The Advanced Glaucoma Intervention Study (AGIS): 7. The Relationship Between Control of Intraocular Pressure and Visual Field Deterioration

THE AGIS INVESTIGATORS*

• PURPOSE: To investigate the association between control of intraocular pressure after surgical intervention for glaucoma and visual field deterioration.
• METHODS: In the Advanced Glaucoma Intervention Study, eyes were randomly assigned to one of two sequences of glaucoma surgery, one beginning with argon laser trabeculoplasty and the other trabeculectomy. In the present article we examine the relationship between intraocular pressure and progression of visual field damage over 6 or more years of follow-up. In the first analysis, designated Predictive Analysis, we categorize 738 eyes into three groups based on intraocular pressure determinations over the first three 6-month follow-up visits. In the second analysis, designated Associative Analysis, we categorize 586 eyes into four groups based on the percent of 6-month visits over the first 6 follow-up years in which eyes presented with intraocular pressure less than 18 mm Hg. The outcome measure in both analyses is change from baseline in follow-up visual field defect score (range, 0 to 20 units).
• RESULTS: In the Predictive Analysis, eyes with early average intraocular pressure greater than 17.5 mm Hg had an estimated worsening during subsequent follow-up that was 1 unit of visual field defect score greater than eyes with average intraocular pressure less than 14 mm Hg (P = .002). This amount of worsening was greater at 7 years (1.89 units; P < .001) than at 2 years (0.64 units; P = .071). In the Associative Analysis, eyes with 100% of visits with intraocular pressure less than 18 mm Hg over 6 years had mean changes from baseline in visual field defect score close to zero during follow-up, whereas eyes with less than 50% of visits with intraocular pressure less than 18 mm Hg had an estimated worsening over follow-up of 0.63 units of visual field defect score (P = .083). This amount of worsening was greater at 7 years (1.93 units; P < .001) than at 2 years (0.25 units; P = .572).
• CONCLUSIONS: In both analyses low intraocular pressure is associated with reduced progression of visual field defect, supporting evidence from earlier studies of a protective role for low intraocular pressure in visual field deterioration. (Am J Ophthalmol 2000;130:429–440. © 2000 by Elsevier Science Inc. All rights reserved.)

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The writing team members for this paper are: Paul C. VanVeldhuisen, MS, Fred Ederer, MA, FACE, Douglas E. Gaasterland, MD, E. Kenneth Sullivan, PhD, Allen Beck, MD, Bruce E. Prum, Jr, MD, Marshall N. Cyrlin, MD, and Howard Weiss, MD, MPH. A complete list of participants in the Advanced Glaucoma Intervention Study appears at the end of this article.

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Correspondence and reprint requests to Paul C. VanVeldhuisen, MS, The Advanced Glaucoma Intervention Study, AGIS Coordinating Center, 11325 Seven Locks Rd, Suite 214, Potomac, MD 20854; fax: (301) 299-3991; e-mail: pvanveldhuisen@emmes.com

OUR APPRECIATION OF ELEVATED INTRAOCULAR pressure as a risk factor for glaucoma dates to the middle of the nineteenth century when Von Graefe reported its association with a characteristic type of optic nerve damage leading to blindness. We now know from population studies that increased intraocular pressure is associated with increased prevalence[1,2] and incidence[3] of glaucoma.

There is some evidence indicating that reduced levels of intraocular pressure slow the progression of glaucomatous optic neuropathy,[4–10] but more conclusive evidence is likely to come from large, long-term, randomized clinical trials specifically designed to address this issue. Two such trials, the Early Manifest Glaucoma Trial,[11] started in Sweden in 1992,

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and the Ocular Hypertension Treatment Study,[12] started in the United States in 1994, are currently in progress.

Armaly and associates[3] in a large prospective study of 5000 patients with open-angle glaucoma found five of 26 potential risk factors for glaucoma to be significantly related to the development of glaucomatous visual field defects—outflow facility, age, intraocular pressure, cup–disk ratio, and pressure change after drinking water—but multivariate analysis showed "their collective predictive power to be undesirably poor, indicating that other factors must play an important role in the development of glaucomatous visual field defects." Since then, it has become increasingly recognized that factors other than intraocular pressure must be involved in the development of glaucomatous optic neuropathy.[13–15] Nevertheless, in the absence of other known factors on which to intervene, the control of intraocular pressure remains the principal goal of all current glaucoma treatment.

