The Fellow Eye in NAION: Report From the Ischemic Optic Neuropathy Decompression Trial Follow-up Study

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• PURPOSE: To examine the prevalence and incidence of second eye nonarteritic anterior ischemic optic neuropathy (NAION) and associated patient characteristics in patients enrolled in the Ischemic Optic Neuropathy Decompression Trial (IONDT) Follow-up Study.
• DESIGN: Randomized clinical trial with observational cohort.
• METHODS: Patients randomized to optic nerve sheath decompression surgery or careful follow-up had a diagnosis of acute unilateral NAION, visual acuity between 20/64 and light perception, and were aged 50 years or older. Eligible patients who declined randomization or whose visual acuity was better than 20/64 were not randomized but followed as part of an observational cohort. Follow-up examinations took place at 3, 6, 12, 18, and 24 months and annually thereafter.
• RESULTS: Four hundred eighteen patients were enrolled; 258 randomized and 160 observed. Previous NAION or other optic neuropathy was present in the fellow eye of 21.1% (88/418) of patients at baseline. Four patients developed optic neuropathy in the fellow eye at follow up that could not be conclusively diagnosed as NAION. New NAION in the fellow eye occurred in 14.7% (48/326) of patients at risk during a median follow up of 5.1 years. Randomized patients experienced a higher incidence (35/201; 17.4%) than nonrandomized patients (13/125; 10.4%). A history of diabetes and baseline visual acuity of 20/200 or worse in the study eye, but not age, sex, aspirin use, or smoking were significantly associated with new NAION in the fellow eye. Final fellow eye visual acuity was significantly worse in those patients with new fellow eye NAION whose baseline study eye visual acuity was 20/200 or worse.
• CONCLUSIONS: Follow-up data from the IONDT cohort provide evidence that the incidence of fellow eye NAION is lower than expected: new NAION was diagnosed in 14.7% of IONDT patients over approximately 5 years. Increased incidence is associated with poor baseline visual acuity in the study eye and diabetes, but not age, sex, smoking history, or aspirin use. (Am J Ophthalmol 2002;134:317–328. © 2002 by Elsevier Science Inc. All rights reserved.)

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NONARTERITIC ANTERIOR ISCHEMIC OPTIC NEUROpathy (NAION) is the most common acute optic neuropathy in the elderly.[1,2] The annual incidence of NAION has been estimated from 2.3 to 10.2 per 100,000 for persons 50 years and older.[3,4] Estimates of the number of new cases that are seen each year in the United States range from approximately 1500 to 6000.[3–5]

NAION in both eyes has been reported in as few as 10.5% and as many as 73% of patients.[6] Most previous studies report prevalence rather than incidence and have considerable variation in length and quality of follow-up; they report widely different times between onset of first eye NAION to end of follow-up. Some studies included only a few patients or included patients with diseases other than

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NAION or with precipitating factors known to increase the risk of bilateral involvement.[6–9]

No therapy for acute NAION or prevention of fellow eye involvement has yet proved to be effective. In the Ischemic Optic Neuropathy Decompression Trial (IONDT), a multicenter randomized clinical trial, optic nerve decompression surgery was compared with careful follow-up in the treatment of patients with NAION. Preliminary results at 6 months[10] and 24 months of follow-up[11] indicated that there was no benefit of optic nerve decompression surgery compared with careful follow-up. The IONDT also followed a natural history cohort of nonrandomized patients. This group comprised patients with NAION whose visual acuity was better than 20/64, making them ineligible for the trial or who were eligible but refused randomization.

We continued to follow both groups at the conclusion of the trial as part of the IONDT follow-up study to obtain a minimum of 5 years post-enrollment data in a cohort of 418 patients. The primary objective of the follow-up study was to determine the baseline prevalence and cumulative incidence of NAION in the fellow eye in this cohort of 418 enrolled patients. We also collected data to explore the following four questions:

(1) What is the risk of NAION occurring in the fellow eye? (2) Are there baseline characteristics that are positively or negatively associated with the incidence of fellow eye NAION? (3) What happens to visual acuity in both the study and fellow eye over the short and long term after NAION occurs in the fellow eye? (4) Are there baseline characteristics associated with the severity of visual acuity loss in either eye?

In this article, we provide the prevalence and incidence of NAION in the fellow eye, explore the relationship of various patient baseline characteristics to the development of fellow eye involvement, and the features of visual acuity loss in those patients with bilateral NAION.

DESIGN

THIS STUDY WAS A RANDOMIZED CLINICAL TRIAL WITH AN observational cohort.

METHODS

• **PATIENTS**: The methods and eligibility requirements used to enroll patients, collect data, and tabulate results in the IONDT have been previously described.[12] Patients who had sudden loss of vision within the previous 14 days, a relative afferent pupillary defect, optic nerve head (disk) edema, visual acuity 20/64 or worse, and an abnormal visual field were eligible. Patients were eligible if they had had a previous NAION in the fellow eye. Exclusion criteria included age younger than 50 years, any medical condition that results in nonischemic optic neuropathy or excessive surgical risk, diagnosis of temporal arteritis, any ophthalmologic condition that precludes reliable visual acuity measurement, and inability to give informed consent.

