CENTRAL RETINAL VEIN OCCLUSION IN PATIENTS TREATED WITH LONG-TERM WARFARIN SODIUM (COUMADIN) FOR ANTICOAGULATION

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Purpose: To describe the clinical features of persons who developed central retinal vein occlusion (CVO) while being treated with Coumadin for chronic anticoagulation.

Methods: In a retrospective, comparative, noninterventional case series of patients diagnosed with CVO while being treated with Coumadin as a systemic anticoagulant, visual and anatomical outcomes were compared with those for a cohort of patients diagnosed with CVO who were not treated with any systemic anticoagulation.

Results: Fourteen eyes of 14 patients treated with Coumadin were identified. At presentation, the median international normalization ratio (INR) was 2.20 (range, 1.3–5.0). Eight patients (57%) had a therapeutic INR at the time of CVO. Their visual acuity and perfusion status were similar to those of patients with subtherapeutic INR. At the last follow-up (median, 16 months), visual acuity and perfusion status of the group of 14 eyes were similar to baseline findings ($P = 0.62$). Clinical features and outcomes were similar to those for a cohort of patients with CVO who were not being treated with systemic anticoagulation.

Conclusion: CVO can occur in patients being treated with Coumadin for systemic anticoagulation. Final visual acuity and perfusion status were similar to those in a cohort of patients with CVO who were not treated with Coumadin. Although visual acuity is unaffected, ensuring that the INR for these patients remains in the therapeutic range may be important to help prevent secondary systemic thrombotic and embolic disease.

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Central retinal vein occlusion (CVO) remains a common retinal vascular cause of unilateral visual loss. It is believed to be due to thrombosis within the central retinal vein at the level of, or immediately posterior to, the lamina cribrosa, although the exact pathology CVO is still debated.[1,2] Central retinal vein

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occlusion in persons older than 55 years of age may be caused by an interplay of risk factors that include systemic hypertension, diabetes mellitus, and chronic open-angle glaucoma.[3–5] A variety of systemic, hematologic, and immunologic abnormalities are also associated with the development of CVO, particularly in younger individuals.[6]

Previous reports have suggested the use of systemic thrombolytic and antithrombotic agents, including streptokinase, recombinant tissue plasminogen activator, urokinase, and warfarin sodium (Coumadin, Bristol-Myers Squibb, Princeton, NJ), in the prevention or treatment of CVO.[7–15] However, to our knowledge, no pharmacologic drug regimen has been proven in a prospective, randomized trial to reduce the incidence or alter the natural disease course in eyes with CVO.

Coumadin is widely used as an anticoagulant for various systemic conditions, including venous thromboembolism, cardiac arrhythmia, postmyocardial infarction, and hematologic abnormalities, among others. Individuals treated with therapeutic doses of Coumadin have significant reduction in rates of new or recurrent systemic thromboses and new migratory embolic disease.[16]

In theory, persons receiving a therapeutic dose of Coumadin for anticoagulation may be protected from thrombotic events even in the central retinal vein and thereby protected from the development of CVO. We describe 14 patients older than 55 years of age who developed CVO while receiving Coumadin for anticoagulation and discuss possible mechanisms of pathogenesis in these patients.

Methods

A retrospective chart review of consecutive patients diagnosed with CVO while being treated with Coumadin (group 1) was performed at the Duke University Eye Center (Durham, NC) and the Medical College of Wisconsin (Milwaukee, WI) between January 1997 and November 2002 and at the Long Island Vitreoretinal Consultants (Great Neck, NY) between January 2001 and March 2003. Institutional review board approval was obtained. Patients were diagnosed with CVO if they had intraretinal hemorrhage in four quadrants, dilated, tortuous retinal veins, and optic disk congestion.

Demographic information, medical history, indication for anticoagulation, and level of anticoagulation (reflected by the patient's international normalization ratio [INR] recorded from the laboratory measurement immediately before CVO) were collected in an unmasked fashion. The level of anticoagulation was considered to be therapeutic or nontherapeutic based on the indication for anticoagulation as monitored by the patient's primary care physician or cardiologist. Additional patient-specific laboratory tests were ordered by the examining ophthalmologist, when indicated, to evaluate for associated systemic causes of CVO.