Eight years of follow-up of 789 eyes of 591 patients in the Advanced Glaucoma Intervention Study provide the opportunity to shed additional light on the role of intraocular pressure reduction in glaucoma by investigating the association between intraocular pressure after surgical interventions and progression of visual field damage. We report herein the results of this investigation.

MATERIALS AND METHODS

THE ADVANCED GLAUCOMA INTERVENTION STUDY DESIGN and methods, described in detail elsewhere,[16–18] are summarized here. Appropriate institutional review boards approved the Advanced Glaucoma Intervention Study protocol, and all enrolled patients provided informed consent.

To be eligible for the Advanced Glaucoma Intervention Study, patients had to be 35 to 80 years old and have open-angle glaucoma that could no longer be adequately controlled by medications alone. Eligible eyes had to be phakic, be on maximum accepted and tolerated medical therapy, have a best-corrected Early Treatment Diabetic Retinopathy Study visual acuity score of at least 56 letters (Snellen equivalent approximately 20/80), and meet specified criteria for combinations of consistently elevated intraocular pressure, glaucomatous visual field defect, and/or optic disk rim deterioration.[16] For eligibility, the minimum visual field defect score was 1 and the maximum 16 (visual field defect scoring is described in the next section).

Between 1988 and 1992, investigators at 11 participating Advanced Glaucoma Intervention Study clinical centers enrolled 789 eyes of 591 patients. Eyes were randomly assigned to be managed with one of two surgical intervention sequences: argon laser trabeculoplasty–trabeculectomy–trabeculectomy or trabeculectomy–argon laser trabeculoplasty–trabeculectomy. Surgical interventions are supplemented by medical glaucoma treatment with the goal of reducing intraocular pressure to less than 18 mm Hg. The second and third interventions of a sequence are offered only after failure, despite supplemental medical treatment, of the preceding intervention. Both eyes of a patient were enrolled only if they were eligible simultaneously: one eye was assigned to argon laser trabeculoplasty–trabeculectomy–trabeculectomy or trabeculectomy–argon laser trabeculoplasty–trabeculectomy, and the fellow eye to the opposite sequence.

Follow-up study visits were scheduled 3 and 6 months after enrollment and every 6 months thereafter. Although patients may be seen between study visits, data from these examinations were not routinely collected. Data in this report are based on a database closure of December 31, 1998, at which time all enrolled eyes had the potential of completing 6 years of follow-up, 82% the potential of completing 7 years, and 64% the potential of completing 8 years.

Intraocular pressure is measured with a Goldmann applanation tonometer on a slit-lamp biomicroscope. The reading in mm Hg is rounded to the next higher integer. Each measurement is repeated, and if the two readings differ by 3 mm Hg or more, a third measurement is taken. The median of the two or three measurements becomes the intraocular pressure determination.

Visual field tests are conducted with a Humphrey Visual Field Analyzer I set for the central 24-2 threshold test, size III white stimulus, and full threshold strategy, with the foveal threshold test turned on. Visual field defect scores range from 0 (no defect) to 20 (end-stage).[17] If an eye has insufficient vision for a patient to count fingers at 30 cm, the visual field defect score is recorded as 20.

Study measurements were made at baseline and at each 6-month follow-up examination. To lessen the effect of regression to and from the mean caused by the restricted lower and upper ranges on the eligibility values,[19] baseline or "reference" measurements were performed after the eligibility measurements but before the first surgical intervention. Changes in visual field defect score in this report are measured from the pre-intervention reference values.

Our primary objective in this report is to examine the relationship between intraocular pressure during follow-up and progression of visual field damage. Two analyses address this objective (Table 1). The first, designated Predictive Analysis, is designed to assess whether intraocular pressure during early follow-up is predictive of subsequent change from baseline in visual field defect score. Each eye was assigned to one of three categories in accordance with its intraocular pressure averaged over the 6-month, 12-month, and 18-month visits: less than 14 mm Hg, 14 to 17.5 mm Hg, and greater than 17.5 mm Hg. Then, for each subsequent 6-month follow-up visit, the mean change from baseline in visual field defect score was calculated for each of the three intraocular pressure groups. The Predictive Analysis excludes 51 eyes with less than 2 years of follow-up, leaving 738 eyes for analysis.

