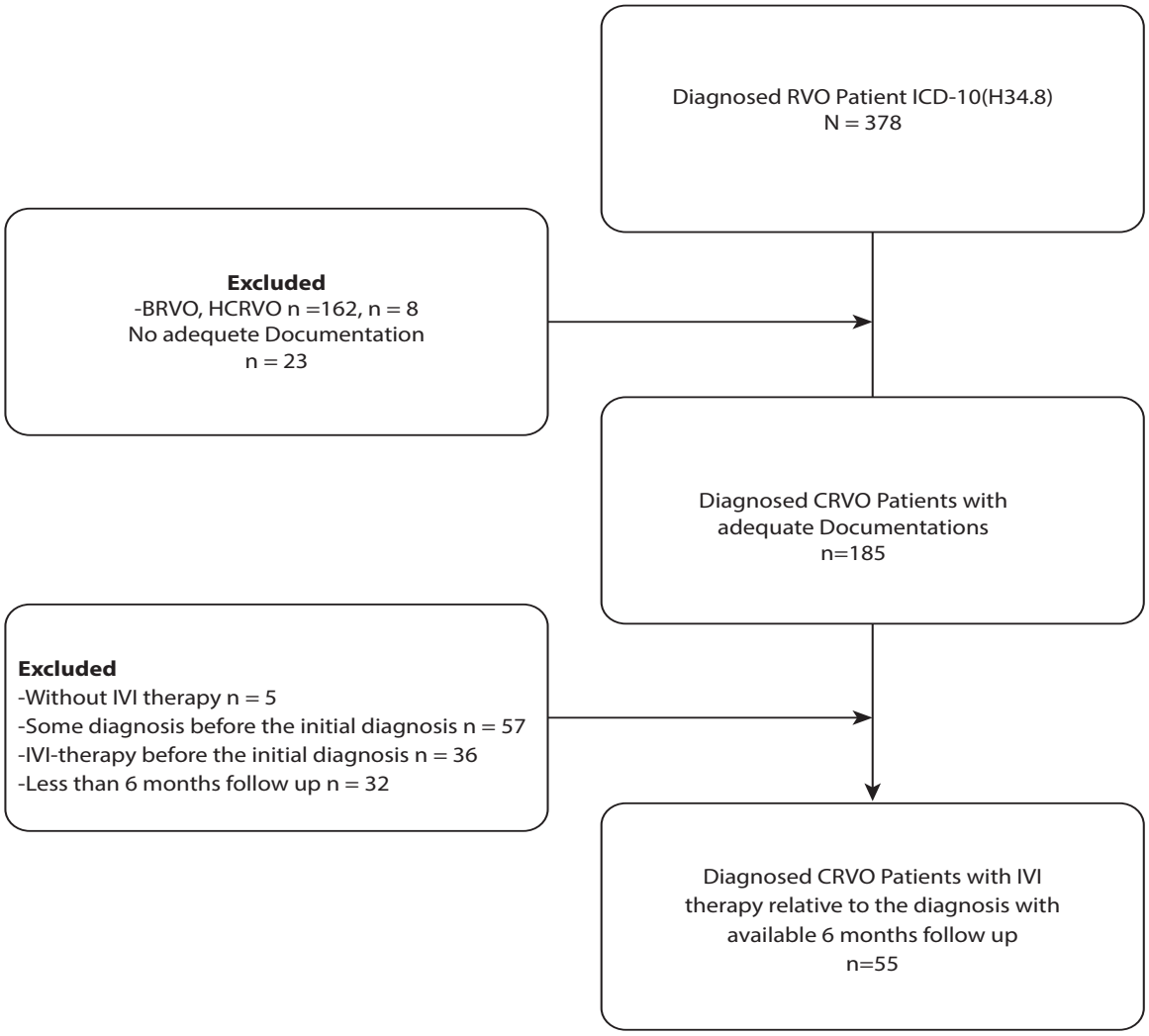

Figure 1: Patients flow chart.

wool spots (occasional). In long-standing cases, the absence of congestion, edema, hemorrhage, and cotton-wool spots was accepted if permanent changes such as collaterals adjacent to the optic disc and photographically undocumented clinical records made by qualified observers supported the diagnosis of CRVO. The concomitant finding of diabetic or nondiabetic microvascular retinopathy was excluded. All patients were 40 years of age or older except for 3 patient 23, 25 and 36 years old of age by the time of therapy.

