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Cardiovascular Risk Factors in Central Retinal Artery Occlusion

Results of a Prospective and Standardized Medical Examination

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Purpose: To analyze the underlying risk factors in patients with nonarteritic central retinal artery occlusion (CRAO) in a well-defined and homogenous group of patients enrolled in the European Assessment Group for Lysis in the Eye (EAGLE) study.

Design: Analysis of the cardiovascular risk factors in a prospective, randomized clinical trial.

Participants: Seventy-seven EAGLE patients with nonarteritic CRAO.

Methods: Analysis of vascular risk factors and underlying diseases detected by questionnaire and standardized physical examination within 1 month after occlusion.

Main Outcome Measures: The standardized physical examination included carotid Doppler ultrasonography, echocardiography, electrocardiography, blood pressure monitoring, pulse rate, urine analysis, body mass index analysis, and laboratory tests.

Results: Seventy-seven of 84 patients had complete datasets for analysis. Fifty-two (67%) patients had cardiovascular risk factors in their medical history, and comprehensive phenotyping identified at least 1 new risk factor in 60 patients (78%; 95% confidence interval, 67%−87%). Thirty-one (40%) had carotid artery stenosis of at least 70%. Eleven patients experienced a stroke, 5 of those within 4 weeks after the CRAO occurred. Arterial hypertension was found in 56 (73%) patients and was newly diagnosed in 12 (16%) study participants. Cardiac diseases were also highly prevalent (22% coronary artery disease, 20% atrial fibrillation, and 17% valvular heart disease).

Conclusions: Previously undiagnosed vascular risk factors were found in 78% of all CRAO patients. The most meaningful risk factor was ipsilateral carotid artery stenosis. A comprehensive and prompt diagnostic workup is mandatory for all CRAO patients. *Ophthalmology 2015;122:1881-1888 © 2015 by the American Academy of Ophthalmology.*

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Acute nonarteritic central retinal artery occlusion (CRAO) is a leading cause of permanent vision loss, and the underlying pathophysiology is still poorly understood. Assuming that thrombus degradation may be an attractive therapeutic target, intra-arterial fibrinolysis has been a major focus of recent research. Although preliminary data from case series showed promising results,[1,2] randomized controlled trials failed to prove benefit.[3,4] In contrast, harm (bleeding events) outweighed potential benefits.

The lifetime of CRAO patients is reduced by 10 years as compared with healthy controls,[5] stroke risk in CRAO patients is 2.7-fold higher as compared with controls,[6] and cardiovascular risk factors are more prevalent in CRAO patients as compared with age-matched controls.[7] Consequently, current research focuses on identifying and treating cardiovascular risk factors, either diagnosed or undiagnosed. Several retrospective analyses already have defined undiagnosed cardiovascular risk factors in CRAO patients.[5,8−13] Because CRAO is a rare event with an incidence of approximately 1 per 100 000 people,[11,14] most studies are retrospective, with data recruitment periods lasting several years or even decades. The medical examinations have not been standardized, nor have they been adapted to new methodologic techniques, which led to a great variation in parameters. Prospective data from a homogeneous group of patients recruited over a short period

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Table 1. European Assessment Group for Lysis in the Eye Study Ocular and Systemic Exclusion Criteria

Ocular Diseases	General Diseases
• Branch retinal artery occlusion • Cilioretinal arteries supplying the macula • Combined arterial–venous occlusion • Proliferative retinal diseases • Elevated intraocular pressure	• Systemic arterial hypertension (systolic pressure >200 mmHg) despite medical therapy • Acute systemic inflammation (erythrocyte sedimentation rate >30 mm within the first hour/C-reactive protein >1.0 mg/dl) • Antithrombin III deficiency, in case of thrombocytopenia <100 000/ml, pathologic clotting time • Acute pancreatitis with elevated pancreas enzymes • Heart attack within the last 6 wks • Intracerebral bleeding or surgery within the last 4 wks • Therapy with Marcumar/warfarin • Allergic reaction to contrast agent • Hemorrhagic diathesis • Aneurysms • Inflammatory vascular diseases (e.g., giant cell arteritis, Wegener's granulomatosis) • Endocarditis • Gastric ulcer • Patient participation in other studies during the previous 4 wks • Patient not willing to participate

are missing. The study by the European Assessment Group for Lysis in the Eye (EAGLE) may be able to close this gap, because a standardized medical examination was mandatory in this study. Therefore, the aim of this subanalysis of the EAGLE study was to assess cardiovascular risk factors prospectively in a large, multicenter, randomized contemporary trial of patients with acute, angiographically proven, and noninflammatory CRAO at presentation.