In the second analysis, designated Associative Analysis, the percent of visits over the first 6 years of follow-up for which an eye presented with intraocular pressure less than

TABLE 1. Definitions of Intraocular Pressure Groups

Predictive Analysis	Associative Analysis	
IOP averaged over the first three 6-month visits	IOP group	Percent of visits with IOP less than 18 mm Hg
<14 mm Hg	A	100
14–17.5 mm Hg	B	75 to <100
>17.5 mm Hg	C	50 to <75
	D	0 to <50

IOP = intraocular pressure.

18 mm Hg was determined. In accordance with this percent, each eye was assigned to one of four categories: 100% (group A); 75% to less than 100% (group B); 50% to less than 75% (group C); and 0% to less than 50% (group D). Then, for each group and for each visit starting with the 6-month visit, the mean change from baseline in visual field defect score was calculated. This analysis includes the 586 eyes followed for at least 6 years having missed no more than two 6-month visits. Of the 203 eyes excluded from the analysis, 180 had not completed 6 years of follow-up, and 23 had not completed the requisite number of visits. The 6-year period was chosen because all eyes had the potential for completing at least 6 years.

The generalized estimating equations method of Liang and Zeger[20] was used in both the Predictive and Associative analyses to estimate and test the association between intraocular pressure and change in visual field defect score. The generalized estimating equations method provides statistical adjustment for potential confounding covariables. In analyses that include multiple visits, this method accounts for the within-eye correlation in visual field defect score between visits. In visit-specific analyses, this method accounts for the between-eye correlation in visual field defect scores from patients with both eyes enrolled.

In the Predictive Analysis, Pearson correlation coefficients were calculated between average intraocular pressure over the first three 6-month visits and 1) intraocular pressure at baseline, 2) intraocular pressure at subsequent visits, and 3) change from baseline in visual field defect score at subsequent visits.

RESULTS

TABLE 2 PRESENTS SOME BASELINE CHARACTERISTICS FOR each of the defined intraocular pressure groups for the 738 eyes in the Predictive Analysis. Some characteristics differ by assigned intervention sequence: the majority of eyes with intraocular pressure averaged over the first three 6-month visits of less than 14 mm Hg were in the trabeculectomy–argon laser trabeculoplasty–trabeculectomy sequence, and a majority of eyes in the 14 to 17.5 mm Hg and greater than 17.5 mm Hg groups were in the argon laser trabeculoplasty–trabeculotomy–trabeculectomy sequence. Patients or eyes represented by the greater than 17.5 mm Hg group have a greater prevalence of diabetes, a higher mean reference intraocular pressure, a lower mean reference visual field defect score, and a lower mean age than those represented by the 14 to 17.5 mm Hg and less than 14 mm Hg groups. There is no evidence of differences among the patients and eyes represented by the various intraocular pressure groups in race, gender, hypertension, or type and frequency of glaucoma medications prescribed at baseline.

The following guidelines may be helpful in interpreting the Pearson correlation coefficients presented in Table 3. Positive correlation coefficients indicate positive correlation, negative coefficients indicate negative correlation, and zero indicates absence of correlation. Coefficient values from 0 to 0.25 indicate little or no correlation, from 0.25 to 0.50 fair correlation, from 0.50 to 0.75 moderate to good correlation, and from 0.75 to 1.00 very good to excellent correlation.[21]

Figure 1 presents the mean intraocular pressure at each semi-annual visit subsequent to the 18-month visit for the three groups defined by the level of intraocular pressure during early follow-up. Throughout follow-up, the mean intraocular pressure values in the three groups are widely separated, retaining the same ranking that they had over the first three 6-month visits. The separation is supported by positive Pearson coefficients of correlation between the mean intraocular pressure over the first three 6-month visits and 1) intraocular pressure at baseline and 2) intraocular pressure at each annual visit after the first three 6-month visits (Table 3). The positive correlation coefficients are generally higher at earlier follow-up visits ($r = .63$ at month 24) than at later ones ($r = .35$ at month 96). The lowest coefficient is for the baseline visit ($r = .16$).