Statistical analysis and the collection of data

The study cohorts were patients who were treated during the 2009-2015 period, receiving a diagnosis of CRVO (ICD-10 H.348). The data were extracted from the written records of CRVO patients and were examined and registered at the participating institution. To make sure that those cases were newly diagnosed episodes and to avoid the potential confounding factor of a chronic Remission of previously diagnosed CRVO, we excluded subjects who had been diagnosed as having CRVO or other ocular conditions that could affect the outcomes of interest during the last 6-year period (n=130). Of the remaining 55 patients we identified a control group from patients without a history of cardiovascular diseases (n= 42) to do a subgroup analysis. The aim was to investigate the association of cardiovascular diseases on the development of vision. The last-observation-carried-forward approach was used to substitute missing values. Statistical analysis was performed with SPSS 24.0 software.

The main outcome was the mean change in the visual acuity at 1st, 3rd and 6th month following initiation of an anti-VEGF treatment. The visual acuity values of 0,0125, 0,0100 and 0,008 were substituted for VA levels reported as "count fingers," "hand movements," and "light perception," respectively [16]. Patients with vision less than 0.4 considered to be visually impaired [16]. To avoid possible confounding patients were stratified in to groups by their initial VA: 0.5 or better, 0.4 or worse, and was distributed into 4 age groups according to

Table 1: Baseline characteristics of CRVO in relation to visual acuity stratification (decimal).

		0.5 or better (n=16)	Less than 0.4 (n=39)
Age in years ± SD	69.9 ± 13.54		
Age Group	<40	1	1
	40-60	5	4
	60-80	10	23
	80+	0	11
Sex	Male	9	22
	Female	7	17
Eye	OD	9	21
	OS	7	18
Baseline injections:			
Bevacizumab		16	39
Aflibercept		2	7
Ranibizumab		10	18
Ozurdex		2	4
Baseline mean visual acuity LogMar ± SD	0.81 ± 0.64		
Baseline mean visual acuity decimal ± SD	0.32 ± 0.33		
Risk Factors:			
Present of macular edema		12	36
History of glaucoma		2	9
History of hypertension		8	26
History of diabetes		5	5
History of myocardial disease		4	9
History of hypercholesterolemia		1	7
History of stroke		0	4

Table 2: Incidence of complications associated with CRVO, %.

Secondary glaucoma	15 (27%)
Laser photocoagulation	19 (35%)

the age of subjects at the date of diagnosis: younger than 40 years, 40 to 60 years, 60 to 80 years, and older than 80 years. At the visit, all patients had a complete ophthalmological check, including best-corrected visual acuity, slit lamp examination, intraocular pressure measurement (Goldmann applanation tonometry) and macular evaluation with optical coherence tomography. Visual acuity was repeated at each follow-up visit. A total of 55 patients were identified, evidence of systemic disease at presentation and the presence of possible aetiological factors such as hypertension, diabetes, cardiac diseases, hypercholesterolemia and glaucoma were recorded. Patients were treated with a specific anti-VEGF injection depends on physician and patient preference. Patients were followed 6 months after the first injection and retreated based on the examiner's decision of the presence of subretinal or intraretinal fluid as seen either by careful ophthalmic examination and/or SD-OCT. Bevacizumab, banibizumab, aflibercept injections of 1.25mg/0.05, 0,5 mg/0.05, 40 mg /0.05ml and dexamethasone intravitreal implant 0.7 mg were administered under sterile conditions in the operating theatre *via* the pars plana into the vitreous, according to the national recommendations [17]. After three initial injections, re-treatment was indicated whenever persistent or recurrent intraretinal edema was documented by OCT. VAs were recorded and converted from Snellen to Log MAR for statistical analyses [18].