Methods

Study Design

The EAGLE study was designed as a randomized, controlled, prospective multicenter clinical superiority trial. Two treatment strategies were compared: local intra-arterial fibrinolysis versus a conservative standard treatment.[15] Inclusion criteria were patient age between 18 and 75 years, nonarteritic CRAO with symptoms lasting fewer than 20 hours, and BCVA worse than 0.5 logarithm of the minimum angle of resolution units, which is a Snellen equivalent of 20/63 (determined using the Early Treatment Diabetic Retinopathy Study chart). Ocular and systemic exclusion criteria are shown in Table 1. Ethics committee approval was obtained at all participating centers. The study was registered at ClinicalTrials.gov (identifier, NCT00637468). Each patient provided written informed consent before participating in the study. Results of the primary analysis have been published previously.[4]

All included patients had to answer a standardized questionnaire regarding their medical history at study entry to exclude any relevant risk factors for intra-arterial fibrinolysis. After assignment and administration of study treatment, all patients were hospitalized for 5 days and underwent a standardized medical and neurologic examination including carotid Doppler ultrasonography (more than 70% stenosis was deemed to be clinically relevant), echocardiography (transthoracic or transesophageal, depending on the cardiologist's decision), electrocardiography, blood pressure monitoring, pulse rate, urine analysis, body mass index (BMI), and laboratory tests, including diabetes testing per protocol.

Statistical Analysis

The statistical methods used for planning and analysis of the study have been published before.[4,15] In this post hoc analysis of the study, the data were analyzed descriptively. Ninety-five percent confidence intervals for proportions were calculated using the exact binomial distribution. All patients who underwent the standardized medical and neurologic examination were included.

Results

Eighty-four patients (84 eyes) were recruited and randomized in the EAGLE study between September 2002 and November 2007.[4] The standardized medical and neurologic examinations were completed for 77 patients. Fifty-four patients were men and 23 were women; the mean age was 62.2 years (range, 24–75 years). With regard to the cardiovascular risk factors and events listed in Table 2, the following results were obtained. Eleven patients (14%) had 1 or more cardiovascular risk factors or events in their medical history and no further factors were newly diagnosed. Forty-one patients (53%) had 1 or more cardiovascular risk factors or events in their medical history and at least 1 further factor was newly diagnosed. Nineteen patients (25%) had no cardiovascular risk factors or events in their medical history and at least 1 factor was newly diagnosed. Thus, after standardized medical and neurologic examination, cardiovascular risk factors or events were newly diagnosed in a total of 60 patients (78%; 95% confidence interval, 67%–87%). In total, 71 (92%) patients had cardiovascular risk factors or events, and 60 (78%) patients had more than 1 risk factor or event. We also checked for the relative yield of the diagnostic procedure itself comparing the newly discovered and the overall incidence of the different diseases. Detailed results are given in Table 2. The relative yield of diagnostic procedures was highest for hypertriglyceridemia (100%) and relevant carotid artery stenosis of 70% or more (94%).

Arterial Hypertension

One of the most common risk factors this patient cohort presented was arterial hypertension, which was diagnosed ultimately in 56 patients (73%). In 44 patients (57%), the diagnosis was known from their medical history, whereas it was unknown in 12 patients

Table 2. Risk Factors from Patient Histories after Medical Investigation and the Overall Incidence Sorted According to Overall Incidence of Each Newly Discovered Risk Factor's Frequency (n = 77)