Table 3 also displays coefficients of correlation between intraocular pressure averaged over the first three 6-month visits and change from baseline in visual field defect score at each subsequent annual visit. These correlation coefficients are positive, although low, and show some tendency to increase from early ($r = .12$ at month 24) to later ($r = .18$ at month 96) follow-up visits. This positive association, particularly in the later follow-up visits, is more evident in Table 4 and Figure 2, which show mean changes from baseline in visual field defect score classified according to intraocular pressure averaged over the first three 6-month visits. After month 48, the three groups are generally ranked according to the intraocular pressure average for the first three 6-month visits, with the greatest increase in mean change of visual field defect score over time in the highest (greater than 17.5 mm Hg) intraocular pressure group.

Table 5 presents results of regression analyses examining whether intraocular pressure averaged over the first three 6-month visits is predictive of subsequent change from

TABLE 2. Baseline Characteristics of Intraocular Pressure Groups: Predictive Analysis

	Groupings Based on IOP Averaged Over First Three 6-Month Visits					
	<14 mm Hg		14–17.5 mm Hg		>17.5 mm Hg	
	N	%	N	%	N	%
Total	229	100.0	291	100.0	218	100.0
Intervention sequence						
ATT	85	37.1	171	58.8	123	56.4
TAT	144	62.9	120	41.2	95	43.6
Race						
Black	126	55.0	171	58.8	123	56.4
White	102	44.5	117	40.2	87	39.9
Other	1	0.4	3	1.0	8	3.7
Gender						
Male	99	43.2	131	45.0	88	40.4
Female	130	56.8	160	55.0	130	59.6
Age >65	125	54.6	171	58.8	113	51.8
Mean age		65.7		66.1		64.5
SD		9.2		9.0		9.4
With diabetes	34	14.8	54	18.6	66	30.3
With hypertension	111	48.5	151	51.9	111	50.9
Reference IOP						
<21	71	31.0	75	25.8	32	14.7
21–<23	53	23.1	64	22.0	38	17.4
23–<26	44	19.2	72	24.7	63	28.9
≥26	61	26.6	80	27.5	85	39.0
Mean reference IOP		23.3		23.7		25.5
SD		5.4		4.5		5.3
Reference VFDS						
0–5	62	27.1	91	31.3	78	35.8
6–11	101	44.1	103	35.4	90	41.3
12–17	58	25.3	88	30.2	43	19.7
18–20	8	3.5	9	3.1	7	3.2
Mean reference VFDS		8.8		8.6		7.9
SD		4.4		4.8		4.8
Number of glaucoma medications at baseline						
0	4	1.7	8	2.7	5	2.3
1	15	6.6	33	11.3	19	8.7
2	77	33.6	80	27.5	56	25.7
3	93	40.6	110	37.8	85	39.0
4	40	17.5	60	20.6	53	24.3
Mean		2.7		2.6		2.7
SD		0.9		1.0		1.0
Type of medication						
Miotic	180	78.6	227	78.0	183	83.9
β-blocker	202	88.2	254	87.3	192	88.1
Epinephrine	110	48.0	136	46.7	101	46.3
CAI	116	50.7	146	50.2	122	56.0

ATT = argon laser trabeculoplasty–trabeculectomy–trabeculectomy; CAI = carbonic anhydrase inhibitor; IOP = intraocular pressure; TAT = trabeculectomy–argon laser trabeculoplasty–trabeculectomy; VFDS = visual field defect score.

baseline in visual field defect score. Regression models considered are an overall analysis that includes all visits from months 24 to 96, and three visit-specific analyses at months 24, 60, and 84. Results, both unadjusted and adjusted for potential confounding baseline variables, are presented for two methods of categorizing intraocular pressure over the first 18 months: the first method (model 1) uses average intraocular pressure as a three-level inter-

TABLE 3. Pearson Coefficients of Correlation Between Intraocular Pressure Averaged Over the First Three 6-Month Visits and 1) Intraocular Pressure and 2) Change From Baseline in Visual Field Defect Score at Follow-up Visits: Predictive Analysis

Follow-up Visit	Intraocular Pressure	Change in Visual Field Defect Score
Baseline	0.16	
24-month	0.63	0.12
36-month	0.51	0.06
48-month	0.46	0.06
60-month	0.37	0.14
72-month	0.39	0.19
84-month	0.35	0.20
96-month	0.35	0.18

val-scaled variable with less than 14 mm Hg as the reference group, and the second (model 2) uses average intraocular pressure as a continuous variable.