NAION patients with initial visual acuity better than 20/64 and whose vision did not deteriorate to 20/64 or worse within 30 days were followed as part of a natural history cohort; this nonrandomized group also included a few patients whose visual acuity was 20/64 or worse but who did not wish to be randomized.

Two patients had both eyes entered into the IONDT. In both these cases, the visual acuity in the first eye entered into the study remained better than 20/64 and the patient became part of the natural history cohort and was followed. When NAION occurred in the fellow eye, the patient was again evaluated for entry to the randomized trial, but visual acuity remained better than 20/64 in the fellow eye as well. Thus, we continued to follow these two patients as part of the nonrandomized cohort. Here we consider the first NAION in each of these patients to be the study eye and determined incidence of NAION in the fellow (second) eye.

Before entry into the IONDT, eligible patients gave informed consent according to the procedures that were determined by each center's institutional review board and which were approved by the coordinating center's institutional review board.

• **OBSERVATION PROCEDURES**: Follow-up visits were scheduled at 1 week and at 1, 3, 6, 12, 18, and 24 months after randomization and then at yearly intervals until closeout of the IONDT. All data were collected on standard pretested forms. Each IONDT patient provided a detailed history with regard to visual symptoms, past and concurrent ocular, neurologic, and systemic problems, and medication use. Each patient underwent a standard neuro-ophthalmic examination by trained and certified study personnel. Visual acuity was measured using the Early Treatment of Diabetic Retinopathy Study (ETDRS) charts (Lighthouse Low Vision Products, Long Island City, New York, USA) by visual acuity technicians masked to patients' treatment assignments using methods described elsewhere.[12,13]

Classification of patients as having NAION in the fellow eye at baseline was based on patient report and verification by the study neuro-ophthalmologist. To verify initial patient report of baseline fellow eye NAION, we sent a checklist to study neuro-ophthalmologists 2 years after completion of enrollment and also directly queried clinicians at each follow-up study visit about baseline NAION in the fellow eye. Any reporting discrepancy was brought to the attention of the clinician who was asked to make a decision based on his or her best clinical judgment. Because it was sometimes difficult for neuro-ophthalmologists to differentiate between a history of NAION and optic neuropathy due to other causes, we also evaluated

the baseline prevalence of fellow eye optic neuropathy, defined as the presence of a pale optic disk at baseline.

Incident NAION in the fellow eye was classified based on best clinical judgment by either the study neuro-ophthalmologist, surrogate provider, or patient report. At baseline and each follow-up visit, the study neuro-ophthalmologist or surrogate provider performed an ophthalmologic exam and evaluated the fellow eye for NAION based on the presence of an optic neuropathy for which there was clinical evidence of NAION (for example, swollen disk, segmental optic atrophy, altitudinal visual field defect). Twice over the course of the IONDT, we asked study ophthalmologists to verify all diagnoses of NAION in the fellow eye based on their medical records. Two new cases of NAION were reported by patients during telephone interviews and four by surrogate providers, but these diagnoses could not be verified. At baseline and follow-up, study ophthalmologists also recorded all cases of optic neuropathy, which was defined as the presence of an optic disk that was swollen or pale. We did not consider a pale optic nerve head sufficient evidence for a diagnosis of NAION, but for the purposes of analysis, patients with NAION were always classified as also having optic neuropathy.

We classified patients as having a vascular risk factor if at baseline the patient reported having had any of the following conditions: hypertension, diabetes mellitus, myocardial infarction, stroke, or transient ischemic attack.

Data on patient smoking history were collected twice: at 3 months after enrollment for randomized patients and at closeout. Smokers were defined as those persons who had smoked at least 100 cigarettes in their lifetimes or who classified themselves as "regular" smokers. Patients who were currently smoking or had stopped smoking less than 1 year before enrollment were classified as current smokers, while those who had stopped smoking more than 1 year before enrollment were classified as previous smokers. Persons who had smoked less than 100 cigarettes in their lifetime were classified as nonsmokers.

Baseline aspirin users were defined as patients who reported using aspirin regularly for at least 1 month before onset of study eye NAION symptoms. Aspirin users at follow up were defined as patients who reported regular aspirin use on at least one follow-up visit. For patients who developed NAION in the second eye, that visit had to be before the onset of new NAION. In practice, most patients whom we classified as aspirin users reported regular aspirin use at most or all follow-up visits.

• **STATISTICAL METHODS:** Statistical analyses were performed using SAS (Statistical Analysis Software, version 8.1, SAS Institute, Carey, North Carolina, USA). For all analyses of incident NAION in the fellow eye, we did not include patients with optic neuropathy in the fellow eye at baseline or with a consistent diagnosis of non-NAION optic neuropathy in the fellow eye following baseline (four patients), because we did not consider these patients at risk for NAION. We define incidence in this report as the estimated incidence over the measured median follow-up period. We explored the association of individual baseline risk factors with incident NAION using log rank tests that compared subgroups defined by risk factor values on occurrence of NAION in the fellow eye, allowing for differing follow-up times. Patients who had not experienced a new NAION by the end of the study were considered censored at that time. Risk factors considered include vascular risk factors, smoking, aspirin use, and baseline study eye visual acuity. We plotted the cumulative probability of the second eye developing NAION using Kaplan–Meier survival analysis and included all patients without NAION or optic neuropathy in the fellow eye at baseline. Cox proportional hazards methods were used to develop multivariable models predicting occurrence of new NAION in the fellow eye.