Cardiovascular Risk Factors	Diagnosis, No. (%)	Positive Results at Inclusion, No. (%)	Positive after Examination, No. (%)	Relative Yield of Diagnostic Procedures, (%)*
Body mass index >25 kg/m^2†	45 (82)	45 (82)	—	—
Arterial hypertension (WHO 2003 criteria)	56 (73)	44 (57)	12 (16)	21
Tobacco use	38 (49)	38 (49)	—	—
Hypercholesterolemia	34 (44)	6 (8)	28 (36)	82
Carotid artery stenosis (≥70%)	31 (40)	2 (3)	29 (38)	94
Coronary heart disease	17 (22)	5 (6)	12 (16)	71
Cardiac arrhythmia	15 (20)	6 (8)	9 (12)	60
Heart valve defect	13 (17)	4 (5)	9 (12)	69
Diabetes mellitus	11 (14)	4 (5)	7 (9)	64
Foramen ovale	10 (13)	1 (1)	9 (12)	90
Hyperlipidemia	10 (13)	2 (3)	8 (10)	80
Coronary vessel stent	9 (12)	4 (5)	5 (6)	56
Hypertriglyceridemia	8 (10)	0 (0)	8 (10)	100
Bypass of coronary vessels	5 (6)	4 (5)	1 (1)	20
Heart failure	4 (5)	3 (4)	1 (1)	25

Cardiovascular Events	Total No. of Events	History of Disease at Study Inclusion (No.)	No. of Events during Follow-up (4 wks)	
Stroke	11	6	5 (3 patients with new stroke and 2 patients after LIF)	45
Myocardial infarction	5	5	—	—
Transient ischemic attack	4	3	1	25

LIF = local intra-arterial fibrinolysis; WHO = World Health Organization.
*Percentage of patients detected after standardized examination among all patients with positive results.
†Body mass index missing for 22 patients.

(16%). Most patients (n = 23) had mild hypertension at presentation (World Health Organization [WHO] grade 1: systolic, 140−159 mmHg; diastolic, 90−99 mmHg), 13 had moderate hypertension (WHO grade 2: systolic, 160−179 mmHg; diastolic, 100−109 mmHg), 17 had severe high blood pressure (WHO grade 3: systolic, ≥180 mmHg; diastolic, ≥110 mmHg), and 3 patients had isolated systolic arterial hypertension (systolic, ≥140 mmHg; diastolic, <90 mmHg).

Body Mass Index and Smoking

Obesity, as defined by an increased BMI, also was frequent. The BMI was measured for 55 patients. Forty-five patients (82%) had a BMI of more than 25 kg/m^2, and in 15 patients (27%), it was more than 30 kg/m^2. Another common risk factor was smoking. At study inclusion, 38 patients (49%) reported being active or former smokers.

Carotid Artery Stenosis, Stroke, and Transient Ischemic Attack

Stenosis of the carotid artery and hypercholesterolemia were the most frequent new diagnoses after thorough medical examination. Only a hemodynamically relevant stenosis was considered in this analysis, which was defined as 70% or more occlusion of the internal or common carotid artery as detected via Doppler ultrasonography. A stenosis was first diagnosed in 29 patients (38%) after the CRAO event. Thirty-one patients (40%) ultimately were diagnosed with a relevant carotid artery stenosis. Six patients (8%) reported a previous stroke, and 5 patients (6%) had a stroke newly diagnosed in MRI imaging during follow-up. One of those had experienced a silent stroke, 2 patients experienced a stroke immediately after local intra-arterial fibrinolysis, and 2 others experienced a stroke a few days after conservative treatment. Of those 5 patients, 4 had an ipsilateral carotid artery stenosis. Three patients (4%) had a history of transient ischemic attack (TIA), and a TIA was newly diagnosed in 1 patient. Taken together, 9 patients had a history of stroke or TIA, and 15 patients had a stroke or TIA diagnosis before or after the CRAO event.

Heart Diseases

Coronary heart diseases were known in 5 patients (6%) and were newly diagnosed in 12 patients (16%) by electrocardiography, coronary angiography, or both. Four patients had received a coronary stent (5%) before study inclusion, and 5 patients (6%) did so within 4 weeks. Coronary bypass was known in 4 patients (5%) and was necessary in another patient after systemic evaluation. Cardiac arrhythmia also was diagnosed frequently. It was known beforehand in 6 patients (8%) and in 9 patients (12%) after the medical examination. A persistent foramen ovale was known in 1 patient and was newly diagnosed in another 9 patients (12%). A heart valve defect was known already in 4 patients (5%) and was newly diagnosed in 9 patients (12%). Seven patients (9%) had an aortic valve stenosis at presentation, 3 patients (4%) had aortic valve insufficiency, 3 patients (4%) had mitral valve insufficiency, and 1 patient (1%) had tricuspid valve insufficiency. Heart failure

was known in 3 patients (4%) and was diagnosed in 1 patient (1%), whereas no new myocardial infarction occurred during the first month after study inclusion.