The date of onset of CVO was defined as the date of onset of symptoms. The initial and final examinations were at the time of first evaluation and last follow-up, respectively. All patients were examined by fellowship-trained vitreoretinal surgeons. In some cases, the patient was examined on a single occasion with no further follow-up. Clinical examination data collected included visual acuity, intraocular pressure, presence of an afferent pupillary defect, iris or anterior chamber angle neovascularization, presence of cystoid macular edema, and presence of vitreous hemorrhage or neovascular glaucoma. Each treating physician classified their patient's CVO as perfused, nonperfused, or indeterminate based on fluorescein angiographic criteria used by the Central Vein Occlusion Study.[17] Interventions used to prevent or treat complications from CVO were also recorded.

A cohort of 43 consecutive patients seen at the Duke University Eye Center between January 1997 and November 2002 who were diagnosed with CVO but were not taking any systemic anticoagulants or antiplatelet agents at the time of onset (group 2) was identified. Similar demographic and clinical data were collected.

Statistical Methods

Descriptive statistics were obtained for all variables including means and SD for continuous variables and frequencies and percentages for categorical variables. Snellen visual acuities were converted to logMAR units. For dichotomous variables that were measured before and after Coumadin usage, McNemar test was used to assess the significance of the difference between the proportions having the attribute at the two time points. Differences with respect to visual acuity and perfusion status between patients in group 1 who had a therapeutic INR and those who did not were compared. The significance of the difference between these two groups was assessed using χ^2 test or Fisher exact test for dichotomous outcome variables and Wilcoxon rank sum test for continuous variables. Similar analyses were carried out for comparison of patients treated with Coumadin (group 1) and those who were not (group 2).

Results

In group 1, 14 eyes of 14 patients developed CVO while the patient was receiving Coumadin for sys-

Table 1. Demographics, Anticoagulation Status, Laboratory Evaluation Results, and Therapeutic Interventions

Patient	Age (y)	Sex	Eye	Indication for Anticoagulation	INR	Therapeutic INR	Systemic Workup	Abnormal Laboratory Test Values	Intervention
1	74	F	OS	CVO in fellow eye	1.3	No	Yes	Low INR, anticardiolipin antibodies, APCR; elevated tHcy, ESR, ANA titer	Folic acid, increased Coumadin dose,IV tPA,PPV/EL
2	63	M	OS	Arrhythmia	2.5	Yes	Yes	Elevated tHcy	Folic acid, vitamin B12,Trental (Aventis Pharmaceuticals, Bridgewater, NJ)
3	67	M	OS	Atrial fibrillation	2.9	Yes	Yes	None	PST Kenalog (Bristol–Myers Squibb, Princeton, NJ)
4	58	M	OS	Prosthetic heart valve	3.7	Yes	Yes	None	PRP,CRA (×3)
5	74	F	OS	Deep vein thrombosis	5.0	Yes	No	—	—
6	83	F	OS	Arrhythmia	2.1	Yes	No	—	PRP
7	72	F	OD	Arrhythmia	1.7	No	Yes	None	—
8	80	F	OD	CVA	1.6	No	No	—	—
9	68	M	OD	Atrial fibrillation	1.8	No	Yes	None	—
10	71	F	OD	Deep vein thrombosis	1.8	No	No	—	PRP
11	82	F	OS	Atrial fibrillation	2.8	Yes	No	—	CE/PPV/EL
12	84	M	OS	Atrial fibrillation	1.6	No	No	—	—
13	68	F	OD	Atrial fibrillation	2.8	Yes	No	—	PRP
14	81	F	OS	Arrhythmia	2.3	Yes	No	—	—

INR, international normalized ratio; CVO, central vein occlusion; APCR, activated protein C resistance; tHcy, plasma total homocysteine; ESR, erythrocyte sedimentation rate; ANA, antinuclear antibody, IV tPA, intravitreal tissue plasminogen activator injection; PPV/EL, pars plana vitrectomy with panretinal endolaser photocoagulation; PST, posterior sub-Tenon triamcinolone acetonide injection; PRP, panretinal photocoagulation; CRA, laser chorioretinal anastomosis; —, no laboratory test performed; CVA, cerebral vascular accident; CE, cataract extraction.

temic anticoagulation. Nine patients (64%) were women, and the left eye was involved more commonly (9 eyes [64%]). The median age at onset of CVO was 72 years (range, 58–84 years). The most common indication for anticoagulation was thromboembolism prevention in 9 patients (64%) with cardiac arrhythmia (atrial fibrillation or other nonspecified arrhythmia) (Table 1). Systemic hypertension and diabetes mellitus were present in 11 (79%) and 4 (29%) patients, respectively.