Further analyses examined the association between visual acuity in the study eye and fellow eye expressed in log of the minimum angle of resolution (logMAR) units and translated into Snellen chart equivalents where appropriate. Pearson correlations were calculated for comparisons at different time points as well as scatter plots. For categorical analyses, baseline study eye visual acuity was categorized as better than 20/64 (logMAR < 0.5), 20/64 to better than 20/200 (logMAR 0.5 to < 1.00) and 20/200 or worse (logMAR ≥ 1.00). Participants in the first category were ineligible for randomization, while those in the last category met the legal definition for blindness. For patients with new NAION in the fellow eye, end of study visual acuity in the fellow eye was the outcome variable in a multiple linear regression analysis comparing baseline study eye visual acuity categories unadjusted and adjusted for any vascular condition at baseline.

RESULTS

BETWEEN OCTOBER 1, 1992 AND OCTOBER 20, 1994, 418 PAtients with NAION were enrolled in the IONDT: 258 were randomized (127 to the surgery group and 131 to the careful follow-up group) and 160 were not randomized. Data collection for the IONDT and IONDT follow-up study ceased on January 21, 2001 when all enrolled patients had had at least 5 years of follow up (range 0–7.4 years; median 5.1 years).

The baseline characteristics of enrolled patients were previously reported.[14] Overall, 61% of patients were men, 95% were white, and they ranged in age from 50 to 89 years (median and mean age = 66 years). Randomized patients were older than nonrandomized patients (mean age = 68 ± 8.5 years compared to 63 ± 8.1 years; $P <$ .0001) and a smaller proportion were men (55% compared to 71%; $P = .001$). Randomized patients reported one or

TABLE 1. Prevalence ("at Baseline") or Incidence ("After Baseline") of NAION and Optic Neuropathy* in Nonstudy Eye by Study Group

Characteristic	Randomized				Nonrandomized		Total	
	Careful follow-up		Surgery					
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Total patients	131	(100)	127	(100)	160	(100)	418	(100)
Patients considered not at risk								
With optic neuropathy at baseline	28	(21.4)	28	(22.1)	32	(20.0)	88	(21.1)
with baseline NAION	25	(19.1)	26	(20.5)	29	(18.1)	80	(19.1)
without baseline NAION	3	(2.3)	2	(1.6)	3	(1.9)	8	(1.9)
With optic neuropathy after baseline†	0		1	(0.8)	3	(1.9)	4	(0.9)
Patients considered at risk								
With NAION after baseline	19	(14.5)	16	(12.6)	13	(8.1)	48	(11.5)
Without optic neuropathy or NAION in nonstudy eye	84	(64.1)	82	(64.6)	112	(70.0)	278	(66.5)

*Optic neuropathy at baseline defined as pale and flat or pale and elevated optic disk; optic neuropathy after baseline defined as pale and flat or swollen optic disk.

†Optic disk consistently classified as swollen or pale and flat at all post-baseline visits. NAION assumed unlikely at follow-up if optic neuropathy present at baseline.

more baseline vascular risk factors more frequently than did nonrandomized patients (64% vs 54%; $P = .04$).

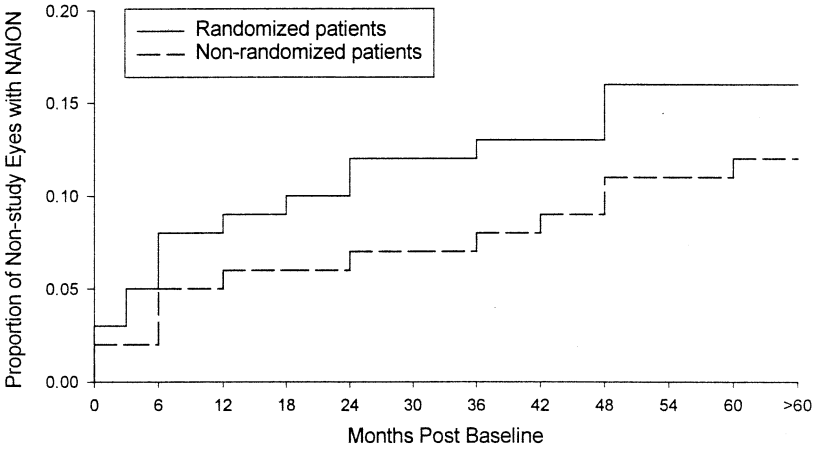
Among all patients at baseline, 12% were current smokers, 37% previous smokers, and 38% had never smoked. We had no data with respect to smoking for 54 patients (13%). Randomized patients tended to report current smoking more often than nonrandomized patients (16% vs 10%). At the baseline visit, 29% of all patients reported taking aspirin on a regular basis for 1 month or longer and 4% reported taking anticoagulants.

• **RISK OF NAION IN THE FELLOW EYE:** Study neuro-ophthalmologists determined at the baseline examination that 80 patients (19% of total) had had an episode of NAION in the fellow eye before enrollment (Table 1). Of these, 51 were randomized and 29 were nonrandomized patients. In some cases, the final decision by the neuro-ophthalmologist regarding the presence of baseline NAION in the nonstudy eye was different than that previously reported.[11] Pallor of the optic nerve head ("optic neuropathy") was found in eight additional fellow eyes at baseline. Optic neuropathy was also consistently diagnosed in four additional patients at follow-up study visits. Although a pale optic nerve head suggests previous NAION, either there was insufficient corroborating evidence to diagnose NAION in the fellow eye or the optic neuropathy was believed secondary to another etiology (for example, previous trauma or vein occlusion) in these four patients.