Discussion

Our study has 3 main findings. First, cardiovascular risk factors are a frequent finding in CRAO patients, but comprehensive work-up identifies a substantial number of patients with previously undiagnosed risk factors (78%). Second, among undiagnosed risk factors, ipsilateral carotid artery stenosis is very frequent (40% of patients), but is diagnosed in only 3% of patients before the event. Third, carotid ultrasound seems to be the most relevant diagnostic procedure in CRAO patients.

Despite many efforts, CRAO remains a disease without a therapy. Moreover, a major issue in CRAO patients is the increased incidence of cardiovascular diseases they present, because CRAO may be one important manifestation of a systemic disease with increased mortality. Arterial hypertension, heart valve and coronary heart diseases, sclerotic alterations of the carotid artery, diabetes, tobacco use, and elevated blood lipids have already been described as underlying risk factors in different studies exacerbating CRAO patients' atherosclerotic risk profile (Table 3).[5,8–13,16,17,18] Consequently, a prompt clarification of the risk factors is mandatory. However, published data need careful assessment because most studies were retrospective and patient recruitment periods comprised even decades. When considering the medical progress made over the last several years, one major study data limitation could be widely varying physical examination procedures. It would be preferable to investigate a clearly defined homogeneous group of CRAO patients within a short period using a prospective and standardized protocol for medical evaluation. This subanalysis of the EAGLE study may be able to narrow this gap because all its study subjects had to undergo a medical check-up within the first days after CRAO was detected. To compare the EAGLE study's results with the literature, we performed a semistructured database research in Medline, Embase, and Cochrane reviews, as shown in Table 3.

We were able to detect new cardiovascular risk factors in 78% of all the study participants. Previous studies found between 61% and 66% of CRAO patients to have no risk factor.[19,20] This difference may be explained by the comprehensive phenotyping in the EAGLE trial, which improved the detection rate of cardiovascular risk factors, or may be biased by the retrospective character of previous studies.

Carotid Artery Stenosis and Cerebrovascular Events

One of the most important findings from this analysis was the remarkable percentage of hemodynamically relevant ipsilateral carotid artery stenosis (CAS) cases we identified. Forty percent of all EAGLE patients had CAS of at least 70% at presentation. This is a much higher rate than that reported in most previous trials (between 15% and 24%; see Table 3). Only 1 retrospective analysis also found a prevalence even slightly higher than that of our trial (54%).[9] The CAS prevalence in the general population is reported to be 4.1% (95% confidence interval, 2.4%–6.8%). Regarding 50% stenoses graded in the North American Symptomatic Endarterectomy Trial, the prevalence of 70% stenoses is approximately 1.7% (95% CI, 0.7%–3.9%).[21] In population-based studies, the CAS prevalence in patients with cardiovascular risk factors is reported to be between 10% and 30%.[22,23] Our findings give very strong indirect evidence for the role of CAS in the pathophysiology of CRAO because we focused on high-grade stenoses (≥70% carotid artery closure) because they currently are regarded as clinically relevant. Our findings can be attributed to the fixed examination with consistent and state-of-the-art sonographic equipment.