The median INR was 2.20 (range, 1.3–5.0). In each patient, the INR was at least 1.3, indicating some degree of systemic anticoagulation. However, the level of anticoagulation immediately before CVO was considered therapeutic for the systemic condition for which it was indicated only in 8 patients (57%) (Table 1). The median INR for these patients was 2.8 (range, 2.1–5.0) compared with a median INR of 1.6 (range, 1.3–1.8) in nontherapeutic cases ($P < 0.01$). At the last follow-up, there was no difference between those patients whose levels of anticoagulation were therapeutic and those whose levels were not therapeutic in the proportion of patients with perfused CVO at the final visit (75% and 67%, respectively). Patients with a therapeutic INR had a median improvement in visual acuity of 0.20 logMAR unit (range, +0.43 to −1.70 logMAR units) compared with no median change in visual acuity (range, +1.42 to −0.30 logMAR units) in patients with subtherapeutic INR ($P = 0.12$).

Additional systemic laboratory tests were performed for six patients (Table 1); two patients had abnormal laboratory test values. Patient 1 was found to have activated protein C resistance with a normal factor V genotype, mildly elevated plasma total homocysteine level (16 μmol/L), elevated erythrocyte sedimentation rate (78 mm/h), and a low, positive antinuclear antibody titer (1:160). Anticardiolipin antibodies were historically elevated in this patient, and repeated analysis disclosed elevated IgG (49; normal, 1–15) and IgM (13; normal, 1–10) fractions but normal IgA (3; normal, 1–10) fractions. Patient 2 had a mildly elevated plasma total homocysteine level (11.6 μmol/L).

The median duration of CVO at the time of the last follow-up was 16 months (range, 2–36 months), and the median follow-up was 14 months (range, 0–33

Table 2. Ophthalmologic Examination Results at Initial and Final Visits

	Initial Visit					Final Visit					
Patient	Acuity	IOP	NVI	Perfusion Status	CME	Follow-up*	Acuity	IOP	NVI	Perfusion Status	CME
1	20/2000	12	No	P	Yes	17	20/50	12	No	P	No
2	20/100	20	No	I	Yes	20	20/100	23	No	P	Yes
3	20/80	14	No	P	Yes	15	20/60	15	No	P	Yes
4	20/200	19	No	P	Yes	22	20/100	15	No	P	Yes
5	20/200	17	No	P	Yes	5	20/100	9	No	P	No
6	20/50	10	Yes	P	No	0	20/1280	9	Yes	N	Yes
7	20/200	14	No	P	Yes	13	20/80	18	No	P	Yes
8	20/1000	11	No	N	Yes	20	20/800	14	No	N	Yes
9	20/100	15	No	I	Yes	23	20/80	19	No	P	Yes
10	20/60	16	No	P	No	0	20/160	12	Yes	N	Yes
11	20/200	17	No	I	Yes	33	20/2000	27	No	N	Yes
12	20/80	NR	No	P	No	6	20/40	NR	No	P	No
13	20/2000	NR	No	N	Yes	6	20/2000	NR	No	P	No
14	20/100	NR	No	P	No	6	20/100	NR	No	P	No

*Follow-up from initial examination (mo).
IOP, intraocular pressure (mmHg); NVI, neovascularization of iris; CME, cystoid macular edema; P, perfused; I, indeterminate; N, nonperfused; NR, not recorded.

months) (Table 2). Two patients were examined only once. Initially, CVO was perfused in 9 eyes (64%), indeterminate in 3 eyes (21%), and nonperfused in 2 eyes (14%) (Table 2). The median visual acuity at presentation was 0.85 logMAR unit (Snellen equivalent, 20/141; range, 0.40–2.00). The median initial intraocular pressure was 15 mmHg (range, 10–20 mmHg). At presentation, one patient (7%) had evidence of anterior segment neovascularization in the affected eye, and no eyes had neovascular glaucoma. Cystoid macular edema was seen in 11 patients (79%).