In model 1 for all visits, the unadjusted and adjusted parameter estimates indicate that the greater the average intraocular pressure during the first 18 months of follow-up, the greater the expected increase from baseline in visual field defect score (Table 5). In the adjusted model, although both the 14 to 17.5 mm Hg and greater than 17.5 mm Hg groups are associated with greater worsening of visual field defect score than the reference group, statistical significance ($P = .002$) is achieved only for the greater than 17.5 mm Hg group estimate of 1.00 (indicating that the difference in expected change from baseline between the greater than 17.5 mm Hg and less than 14 mm Hg groups is one unit of visual field defect score). In the visit-specific models, the estimate of change in visual field defect score in the higher intraocular pressure groups relative to the less than 14 mm Hg group is greater at the later than at the earlier visits. For example, at 84 months in the adjusted model the estimated change in visual field defect score is 1.89 ($P < .001$) for the greater than 17.5 mm Hg group relative to the less than 14 mm Hg group, compared with an estimate of 0.64 ($P = .071$) at 24 months.

In the adjusted model 2 for all visits there is a predicted worsening in visual field defect score of 0.10 from baseline for each 1 mm Hg increase in average intraocular pressure, a finding that is statistically significant ($P = .002$; Table 5). As in model 1, the estimated change in visual field defect score increases from earlier to later visits (for example, 0.08 at 24 months to 0.18 at 84 months).

The adjusted models in Table 5 account for race, assigned intervention sequence, age at randomization, diabetes, gender, reference intraocular pressure, and reference visual field defect score. These covariates were included because of the imbalances in these characteristics between intraocular pressure groups noted earlier, and because each is a possible risk factor for subsequent visual field deterioration. The effect of cataract formation, another possible risk factor, is addressed in the Discussion section of the article.

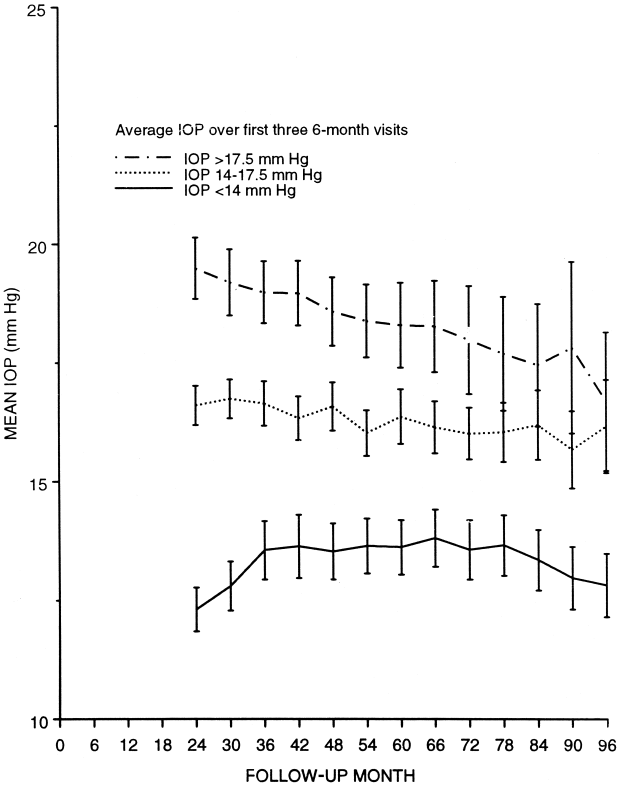

FIGURE 1. Predictive Analysis. Mean intraocular pressure (±2 SE) in the three intraocular pressure groups classified according to intraocular pressure averaged over the first three 6-month visits.

The 586 eyes in the Associative Analysis are rather evenly distributed among the four groups (A, B, C, and D) defined by the percent of visits over the first 6 years of follow-up at which the eye presented with intraocular pressure less than 18 mm Hg (Table 6). The mean intraocular pressure over the first 6 years of follow-up is 12.3 mm Hg for group A, 14.7 mm Hg for group B, 16.9 mm Hg for group C, and 20.2 mm Hg for group D. For group A (eyes presenting with intraocular pressure less than 18 mm Hg at each visit over 6 years), the mean changes in visual field defect score remain close to zero, whereas in each of the other three groups (B, C, and D), the mean change progressively increases over time to an average worsening in visual field defect score of about two to three points by 96 months (Figure 3). Starting at 54 months, mean changes for the four groups diverge and remain consistently ranked according to the percent of visits with intraocular pressure less than 18 mm Hg.