We calculated incidence of fellow eye NAION after baseline on 326 patients after excluding the 92 patients not "at risk" from the original cohort of 418 patients (80 patients with baseline NAION, eight patients with baseline optic neuropathy, and four patients with optic neuropathy at follow-up). Over the course of the IONDT patient follow-up, 14.7% of patients at risk (48/326) experienced new NAION in the fellow eye. Incidence was greater for the randomized compared to the nonrandomized patients (35/20 [17.4%] vs 13/125 [10.4%], respectively; see Table 1).

The median interval between study eye NAION (using enrollment date) and occurrence of new NAION in the fellow eye was 1.2 years (range = 16 days–6.0 years). Nearly half of the fellow eye NAION events (22/48; 46%) occurred during the first year in both the randomized (17/35; 49%) and nonrandomized (5/13; 38%) groups and the remainder occurred relatively evenly over the following 4 years. We calculated and plotted the cumulative incidence of new NAION in the fellow eye over the entire study period based on Kaplan–Meier survival analysis (see Figure 1). Overall, 128 of 418 patients (30.6%) had NAION diagnosed either at baseline or consistently over the follow-up period (cumulative prevalence).

• **BASELINE CHARACTERISTICS ASSOCIATED WITH THE INCIDENCE OF FELLOW EYE NAION:** The baseline characteristics of patients with and without bilateral NAION are shown in Table 2. Having a vascular condition at baseline, defined as patient report of diabetes or history of myocardial infarction, hypertension, stroke, or transient ischemic attack was weakly associated in univariate analyses with the occurrence of NAION in the fellow eye (log rank $P = .06$). This association was further weakened when vascular risk factor was defined to include current smoking status ($P = .09$). We found no association



# months post baseline	0	3	6	12	18	24	30	36	42	48	54	60	>60
Randomized patients													
# new NAION in non-study eye		6	4	7	1	2	3	0	2	1	4	1	4
# patients at risk	201	201	193	189	180	177	170	161	159	155	153	145	138
Non-randomized patients													
# new NAION in non-study eye		2	0	3	2	0	1	0	1	1	2	0	1
# patients at risk	125	107	105	105	102	100	100	99	99	97	96	94	92

Note:
- Persons at risk include all patients not officially withdrawn and without NAION in non-study eye who completed a visit for that time point or a visit beyond that time point. 28 patients in the careful followup group, 28 patients in the surgery group, and 32 patients in the non-randomized group had NAION or optic neuropathy in the non-study eye at baseline and thus are not considered at risk.

FIGURE 1. Proportion of nonstudy eyes with nonarteritic anterior ischemic optic neuropathy (NAION), in patients without NAION or optic neuropathy in the nonstudy eye at baseline, by treatment group, and months post baseline.

between a history of smoking and the occurrence of new NAION in the fellow eye (log rank $P = .55$, Table 2).

We found a suggestion of an association between baseline visual acuity in the study eye (examined using three categories (better than 20/64, 20/64 to better than 20/200, and 20/200 or worse) and occurrence of new NAION in the fellow eye (log rank $P = .10$). When we tested for homogeneity among categories, we found no difference between the first two categories (better than 20/64, 20/64 to better than 20/200; log rank = 0.95) and so combined them as one category for these analyses. We found that patients with baseline visual acuity at 20/200 or worse were significantly more likely to experience NAION in the fellow eye than all those with vision better than 20/200 (log rank $P = .03$).

We noted that baseline vascular condition was significantly associated with worse baseline visual acuity in the study eye ($P = .006$, Mantel–Haenszel test of trend), persisting even after adjustment for age. We then examined the occurrence of new NAION in the fellow eye using Cox proportional hazards modeling, including in the model age, vascular condition, and baseline visual acuity in the study eye (Table 3, model 1). We found that visual acuity at 20/200 or worse, but not vascular condition, was significantly associated with occurrence of NAION in the fellow eye, adjusted for vascular condition and age. We also performed analyses examining components of "vascular condition" separately (that is, diabetes, hypertension, myocardial infarction, and transient ischemic attack). In one of these models, both baseline study eye visual acuity of 20/200 or worse and diabetes were associated with significantly increased risk of NAION in the fellow eye (Table 3, model 2). We found no association between regular aspirin use and incidence of new NAION in the fellow eye, whether we looked at regular aspirin use at baseline or aspirin use at any point before NAION occurred in the fellow eye (see Table 2).

• **ASSOCIATIONS BETWEEN VISUAL ACUITY IN THE STUDY AND FELLOW EYES AT BASELINE, TIME OF NEW NAION, AND END OF STUDY:** Forty-eight percent (23/48) of patients with a new NAION in the fellow eye had visual acuity better than 20/64 in the fellow eye immediately after the occurrence of new NAION (Table 4). There was no evidence of change in the mean visual acuity of the fellow eye that developed new NAION during the interval immediately following the new NAION to the last study visit ($P = .25$, paired t test for change in logMAR). We observed a small, but nonsignificant decline in visual acuity in the study eye after occurrence of fellow eye NAION (mean increase in logMAR = 0.15, paired t test, $P = .07$).