Eight patients (57%) underwent interventions to prevent or treat the complications of CVO (Table 1). Patient 1 received an intravitreal injection of recombinant tissue plasminogen activator under an investigational protocol and subsequently required pars plana vitrectomy and panretinal endolaser photocoagulation for nonclearing vitreous hemorrhage. Four patients (29%) required panretinal photocoagulation for significant iris neovascularization. Two patients (15%) required pars plana vitrectomy with endolaser photocoagulation for nonclearing vitreous hemorrhage attributed to the CVO.

At the last follow-up (Table 2), the median visual acuity was 0.70 logMAR unit (Snellen equivalent, 20/100; range, 0.30–2.00). The median visual acuity improved over time (median follow-up, 16 months) by 0.10 logMAR unit ($P = 0.62$). The median intraocular pressure increased by 3 mmHg ($P = 0.51$). At the last follow-up, 10 eyes (71%) were perfused, and 4 eyes (29%) were nonperfused. Perfusion status was unchanged in 8 eyes (57%), improved (from nonperfused or indeterminate to perfused status) in 3 eyes (21%), and worsened (perfused or indeterminate to nonperfused status) in 3 eyes (21%). Cystoid macular edema persisted in 7 eyes (50%) and resolved in 3 eyes (21%).

Demographic and clinical features of patients treated for systemic anticoagulation with Coumadin at the time of CVO (group 1) were compared with those of a cohort of patients with CVO who were not using systemic anticoagulants or antiplatelet agents (group 2; $n = 43$) (Table 3). The two groups were well matched demographically and for medical history with the exception that group 1 eyes more commonly had a history of systemic hypertension ($P = 0.03$) and cardiac arrhythmia ($P < 0.01$). The overall duration of CVO at the final follow-up was similar in the two groups. Group 1 eyes had better initial and final visual acuities than group 2 eyes, but these differences were not statistically significant. In group 2, the initial percentage of eyes with perfused CVO was higher, which declined slightly at the final follow-up. No significant difference in perfusion status was noted between the two groups. In group 2 eyes, neovascularization of iris was observed in 7 eyes (16%), but no eyes developed neovascular glaucoma. Two group 2 eyes (5%) required pars plana vitrectomy with endolaser photocoagulation for nonclearing vitreous hemorrhage. The observed frequency of these neovascular sequelae was not significantly different between group 1 and group 2 eyes.

Table 3. Comparison of Patients Developing CVO While Being Treated With Coumadin (Group 1) With Patients Developing CVO While Not Using Any Systemic Anticoagulants or Antiplatelet Medications (Group 2)

Finding	Group 1	Group 2	P
Demographic			
No.	14	43	
Age (y)	73	70	0.39
Female sex, no. (%)	9 (64)	21 (49)	0.37
Right eye, no. (%)	5 (36)	20 (47)	0.48
Medical history, no. (%)			
HTN	11 (79)	18 (42)	0.03
Cardiac arrhythmia	9 (64)	0	<0.01
Hypercholesterolemia	2 (14)	5 (12)	1.00
CAD	5 (36)	7 (16)	0.14
Total follow-up (mo)	14	7	0.17
Duration of CVO (mo)	16	12.2	0.49
Perfusion status, no. (%)			
Initial perfused	9 (82)	31 (79)	
Initial nonperfused	2 (14)	8 (21)	1.00
Final perfused	10 (71)	27 (73)	
Final nonperfused	4 (29)	10 (27)	0.91
Median visual acuity			
Initial	20/141	20/224	0.45
Final	20/100	20/200	0.26
Vision change (logMAR unit)	-0.1	0	0.11

CVO, central retinal vein occlusion; HTN, systemic hypertension; CAD, coronary artery disease.

Discussion

This case series details the characteristics of 14 individuals who developed CVO while receiving long-term treatment with Coumadin for anticoagulation. In most cases, anticoagulation was initiated solely for a nonocular, systemic condition. Eight patients (57%) had therapeutic INR at the time of onset of CVO, but compared with patients who had subtherapeutic anticoagulation, they did not have a statistically significant difference in final visual acuity or perfusion status. At the last follow-up, 64% of this study population had perfused CVO. Overall, visual acuity remained stable despite attempted therapeutic interventions in some of these patients.