Table 6 displays the results of regression analyses used to estimate the change from baseline in visual field defect score for each of the groups defined in the Associative Analysis. We designate group A (eyes with 100% of visits less than 18 mm Hg) as the "reference" group, and groups

TABLE 4. Mean Change From Baseline in Visual Field Defect Score, by Intraocular Pressure Grouping: Predictive Analysis

Follow-up Visit	Intraocular Pressure Averaged Over First Three 6-Month Visits								
	<14 mm Hg			14–17.5 mm Hg			>17.5 mm Hg		
	N	Mean	SE	N	Mean	SE	N	Mean	SE
24-month	222	−0.09	0.21	281	0.03	0.20	210	0.87	0.27
36-month	209	0.40	0.23	270	0.36	0.22	196	0.97	0.31
48-month	203	0.77	0.25	246	0.41	0.25	194	1.19	0.35
60-month	191	0.45	0.28	230	0.85	0.25	181	1.72	0.35
72-month	177	0.33	0.29	223	1.11	0.27	166	2.60	0.40
84-month	147	0.63	0.33	163	1.42	0.34	120	3.11	0.46
96-month	106	0.71	0.40	123	1.97	0.41	87	2.97	0.54

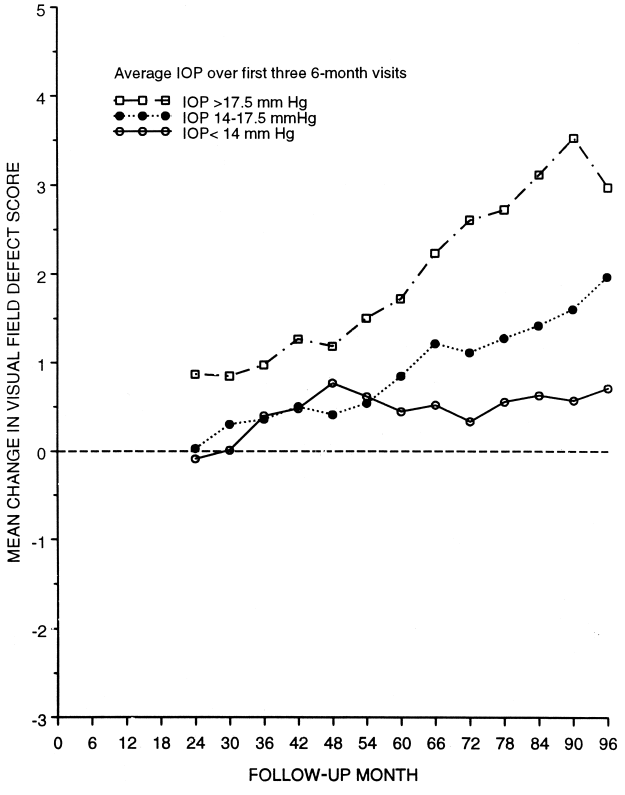

FIGURE 2. Predictive Analysis. Mean change from baseline in visual field defect score by intraocular pressure classified according to average value over the first three 6-month visits.

B, C, and D as the "elevated" intraocular pressure groups. Both the unadjusted and adjusted models for all visits predict a greater worsening of visual field defect score for each of the three elevated intraocular pressure groups than for the reference group, although for the adjusted model, the *P* value is less than .05 ($P = .016$) only for group C. In models for the 24-month, 60-month, and 84-month visits, *P* values for worsening in visual field defect score are less than .05 at the 60-month and 84-month visits. At 84 months, the adjusted model predicts a one-point worsening in visual field defect score for group B relative to group A ($P = .034$), and approximately a two-point worsening in visual field defect score for group C ($P < .001$) and group D ($P < .001$) relative to group A. For all models presented in Table 6, estimates of change in visual field defect score are similar for groups C and D, with both groups generally having larger estimates of change in visual field defect score than group B. Covariates in the adjusted models were the same as those in the Predictive Analysis.