The correlations between visual acuities measured in the study and fellow eyes with NAION, at both the first and

TABLE 2. Baseline Characteristics of Patients With no Baseline NAION in Fellow Eye by Incidence of New NAION in Fellow Eye

Variable	New NAION		No new NAION		*P* Value
	No.	(%)	No.	(%)	
Total number	48	(15)	278	(85)	
Age					
<65	22	(15)	124	(85)	0.75
≥65	26	(14)	154	(86)	
Sex					
Male	28	(14)	171	(86)	0.72
Female	20	(16)	107	(84)	
Study group					
Careful follow up	19	(18)	84	(82)	0.46
Surgery	16	(16)	82	(84)	
Nonrandomized	13	(10)	112	(90)	
Baseline visual acuity*					
Better than 20/64	13	(11)	110	(89)	0.10
20/64 to better than 20/200	10	(12)	72	(88)	
20/200 or worse†	24	(20)	95	(80)	
Smoking status*					
Current	8	(19)	35	(81)	0.55
Previous	19	(16)	100	(84)	
Never	14	(12)	104	(88)	
Vascular condition*					
No	13	(10)	114	(90)	0.06
Yes	35	(18)	163	(82)	
Diabetes*					
No	31	(12)	222	(88)	0.02
Yes	17	(24)	55	(76)	
Hypertension*					
No	20	(12)	149	(88)	0.12
Yes	28	(18)	128	(82)	
Myocardial infarction*					
No	40	(14)	245	(86)	0.27
Yes	8	(20)	32	(80)	
Cerebrovascular accident*					
No	46	(15)	267	(85)	0.96
Yes	2	(17)	10	(83)	
Transient ischemic attack*					
No/don't know	48	(15)	265	(85)	0.19
Yes	0		12	(100)	
Aspirin use (at baseline)‡					
No	31	(13)	206	(87)	0.25
Yes	17	(20)	70	(80)	
Aspirin use (after baseline)§					
No	35	(15)	205	(85)	0.65
Yes	13	(15)	73	(85)	

*One or more missing values at baseline; percentages determined by using total number of patients.

†$P = .03$ for 20/200 or worse compared to other two groups.

‡Reported starting regular aspirin use ≥1 month before onset of symptoms at baseline visit.

§Responded positively to "started regular use" of aspirin on at least one study visit after baseline. For patients with new NAION, the study visit must have taken place before occurrence of new NAION.

TABLE 3. Cox Proportional Hazards Models for Occurrence of New NAION

Variables (Baseline)	Hazard Ratio	95% Confidence Interval
Model 1		
Age	0.99	(0.96–1.03)
Any vascular condition	1.72	(0.90–3.29)
Visual acuity study eye, 20/200 or worse vs better	1.80	(1.00–3.23)
Model 2		
Age	1.00	(0.96–1.04)
Diabetes	1.92	(1.05–3.52)
Visual acuity study eye, 20/200 or worse vs better	1.87	(1.05–3.35)

last study visit, were higher in patients with baseline fellow eye NAION or optic neuropathy (r = 0.51, Table 5) and for the 48 patients with new NAION (r = 0.36) following the event (see Table 5). The associations between the last measured visual acuities in the study and fellow eyes are shown in Figure 2. For close to half (61/128) of the patients with bilateral NAION, visual acuity in the fellow eye was within 0.3 logMAR units of the study eye. This amount of variation is equivalent to a doubling of the minimum angle of resolution (or three lines of vision on an ETDRS chart) and is shown in Figure 2 as the area bounded by the dotted lines. Visual acuity in the two eyes was within 0.6 logMAR units for 70% of patients (89/128) with fellow eye NAION. For all patients with bilateral NAION, mean visual acuity in logMAR at the end of study in the first eye affected was not different from mean visual acuity in the second eye (0.88 ± 0.77 vs 0.94 ± 0.77, $P = .39$).

We estimated mean end of study visual acuity in the fellow eye with new NAION by categories of study eye baseline visual acuity (see Table 6), unadjusted and adjusted for vascular condition, using multiple linear regression. End of study fellow eye visual acuity was significantly worse for patients with baseline values of 20/200 or worse (mean 0.85 logMAR) compared to patients with better than 20/64 at baseline (mean 0.29 logMAR, $P = .04$), adjusted for vascular condition.

DISCUSSION

THE IONDT IS THE ONLY LARGE PROSPECTIVE STUDY TO evaluate patients immediately after onset of NAION and then to follow them using standardized measurement techniques. We observed a cumulative prevalence of 30.6% and a cumulative incidence of 14.7% of second eye NAION over a median patient follow up of 5.1 years. Our cumulative prevalence falls within the range observed in other studies of 23% to 48% (see Table 7).[7,14–22] However, the other studies are observational, had small sample sizes, were subject to substantial selection bias, and included patients with conditions other than NAION or with precipitating events or diseases known to be associated with bilateral anterior ischemic optic neuropathy. Thus, we think the IONDT estimates may be the most reliable.