Coumadin is a potent oral anticoagulant that works by inhibiting vitamin K interconversion and subsequent inactivation of the vitamin K–dependent coagulation factors (II, VII, IX, and X).[16] This results in the hepatic production of partially carboxylated proteins with decreased procoagulant activity. Upon initial administration, there is also inhibition of the vitamin K–dependent anticoagulant proteins C and S, which can induce a procoagulant state transiently until full inactivation of the procoagulant proteins occurs. The anticoagulant response to Coumadin is dependent on pharmacokinetic and systemic factors. Hepatic disease, drug interactions, dietary intake of vitamin K, and, in some cases, hereditary resistance to Coumadin may contribute to variability in the anticoagulation effect of the drug. Patients treated with Coumadin require careful monitoring of their protime to gauge the response of the vitamin K–dependent factors. Laboratory standardization in the United States occurs through reporting the protime result compared with a standard INR.[16] A supratherapeutic INR is an indication of excessive anticoagulation and may lead to hemorrhagic complications, including wound site bleeding and gastrointestinal hemorrhage.

Clinical applications of oral anticoagulant use have been validated in numerous clinical trials. Oral anticoagulants have been proven effective in the prevention of deep venous thromboembolism, systemic emboli showers from prosthetic heart implants or chronic cardiac arrhythmias, myocardial infarction, and cerebrovascular accidents. The target INR in patients with each of these conditions is generally within a clinically accepted range but is often tailored to the individual.[16] Despite what may be considered therapeutic levels of anticoagulation, patients may still have stroke and other complications from failed anticoagulant therapy. In our study, only 57% of patients with CVO had a therapeutic INR for the systemic condition that required anticoagulation. Five patients (36%) had evidence of systemic anticoagulation, indicated by an INR of at least 1.6, but it was still considered subtherapeutic for their underlying medical condition requiring anticoagulation.

For the systemic conditions identified in this series, an INR of $\geq$2.0 is generally an accepted target level.[16] An INR of $\leq$1.7, although suboptimal, still suggests pharmacologic inhibition of the patient's normal coagulation cascade. One patient, who was found to have a borderline normal INR of 1.3 immediately before CVO, was being treated with Coumadin as prophylaxis for CVO, which had occurred in the fellow eye 5 years earlier. The patient also had elevated anticardiolipin antibodies, activated protein C resistance, and an elevated plasma total homocysteine level, which are all associated with a hypercoagulable state. The recommended INR for patients with laboratory evidence of a prothrombotic state is between 2.0 and 3.0, although some investigators suggest an even higher level due to false-positive INR in patients with anticardiolipin antibodies.[18] With an increase in the oral Coumadin dose, the INR remained >2.5 in this patient. Patient 5 had a supratherapeutic INR of 5.0. It is unclear whether this level of anticoagulation could have potentiated CVO, but this seems unlikely.

Systemic laboratory evaluation for hypercoagulable states in patients with CVO is more commonly per-

formed for younger persons.[6] Because most CVO patients are older than 50 years of age [3,6,19–21] and may have one or more of the systemic vascular diseases associated with CVO,[3,4,19] routine systemic evaluations are typically not recommended. Although numerous hematologic abnormalities have been described in patients with CVO, there is strong evidence that an elevated plasma total homocysteine level is an independent risk factor for CVO.[22–24] Systemic laboratory workups for CVO patients older than 60 years of age were not routinely performed in our practices during the period of this study, unless atypical features in patient history were identified, such as previous episodes of peripheral vascular thrombosis or documented family history of thrombosis or thrombophilia, or if CVO was bilateral and sequential. In the current series, five patients were evaluated for thrombophilia with laboratory tests to search for evidence of vascular thrombosis during systemic anticoagulation. Two patients had abnormal test results (patients 1 and 2). Patient 1 had a known history of anticardiolipin antibodies, which are associated with thrombophilia.[18] In addition, patient 1 had an elevated erythrocyte sedimentation rate, which had been documented as elevated previously; temporal arteritis had been considered but not thought to be the underlying etiology by the primary care physician, although temporal artery biopsy was not performed. Patient 2 was found to have an elevated plasma total homocysteine level, which was treated with oral folic acid.