Results

A total of 185 patients were identified at baseline from inclusion and exclusion criteria. At 1st, 3rd and 6th month, 55 patients remained in the study, either due to loss of follow-up or visits outside of the target time point. We conducted a cohort study to assess the clinical development of visual acuity and the combination of therapies. No published articles examined the clinical development of CRVO incidence in association with receiving individual or a combination of anti-IVGF Therapy and/ordexamethasone intravitreal implant in the routine clinical practice (Table 3 and 4). From 55 patients there were 30 patients that became visually impaired at the end of the study despite the therapy (Kaplan-Meier analysis, Figure 2). Significant associations of visual deterioration with time due to CRVO were found with the history of development of cardiovascular diseases, time to event cox-regression module was performed (figure 3), HR: 3.33 (log rank mantel-cox = 0.004, CI = 1.38-8.06). There were no significant association found between sex of the patient and the visual deterioration with time due to CRVO. This study demonstrates that some patients responded better than others to anti-VEGF treatment, though the factors for the variability in these visual outcomes have been disputed. In the current study, the age showed a relationship with the visual impairment intreated CRVO patients, Cox-Regression module (P = 0.043, HR = 1.038, 95% CI = 1.001-1.077). Patients with initial visual acuities 0.4 or better showed a nonsignificant change in VA over 6 months, the patients with the worst initial VAs showed more improvements in vision. None of the patients showed any severe complications such as uveitis, retinal detachment or endophthalmitis. This study emphasizes CRVO as an important cause of unilateral visual loss in an older population. During the study period, 15 have developed secondary glaucoma, and 19 have required laser photocoagulation therapy (Table 2). The most frequently used combination of IVEGF-Therapy is bevacizumab and ranibizumab group, their mean baseline vision (decimal) was 0.25 and at the last control 0.4 (decimal). Another frequent combination was bevacizumab, and laser photocoagulation, their mean baseline vision (decimal) was 0.05 and at the last control was the same. The third frequent therapy was bevacizumab alone, their mean baseline vision (Decimal) was 0.33 and at the last control 0.7 (decimal, Table 4). In the bevacizumab and ranibizumab group, one patient has had a visual gain more than 0.5 (decimal), 8 patients have had less than 0.05 vision gain. Vision loss was reported in 4 patients. The combination of bevacizumab and laser photocoagulation, on the other hand, had non-significant vision gain of less than 0.05 in 6 patients and only 1 patient has vision gain of 0.32. In the bevacizumab group, only 2 patients out of 10 patients have had vision loss (Table 4).

Table 3: Vision (decimal) in relation to one or combination of treatments.

			Baseline vision	Vision last Control
Vision (decimal) in relation to one or combination of treatments	n	%		
Bevacizumab	10	18%	0.32	0.7
Bevacizumab + Aflibercept	3	5%	0.16	0.08
Bevacizumab + Ranibizumab	17	31%	0.25	0.4
Bevacizumab + Ranibizumab + Aflibercept (IVEGF)	2	4%	0.32	0.4
Bevacizumab + Laser photocoagulation	11	20%	0.05	0.05
Bevacizumab + Ozurdex + Laserphotocoagulation	1	2%	0.32	0.06
Bevacizumab + Aflibercept + Laser photocoagulation	2	4%	0.06	0.01
Bevacizumab + Ranibizumab + Laser photocoagulation	4	7%	0.125	0.13
Bevacizumab+ Ranibizumab + Ozurdex	3	5%	0.16	0.13
Bevacizumab + Ranibizumab + Aflibercept + Ozurdex (IVEGF+ Ozurdex)	1	2%	0.1	0.04
Bevacizumab + Aflibercept + Ranibizumab + Ozurdex + Laser photocoagulation	1	2%	1	0