Only a few studies provide information regarding the incidence of second eye involvement with NAION over defined periods of follow up. The incidence rate of 14.7% that we find for new NAION in the second eye is perhaps most comparable to the estimate by Beck and associates,[21] where patients were excluded if they were not seen until the fellow eye was involved. Using life table analyses to account for varying lengths of follow up, they estimated risk of second-eye NAION at 12% within 2 years and 19% within 5 years. When they assumed that none of the patients with incomplete follow up in this cohort developed NAION in the fellow eye, then the risk estimates were 9% after 2 years and 12% after 5 years.

In the IONDT, the majority of new cases (22/48; 46%) of fellow eye NAION in all patients occurred during the first 12 months of follow-up (Figure 1). The rate of second eye involvement appears to remain fairly constant thereafter up to 6 years of follow-up, arguing against any defined period of time after which a patient is unlikely to suffer fellow eye NAION. It has been suggested that the risk of second eye involvement in NAION is highest within the first year, leveling off and, perhaps, even decreasing after 10 years (Feldon, S, written communication, January 19, 2002). We found a median interval of 1.2 years and a mean interval of 2.1 years between the occurrence of NAION in the study eye and new NAION in the fellow eye. Since not all patients were followed for the full 5 years (182/326 [55.8%] of patients at risk for NAION were followed 5 years), it is possible that additional NAION events occurred and that patient risk is higher than what we observed. In addition, our follow-up data do not extend reliably beyond 5 years after the occurrence of NAION in the study eye. Previous studies are difficult to evaluate given their retrospective nature and the varied lengths of follow-up, but there are examples of second eye involvement after as many as 30 years.[6]

The IONDT found no relationship between age or sex and the risk of second eye NAION, similar to the findings of two previous studies.[20,22] However, the large cohort study reported by Beri and associates[6] did find a significantly increased risk (1.5 times) of NAION bilaterality among men compared with women.

NAION has been hypothesized to be a vascular disease. Sixty percent of all IONDT patients had one or more risk factors thought to be associated with small vessel cerebrovascular disease, including hypertension, diabetes mellitus, and cigarette use;[14] this prevalence of systemic disease is similar to that reported by others.[3,7–9,15–18,24–27] This does not assure that the disease is vascular, however, as similar

TABLE 4. Visual Acuity in Study and Fellow Eyes in Patients With Incident NAION in Fellow Eye by Study Visit*

	Baseline		Study Visit After New NAION			
			First		Last	
Visual Acuity	No.	(%)	No.	(%)	No.	(%)
Study eye						
Better than 20/64	11	(25)	16	(36)	15	(34)
20/64 to better than 20/200	11	(25)	13	(29)	10	(23)
20/200 or worse	22	(50)	15	(34)	19	(43)
Total	44	(100)	44	(100)	44	(100)
Fellow eye						
Better than 20/64	41	(93)	22	(50)	23	(52)
20/64 to better than 20/200	3	(7)	11	(25)	8	(18)
20/200 or worse	0		11	(25)	13	(30)
Total	44	(100)	44	(100)	44	(100)

*Includes data on patients who completed visits at all three time points (44/48 patients with new NAION).

TABLE 5. Correlation Between Eyes by Fellow Eye Involvement and Study Visit

	Fellow Eye Involvement								
	Baseline NAION or ON			New NAION or ON			No new NAION or ON		
Correlation between	No.	r	95% CI	No.	r	95% CI	No.	r	95% CI
Baseline study eye and Baseline fellow eye	85	0.51	0.33–0.65	47	0.29	0.003–0.53	275	0.18	0.06–0.29
Last visit study eye and Last visit fellow eye	87	0.51	0.34–0.65	48	0.36	0.08–0.58	274	0.16	0.04–0.27

proportions might be observed in a comparable patient population without NAION.

In the IONDT, we did not see any association between age or smoking and risk of second eye NAION. We defined vascular condition in our study to include diabetes or a history of myocardial infarction, hypertension, stroke, or transient ischemic attack; the associations that we observed between that variable and incidence of second eye NAION were not statistically significant (18% in patients with a vascular condition vs 10% without; log rank, $P = .06$). When we examined diabetes separately, we observed a statistically significant association between baseline diabetes and new second eye NAION (24% in patients with diabetes vs 12% in patients without, log rank $P = .02$).

Our results relating to vascular disease are supported by findings from some observational studies which found no association between bilateral NAION and hypertension,[6,21,23] anemia,[6,21] migraine,[6,21] ischemic heart disease,[6,21] or arrhythmia.[23] In contrast, Moro and associates[8] reported fewer fellow eye NAION events among the "idiopathic" NAION patients than among those patients with assorted systemic diseases, including hypertension, diabetes, and migraine. However, patients as young as 33 years old were included in that study, while no patient under the age of 50 years was included in the IONDT. Kupersmith and associates[21] also reported a significant association between diabetes mellitus and second eye involvement. Beri and associates[6] used Cox proportional hazards analysis to examine the association between bilateral AION and age, sex, and systemic diseases. They found two factors to be significantly positively associated with risk of AION: (1) an interaction between young (<45) age and diabetes ($P = .02$) and (2) male sex ($P = .01$). Thus, although diabetes alone was not associated with bilateral AION, it did confer increased risk in younger patients in the study by Beri.