The true prevalence of CVO among patients who are treated with Coumadin for anticoagulation is unknown. Hayreh et al[19] described 13 patients (2%) taking Coumadin at the time of onset of CVO in a prospective cohort of 612 CVO patients. In a retrospective analysis of 286 newly diagnosed cases of branch vein occlusion and CVO, five patients (2%) developed CVO while being treated with Coumadin. In a retrospective report, Browning and Fraser[25] identified 11 (3%) of 354 patients with CVO or hemiretinal vein occlusion during Coumadin treatment for anticoagulation. We suspect that the prevalence of Coumadin use among the CVO population is higher than among the general population due to the overlap in systemic conditions that may be associated with CVO.

The visual outcome for our patients was similar to that described by the Central Vein Occlusion Study,[26] even though various interventions were attempted in our series. There was no statistically significant difference in initial and final visual acuities for our group 1 patients. The perfusion status deteriorated to nonperfused in only one patient. Although the current patient population was small, this represents a lower rate of conversion than among the natural history cohort of the Central Vein Occlusion Study (16% vs. 34% overall, respectively). This suggests that although the anticoagulant did not prevent CVO, it may have lessened the severity of the occlusion or reduced the risk of conversion to a nonperfused status. However, our results cannot be generalized because several nonstandardized therapeutic interventions were performed, and we acknowledge the notable differences in the two study populations. We, instead, directly compared the features and outcomes for our study cohort (patients treated with Coumadin) with those for a consecutive group of 43 patients retrospectively identified with CVO who were not taking any systemic anticoagulants or antiplatelet agents at the time of occlusion. There was no significant difference in visual acuity and perfusion status between the two groups at the final follow-up. We are cautious in our interpretation because these were small groups accrued in three institutions and treated by different therapeutic interventions performed on an individual basis by the treating ophthalmologist. However, the comparison may suggest that systemic anticoagulants may not alter one's predisposition to develop CVO or the natural history once such occlusions occur.

Despite the proven anticoagulation effects in systemic diseases, Coumadin for anticoagulation did not prevent CVO in these 14 individuals. Histologic reports suggest that thrombosis in the central retinal vein at the level of the lamina cribrosa is the common end point in the pathophysiology of CVO.[27] However, CVO pathogenesis is believed to be multifactorial involving abnormal blood flow and mechanical abnormalities in the vessel configuration at the level of the lamina cribrosa.[21] The observation that CVO can occur despite effective neutralization of the coagulation cascade in our subset of patients may help to confirm that thrombosis is a late end point in CVO. Local vascular endothelial disruption and inflammation may result in liberation of tissue proteins that promote platelet aggregation and create a microenvironment at the level of the lamina cribrosa that is conducive in activating the coagulation cascade. Reports of the use of systemic immunosuppressive agents in treating CVO support the concept of localized inflammation in the pathoetiology of CVO.[28]

This study has several limitations inherent in a retrospective, uncontrolled study design. Most importantly, both group 1 and group 2 were small sample sizes, which must lead us to interpret our statistical comparisons with caution. Our cases were collected from different clinical settings without standardized examinations and follow-up. There was a selection

bias in this study because many of these patients may have been referred specifically for consideration of experimental treatments or because CVO occurred during Coumadin treatment. This does not allow for generalization or meaningful comparison with findings from other previously reported studies.

In conclusion, CVO can occur in patients who are receiving therapeutic doses of Coumadin. Systemic anticoagulation with Coumadin may not be protective against vascular occlusion in the retinal vessels. Most of these CVOs were perfused at the final follow-up with stability of visual acuity. This study was not designed to evaluate the impact of concurrent use of systemic anticoagulants on the natural history of CVO eyes, and we acknowledge the variability in the outcomes for such eyes. Extensive laboratory evaluation is not necessary in all cases; however, ensuring that the INR is in the therapeutic range for the systemic condition is important to confirm. Referral to the patient's internist to ensure that the INR remains therapeutic may aid in the prevention of secondary systemic thrombotic and embolic disease in these patients.

Key words: anticoagulation, central retinal vein occlusion, Coumadin, international normalization ratio, retinal vein occlusion, systemic, therapeutic.

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