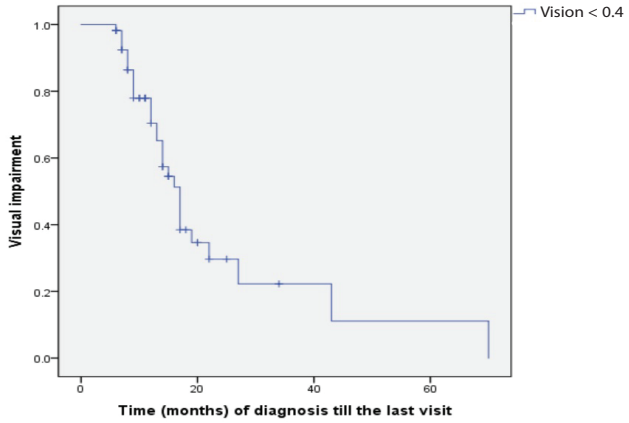

Figure 2: Kaplan-meier analysis, visual impairment (Vision < 0.4) during follow up.

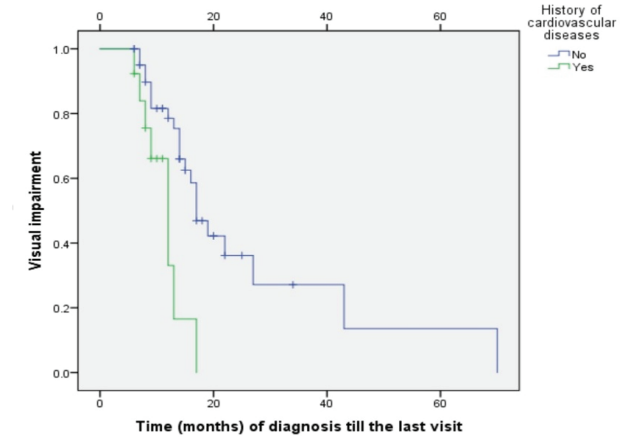

Figure 3: Kaplan-meier analysis, visual impairment (Vision < 0.4) in patients with history of cardiovascular diseases compared to the control group. HR = 3.33, Log Rank Mantel-Cox = 0.004, CI = 1.38-8.06.

Discussion

In this study, we retrospectively examined the clinical history of CRVO, the related comorbidities and the outcomes of the clinical use of intravitreal therapies and/or laser photocoagulation. We also examined whether there is a relation between cardiovascular diseases and the vision development with time. Inclusion criteria, Fundus photographs, written records from patients with the diagnosis of CRVO were examined and registered at the participating institution. The therapy combination of bevacizumab and ranibizumab seems to be effective in improving the mean baseline vision (mean visual gain approximately 0.2 decimal). The monotherapy with bevacizumab appears to be also effective with a mean visual gain of 0.5 (decimal).The laser treatment, on the other hand, had a beneficial effect on neovascularization, but it failed to produce visual improvement, our findings was compatible to the previous studies [16].

There were few limitations that should be considered; the unbalanced sample size in the subgroup analysis of the history of cardiovascular disease. This is due to relatively large control group. As a result there was a relatively large confidence interval in this subgroup analysis. Nevertheless, a larger control group have a better estimate of the mean, variance and a better representation of the population, i.e. selecting a balanced sample size is counterintuitive. Furthermore, a small sample size was used, this is due to very strict exclusion criteria. Because of our primary outcome of interest "the change in visual acuity from the baseline." It's a very delicate outcome that could be easily affected by various confounders, especially in the old age group. This was confirmed in our study, which has showed that CRVO affected mostly the patients between 60-80 years old. Thus, the strict exclusion criteria result in an accurate check of the true effect of CRVO on vision, which is reflected in our statistical analysis. Last, because of the retrospective manner of data acquisition, the patient population did not always have regular follow-up periods, and some patients were lost to follow-up, last observation carried forward was used. This method gives a biased estimate of the treatment effect and underestimates the variability of the estimated result [19]. However one might say that using this method decrease the number of the subjects who are removed from the analysis, it enables the analysis to examine the trends over time, rather than focusing only on the endpoint and doing analyze retrospectively truly reflect the natural history of CRVO.