The history of stroke and TIA in the present study falls in line with the data in the literature.[8,9,12] In total, 15 EAGLE patients (19%) had a stroke or TIA, 6 of them after CRAO. A recent population-based study from Taiwan described a 2.7-times higher rate of stroke within the first 3 years compared with matched controls. Incidence was highest within the first month after CRAO (incidence rate, 9.5), which remained elevated between months 1 and 6 (incidence rate, 5.6) as compared with matched controls.[6] This is in line with other reports concerning the survival rate, which reported that time-corrected mortality was 4 to 5 times greater than the expected rate in an age- and gender-matched population.[24] Douglas et al[18] observed a strong association between CRAO and ipsilateral carotid artery disease, with a significantly higher incidence of subsequent ipsilateral stroke. Their 1-year stroke rate was 13%. Bruno et al[25] reported an annual rate of stroke 10 times higher after 3.4 years of follow-up. Hankey et al[17] reported that 30 of 98 CRAO patients experienced a stroke, myocardial infarction, or vascular death within 6 years after retinal artery occlusion, with more patients experiencing heart disease rather than stroke. In conclusion, ipsilateral carotid artery occlusion, TIA, and stroke frequently are described in literature. In this study cohort, we documented vascular events only within the first month after CRAO. In 6 of 77 patients (8%), a stroke or TIA was diagnosed after the CRAO. Some of these cases are thought to be potentially related to therapy.[4,26]

Among different stroke subtypes, strokes caused by large artery atherosclerosis have the highest recurrence rate, and consequently carotid ultrasound is recommended early after ischemic stroke and urgent revascularization has been shown to reduce stroke recurrence.[27] Our data with a high prevalence of carotid artery stenosis (40% as compared with 30% to 32% in current stroke trials)[28–30] have the clinical consequence to extend these diagnostic recommendations to patients with CRAO.

Central Retinal Artery Occlusion and Cardiovascular Risk Factors

One of the most common risk factors was arterial hypertension. In the EAGLE study, 73% of all patients had high blood pressure (WHO grade 1 or higher), which falls in line with several retrospective studies,[8–11,20,31] but is higher

Table 3. Semistructured Database Research in Medline, Embase, and Cochrane Reviews in Comparison with European Assessment Group for Lysis in the Eye Study Data

	Studies in Chronological Order										
	Lorentzen (1969)[5]	*Douglas et al (1988)*[18]	*Duker et al (1991)*[16]	*Hankey et al (1991)*[17]	*Arnold et al (2005)*[12]	*Schmidt et al (2007)*[9]	*Hayreh et al (2009)*[8]	*Rudkin et al (2010)*[10]	*Leavitt et al (2011)*[11]	*Leisser (2014)*[13]	*European Assessment Group for Lysis in the Eye Study*
No. of patients	37	66	33	98	56	253	234	33	43	110	n = 77
Study notes	—	Surgical study	Mixed races	Mixed CRAO and BRAO	—	—	—	—	Mixed races	Mixed CRAO and BRAO	Multicenter
Recruitment period	1950–1961	1965–1984	—	1977–1986	1990–2003	1980–2004	1973–2000	1997–2008	1976–2005	2006–2013	**2002–2007**
Recruitment (R/P)	R	R	P	P	R	R	R	R	R	R	**P**
Male gender (%)	—	58	64	56	59	67	56	—	60	63	**70**
Right eye (%)	59	47	52	—	—	57	44	—	63	58	**60**
Patient age (yrs) mean±SD or mean (range)	63 (37–84)	60 (22–87)	69 (34–87)	64 ± 14	63 (23–83)	67 (18–90)	66 ± 14	73 ± 9.7	74 (46–90)	72	**62 (24–75)**
Arterial hypertension (%)	86	64	46	57	34	80	52	69	88	68	**73**
Diabetes mellitus (%)	—	15	27	5	—	22	20	33	21	23	**14**
Smokers (%)	—	38	—	40	9	34	33	36	16	—	**49**
Hypercholesterinemia (%)	—	—	—	54	18	38	39	73	40	62	**44**
History of stroke or TIA (%)	16	12	—	—	7	13	19	—	—	21	**12**
Carotid stenosis (%)	—								23 (>50% stenosis)		
≥70% stenosis		—	18	24	7	54	18	15		—	**40**
50%–70% stenosis		—	—	—	—	29	16	12		—	—
<50% stenosis		—	—	—	—		66	73		—	—
Plaques		—	—	—	—	4	71			67	—
Coronary heart disease (%)	3	—	—	18	—	—	26	—	—	6	**22**
Persistent foramen ovale (%)	—	—	—	—	—	5	2	—	—	11	**13**
Heart valve disease (%)	—	—	—	25	—	21	29	12	38	55	**17**
Cardiac arrhythmia (%)	—	—	—	4	—	19	—	12	—	10	**20**
Obesity (%)	—	—	—	—	—	—	—	—	—	—	**82**
Family history of vascular disease (%)	—	—	—	—	—		—	24		—	—
Renal artery stenosis (%)	—	—	—	—	—	—	—	3	—	—	**0**
Multiple risk factors (%)	—	—	—	—	—	—	—	—	56	—	**78**
New risk factors (%)	—	—	—	—	—	—	—	64	—	—	**78**