Although some observational studies have suggested that cigarette smoking may be an important risk factor for NAION,[18,19] we found no association between smoking and new NAION in the second eye. Similarly, in a case-control study of 63 patients with NAION, Johnson and associates[28] found no difference in the proportion of cigarette smokers between patients and controls. In a case-control study of 41 patients with NAION, Talks and associates[19] reported that smoking was significantly associated with NAION, but the percentage of smokers in the control group was lower than the national average. No previous studies have commented specifically on the relationship between smoking and the risk of second eye involvement.

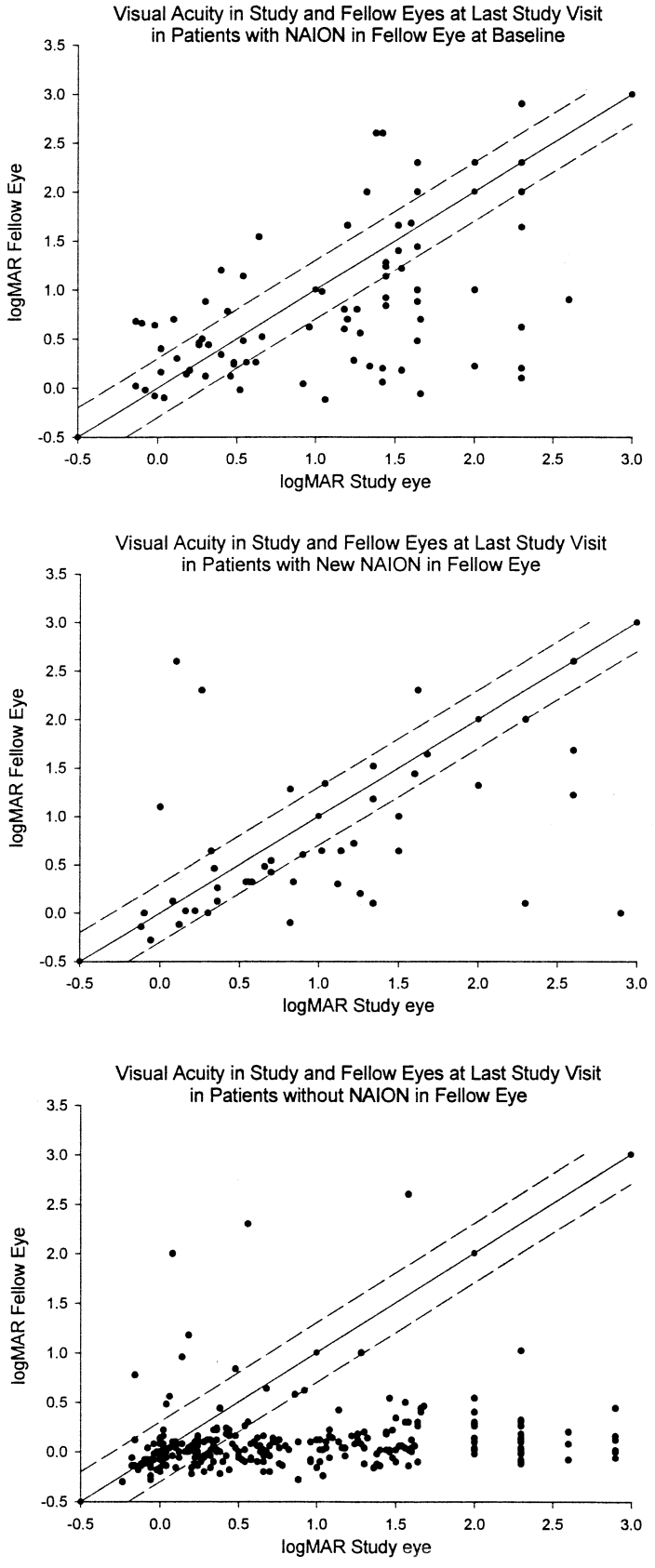


FIGURE 2. (Top) Visual acuity in study and fellow eyes at last study visit in patients with nonarteritic anterior ischemic optic neuropathy (NAION) in fellow eye at baseline. (Middle) Visual acuity in study and fellow eyes at last study visit in patients with new NAION in fellow eye. (Bottom) Visual acuity in study and fellow eyes at last study visit in patients without NAION in fellow eye.

TABLE 6. Unadjusted and Adjusted Mean Visual Acuity* at End of Study in Fellow Eyes With New NAION (n=47), by Baseline Visual Acuity in Study Eye, From Multiple Linear Regression Analysis

Baseline Variables	Fellow Eye Mean Visual Acuity (SE)*	*P* Value
Unadjusted		
Study eye visual acuity		
Better than 20/64 (logMAR $<$ 0.5)	0.37 (0.21)	0.05
20/64 to better than 20/200 (logMAR 0.5 to $<$1.0)	0.64 (0.24)	0.36
20/200 or worse (logMAR $\geq$ 1.00)	0.90 (0.15)	Reference
Adjusted for Vascular Condition		
Study eye visual acuity		
Better than 20/64 (logMAR $<$ 0.5)	0.29 (0.22)	0.04
20/64 to better than 20/200 (logMAR 0.5 to $<$1.0)	0.55 (0.25)	0.29
or worse than 20/200 (logMAR $\geq$ 1.00)	0.85 (0.16)	Reference
Any vascular condition		
No	0.43 (0.22)	0.26
Yes	0.71 (0.13)	

*Fellow eye visual acuity in logMAR units.