One may hypothesize that the very different vision prognosis of patients receiving anti-VEGF therapy could be due to the extent of the initial retinal damage. Therefore, a practical

Table 4: Eyes with vision gains and losses from Baseline at Month 6 in relation to the treatment.

Vision gain	Bevacizumab		Bevacizumab+Ranibizumab		Bevacizumab+Laserphotocoagulation	
(decimal), n (%)	N 10	%	N 17	%	N 11	%
0.5	3	30%	1	6%		
0.4	1	10%	2	12%		
0.32	2	20%	2	12%	1	9%
< 0.05	2	20%	8	47%	6	55%
Vision loss						
(decimal), n (%)						
0.5					1	9%
0.4	1	10%	1	6%		
0.32			1	6%	1	9%
< 0.05	1	10%	2	12%	2	18%

option would be freely adjusting the treatment period using a treat-and-extend algorithm. This may help to maintain visual and anatomic gains as well as reduce the challenges and cost of monthly monitoring. In addition, a detailed evaluation of possible long-term adverse events of a combination of anti-VEGF agents is essential, even if previous studies showed no evidence of any toxicity of an individual Anti-VEGF therapy in the dosage used for ophthalmological purposes. The results of the COPERNICUS and GALILEO trials suggest that early, regular intravitreal aflibercept injections are effective at improving visual and anatomic outcomes in patients with CRVO-related macular edema. However, the results from the study of comparative treatments for retinal vein occlusion 2 trial (SCORE 2) trial showed that intravitreal bevacizumab was non-inferior to intravitreal aflibercept regarding the visual acuity outcomes in patients who had macular edema as a result of CRVO [9,20,21]. Since currently used treatments for retinal vein occlusions have achieved only limited success, a combination of anti-VEGF therapy seems to be a novel and innovative approach, which should be further assessed in large, prospective, controlled clinical studies.

It is already been established that there is a positive association between retinal vascular events to mortality, stroke, and MI [22]. We reported however a negative results regarding the occurrence of stroke in our study (only one patient had a stroke during the period of our study). On the other hand, we found a positive correlation between the history of cardiovascular diseases and visual impairment due to CRVO. Given that CRVO patients would present to ophthalmologists, their high cardiovascular risk should be considered, and referral for cardiovascular assessment is recommended. There are many clinical ophthalmological manifestations due to vascular brain damage. Therefore a proper recognition and diagnosis of the disease may protect the patient against serious cardiovascular threatening complications. One may hypothesize that CRVO may play a significant role in preventing cardiovascular and cerebrovascular diseases in young adults because CRVO often leads to acute visual disturbances that may motivate the patient's first visit for medical care. Ophthalmologists should watch for young adults with CRVO, because this symptom could be the first sign of hypertension or cardiovascular diseases, perhaps displaying greater predictive relevance among these patients than among middle-aged or elderly patients.