BRAO = branch retinal artery occlusion; CRAO = central retinal artery occlusion; P = prospective; R = retrospective; SD = standard deviation; TIA = transient ischemic attack.
Studies with more than 30 CRAO patients an at least 3 systemic risk factors are included.

than in the 2 prospective studies of Duker et al[16] and Hankey et al[17] (Table 3). This may be the result of the different definition of arterial hypertension used by Hankey et al, because they included only patients with a diastolic pressure of 100 mmHg or more. In the present analysis, we considered the current guidelines of the German Hypertension Society (2011) and the WHO (2003), which define a diastolic pressure of 90 mmHg or more, or a systolic pressure of 140 mmHg or more as defining hypertension. Of note, the Framingham Heart Study results revealed a reduction in total life expectancy of 5 years in hypertensive individuals compared with normotensives.[32]

We also detected obesity and smoking frequently. Although reliably assessed in the literature,[33] a tendency toward elevated BMI has never been described in CRAO patients, but it is not a surprising finding. Smoking has already been described as an underlying risk factor in CRAO and many other cardiovascular diseases.[34,35] In this study, we discovered a higher smoker rate than in the corresponding literature, which may be explained by our prospective protocol using a standardized questionnaire.

The number of heart valve diseases (17%) was lower than that reported previously. Numerous reasons may explain this finding (e.g., different definitions, different grading systems). Older studies report a rate of cardiac valve diseases in CRAO patients falling between 7% and 25%.[36,37] Sharma[38] also reported echocardiographic abnormalities in every second CRAO patient, and the likelihood of detecting cardiac pathologic features was 25 times more likely in patients with a high-risk cardioembolic profile. Those data are closely related to their study inclusion risk factors like endocarditis, rheumatic heart disease, cardiac valvular disease, myocardial infarction, prosthetic heart valve, congenital heart disease, intravenous drug use, cardiac tumor, atrial fibrillation, or a cardiac murmur. In the absence of any of these risk factors (corresponding to a low-risk profile), the likelihood of requiring systemic treatment was very low (1.5%).[39] Most of those high-risk diseases were excluded from this study, which may explain our lower detection rate of heart valve diseases. It is still a matter of discussion as to whether the transesophageal or transthoracic approach is preferable in echocardiography.[40,41] Our analysis cannot answer this question because in our study protocol, the responsible cardiologist at each center chose the appropriate method. But our data emphasize the importance of echocardiography as a standard diagnostic examination in CRAO patients.

Diabetes increases cardiovascular morbidity, because diabetic patients 50 years of age and older live on average 8 years less than their nondiabetic counterparts.[42] Fourteen percent of our patients had diabetes, whereas most studies report a prevalence rate between 20% and 30%.[8–11,16] This is probably because of our exclusion criterion of diabetic retinopathy at any stage. The prevalence of diabetes likely was underestimated because more comprehensive testing (e.g., oral glucose tolerance testing) may increase the number of diabetes cases.[43]

The limitations of the current study are its retrospective analysis without a control group and the strict inclusion criteria of the EAGLE study to avoid serious systemic side effects during study treatment. We therefore present a study population that is most likely healthier than the CRAO patients in clinical practice.

In conclusion, we confirmed a cardiovascular risk profile in most acute nonarteritic CRAO patients, and in 78%, prompt work-up showed new risk factors. The most significant finding was ipsilateral carotid artery stenosis meeting criteria for revascularization in 40% of CRAO patients. We consider CRAO patients at high risk for future vascular events and recommend a comprehensive diagnostic work-up in all patients with CRAO.

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Abbreviations and Acronyms:
BMI = body mass index; **CAS** = carotid artery stenosis; **CRAO** = central retinal artery occlusion; **EAGLE** = European Assessment Group for Lysis in the Eye; **TIA** = transient ischemic attack; **WHO** = World Health Organization.

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