There is no effective therapy for acute NAION,[10,11] nor is there a consensus on an effective therapeutic intervention to prevent second eye involvement. Aspirin has been shown to reduce systemic vascular events such as myocardial infarction and ischemic stroke.[29–31] For this reason, it is frequently prescribed for patients with NAION, primarily for its potential role in second eye NAION prevention.[32] Although two observational studies[21,23] claimed a positive effect of aspirin use on the reduction of second eye involvement in NAION, a subsequent large cohort life table analysis of NAION patients[22] concluded that there was little or no benefit of aspirin in reducing fellow eye risk within 5 years. Similarly, in the IONDT, aspirin use appears to have no effect on the incidence of second eye involvement 5 to 8 years (mean = 5.1 years) after the occurrence of NAION in the first eye. Results were similar for randomized and nonrandomized patients and for patients treated surgically or receiving careful follow up. Because the IONDT was not designed specifically to answer the question of aspirin efficacy and aspirin use was not randomly assigned or systematically monitored, we cannot provide conclusive data to answer the question of aspirin's prophylactic efficacy in NAION. Given the fairly low risk of second eye involvement, the need for a very large sample size to detect a beneficial effect, and the almost routine use of aspirin for systemic vascular diseases in this patient population, a randomized trial of aspirin use in NAION would likely not be feasible.

Patients who have suffered NAION in one eye often ask whether the degree of visual dysfunction will be the same in the fellow eye should it become affected. Some observational studies have noted a correlation,[8,20,33,34] while others have not.[15,21,35] In the IONDT, increased incidence was associated with poor baseline visual acuity and there were significant correlations between visual acuity in the two eyes of patients with bilateral NAION at baseline and follow-up. Approximately half of the IONDT patients with NAION in both eyes had Snellen visual acuities within three lines of one another. However, given that 30% of patients had a difference in visual acuities between eyes of greater than six lines, predicting the visual acuity for the second eye in any individual still remains problematic.

Many patients, and some physicians, felt that the vision in the previously affected eye with NAION will "improve" when its fellow eye suffers visual loss. In the IONDT, there was little change in visual acuity in the study eye from baseline to after occurrence of fellow eye NAION. We examined this hypothesis by plotting the visual acuity of the study eye over time for all patients and found no discernible pattern of improvement in the first eye relative to the occurrence of NAION in the fellow eye.

• **CONCLUSIONS**: In this large cohort of patients with NAION, new NAION in the fellow eye occurred in 14.7% of patients at risk, over a median follow up of 5.1 years, a lower percentage than previously assumed. Increased incidence is associated with poor visual acuity in the first eye and a history of diabetes mellitus, but not with age, sex, smoking history, or aspirin use. Although visual acuities between eyes in patients with bilateral NAION are highly correlated, predicting visual outcome for the second eye in any individual is impossible. Clinicians are encouraged to

TABLE 7. Comparison of Studies Examining Bilateral NAION

Author	Year	Patients No.	Fellow Eye With NAION at Baseline No. (%)	Fellow Eye With NAION at Follow-up No. (%)	Cumulative Prevalence (%)	Length Follow-up Range (Mean)	Interval to new NAION Range (Mean)
Ellenberger[7]	1973	48*	20/48 (42)	3/40 (7.5)	48	1 mo to 11 yrs	1 mo to 7 yrs
						(2.9 yrs)	(2.4 yrs)
						median, 1 yr	
Boghen[15]	1975	37	13/33 (39)	1/20 (5)	42	93% ≥ 3 yrs	5 mo to 22 yrs
						79% ≥ 5 yrs	< 1 yr for 1/3rd
Repka[16]	1983	169	—	20/83 (24)	—	3 to 13 yrs	≤ 2 weeks in 4
						(5 yrs)	(20%)
							≥ 1 yr in 10
							(50%)
							(2.9 yr)
Moro[8]	1989	84*	—	—	31	3 mo to 12 yrs	—
						(4.1 yrs)	
Sawle[17]	1990	71	3/71 (4.2)	17/68 (25)	28	(5.3 yrs)	≤ 1 yr in 10
							(57%)
							maximum, 10.5 yr
Chung[18]	1994	137	—	—	36	over 10 yrs	—
Talks[19]	1995	41	2/41 (4.9)	5/39 (12.8)	17	(2.3 yrs)	—
Boone[20]	1996	99	12/99 (12)	11/87 (12.6)	23	over 3.5 yrs	—
Kupersmith[21]	1997	100	15/100 (15)	18/85 (21)	33	minimum, 2 yrs	0.02 to 16 yrs
							≤ 1 yr in 22
							(67%)
Beck†[22]	1997	643	154/643 (24)	48/431 (11.2)	31	0 to ≥ 5 yrs	≤ 1 yr in 47%
Salomon[23]	1999	52	—	—	31	—	(8.0 yrs)
IONDT	2002	418	80/418 (19)	48/326 (14.7)	30.6	median, 5.1 yrs	16 days to 6 yrs
						0 to 7.4 yrs	(2.1 yrs)
							≤ 1 yr in 22
							(46%)

*Includes three patients with giant cell arteritis.
†Includes patients from Beri and associates (1987); at 5 years, using life table analyses.

use data from large prospective studies such as the IONDT when they counsel their patients with NAION.

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