Funding

The research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Bertelsen M, Linneberg A, Christoffersen N, Vorum H, Gade E, et al. (2014) Mortality in patients with central retinal vein occlusion. Ophthalmology 121: 637-642.
2. Rogers S, McIntosh RL, Cheung N, Lim L, Wang JJ, et al. (2010) The prevalence of retinal vein occlusion: pooled data from population studies from the United States, Europe, Asia, and Australia. Ophthalmology 117: 313-319.
3. Zhou JQ, Xu L, Wang S, Wang YX, You QS, et al. (2013) The 10-year incidence and risk factors of retinal vein occlusion: the Beijing eye study. Ophthalmology 120: 803-808.
4. Thapa R, Maharjan N, Paudyal G (2012) Intravitreal bevacizumab in macular edema secondary to branch retinal vein occlusion: 12-month results. Clin Ophthalmol 6: 1057-1062.
5. Figueroa MS, Contreras I, Noval S, Arruabarrena C (2010) Results of bevacizumab as the primary treatment for retinal vein occlusions. Br J Ophthalmol 94: 1052-1056.
6. Spaide RF, Chang LK, Klancnik JM, Yannuzzi LA, Sorenson J, et al. (2009) Prospective study of intravitreal ranibizumab as a treatment for decreased visual acuity secondary to central retinal vein occlusion. Am J Ophthalmol 147: 298-306.
7. Sakamoto A, Tsujikawa A, Ota M, Yamaike N, Kotera Y, et al. (2009) Evaluation of potential visual acuity in eyes with macular oedema secondary to retinal vein occlusion. Clin Exp Ophthalmol 37: 208-216.
8. Chang LK, Spaide RF, Klancnik JM, Sorenson J, Slakter JS, et al. (2011) Longer-term outcomes of a prospective study of intravitreal ranibizumab as a treatment for decreased visual acuity secondary to central retinal vein occlusion. Retina 31: 821-828.
9. Korobelnik JF, Holz FG, Roider J, Ogura Y, Simader C, et al. (2014) Intravitreal Aflibercept Injection for Macular Edema Resulting from Central Retinal Vein Occlusion: One-Year Results of the Phase 3 GALILEO Study. Ophthalmology 121: 202-208.

10. Saishin Y, Ito Y, Fujikawa M, Sawada T, Ohji M (2017) Comparison between ranibizumab and aflibercept for macular edema associated with central retinal vein occlusion. Jpn J Ophthalmol 61: 67-73.

11. Beutel J, Ziemssen F, Luke M, Partsch M, Bartz-Schmidt KU, et al. (2010) Intravitreal bevacizumab treatment of macular edema in central retinal vein occlusion: one-year results. Int Ophthalmol 30:15-22.

12. Mansour AM, Walsh JB, Henkind P (1992) Mortality and morbidity in patients with central retinal vein occlusion. Ophthalmologica 204: 199-203.

13. Patton N, Aslam T, MacGillivray T, Pattie A, Deary IJ, et al. (2005) Retinal vascular image analysis as a potential screening tool for cerebrovascular disease: a rationale based on homology between cerebral and retinal microvasculatures. J Anat 206: 319-348.

14. Ho JD, Liou SW, Lin HC (2009) Retinal vein occlusion and the risk of stroke development: a five-year follow-up study. Am J Ophthalmol 147: 283-290.

15. McIntosh RL, Rogers SL, Lim L, Cheung N, Wang JJ, et al. (2010) Natural history of central retinal vein occlusion: an evidence-based systematic review. Ophthalmology 117: 1113-1123.

16. Ferris FL, 3rd, Kassoff A, Bresnick GH, Bailey I (1982) New visual acuity charts for clinical research. Am J Ophthalmol 94: 91-96.

17. Jaissle GB, Szurman P, Bartz-Schmidt KU (2005) Empfehlung für die Durchführung von intravitrealen Injektionen. Klin Monatsbl Augenheilkd 222: 390-395.

18. Gregori NZ, Feuer W, Rosenfeld PJ (2010) Novel method for analyzing snellen visual acuity measurements. Retina 30: 1046-1050.

19. Molnar FJ, Man-Son-Hing M, Hutton B, Fergusson DA (2009) Have last-observation-carried-forward analyses caused us to favour more toxic dementia therapies over less toxic alternatives? A systematic review. Open Med 3: e31-e50.

20. Heier JS, Clark WL, Boyer DS, Brown DM, Vitti R, et al. (2014) Intravitreal aflibercept injection for macular edema due to central retinal vein occlusion: two-year results from the COPERNICUS study. Ophthalmology 121: 1414-1420.

21. Pielen A, Clark WL, Boyer DS, Ogura Y, Holz FG, et al. (2017) Integrated results from the COPERNICUS and GALILEO studies. Clin Ophthalmol 11: 1533-1540.

22. Rath EZ, Frank RN, Shin DH, Kim C (1992) Risk factors for retinal vein occlusions. A case-control study. Ophthalmology 99: 509-514.