DISCUSSION

WE UNDERTOOK THE PRESENT ANALYSES TO DETERMINE whether the achievement of low levels of intraocular pressure after surgical intervention in eyes of Advanced Glaucoma Intervention Study patients is associated with a slowing of visual field deterioration. We found from both the Predictive Analysis and Associative Analysis that low postintervention intraocular pressure is associated with reduced progression of visual field defect. Moreover, the association became stronger as follow-up lengthened.

The Predictive Analysis and Associative Analysis are each in a "dose–response" form, the "dose" in the Predictive Analysis being intraocular pressure during the first 18 months of follow-up and in the Associative Analysis the percent of visits for which eyes presented with intraocular pressure less than 18 mm Hg in the first 6 years of follow-up. In both analyses the "response" is change from baseline in follow-up visual field defect score, with follow-up beginning at 2 years for the Predictive Analysis and at 6 months for the Associative Analysis. Regarding the "dose," the fair to good positive correlations between average intraocular pressure during the first 18 months and subsequent intraocular pressure (correlation coefficients range from 0.63 to 0.37 between 2 and 6 years of follow-up; Table 3) indicate that the ranking of eyes according to intraocular pressure during the first 18 months is similar to their ranking according to intraocular pressure during subsequent follow-up. In this light, the similarity of the outcomes of the Predictive Analysis and Associative analysis is not surprising. We also note that in this study, where

TABLE 5. Summary of Regression Analysis: Predictive Analysis

Follow-up Visit		Unadjusted			Adjusted*		
		Estimate of Change in VFDS	*P* Value	95% Confidence Limits	Estimate of Change in VFDS	*P* Value	95% Confidence Limits
Model 1: average IOP as a three-level interval-scaled variable†							
All visits‡	<14 mm Hg	—	—	—	—	—	—
	14–17.5 mm Hg	0.45	.115	−0.11, 1.02	0.42	.119	−0.11, 0.95
	>17.5 mm Hg	1.34	<.001	0.67, 2.01	1.00	.002	0.37, 1.62
24-month	<14 mm Hg	—	—	—	—	—	—
	14–17.5 mm Hg	0.10	.716	−0.45, 0.65	0.14	.606	−0.38, 0.66
	>17.5 mm Hg	0.89	.015	0.17, 1.61	0.64	.071	−0.05, 1.33
60-month	<14 mm Hg	—	—	—	—	—	—
	14–17.5 mm Hg	0.46	.210	−0.26, 1.17	0.47	.185	−0.22, 1.15
	>17.5 mm Hg	1.23	.007	0.34, 2.11	0.97	.026	0.12, 1.82
84-month	<14 mm Hg	—	—	—	—	—	—
	14–17.5 mm Hg	0.81	.085	−0.11, 1.72	0.76	.095	−0.13, 1.64
	>17.5 mm Hg	2.45	<.001	1.29, 3.61	1.89	<.001	0.79, 2.98
Model 2: average IOP as a continuous variable§							
All visits‡	IOP, continuous	0.13	<.001	0.07, 0.20	0.10	.002	0.04, 0.16
24-month	IOP, continuous	0.10	.004	0.03, 0.17	0.08	.034	0.01, 0.14
60-month	IOP, continuous	0.13	.002	0.05, 0.22	0.12	.006	0.03, 0.20
84-month	IOP, continuous	0.22	<.001	0.12, 0.33	0.18	<.001	0.07, 0.28

Abbreviations as in Table 2.

*Models are adjusted for race, assigned intervention sequence, age at randomization, diabetes, gender, reference IOP, and reference visual field defect score.

†Estimates of change in VFDS in Model 1 are relative to the <14 mm Hg group.

‡Data from the 24-month to 96-month visits are used in the analysis.

§Estimates of change in VFDS are per 1 mm Hg increase in average IOP.

a surgical intervention occurred after enrollment, baseline intraocular pressure is a positive but weak predictor of postintervention intraocular pressure, as indicated by the low correlation between intraocular pressure during the first 18 months and intraocular pressure at baseline (r = .16).

Of the baseline characteristics examined in Table 2, most show small differences among the three postintervention intraocular pressure groups of the Predictive Analysis. Exceptions are age and diabetes: patients with high intraocular pressure (greater than 17.5 mm Hg) during follow-up are on average younger and have a higher prevalence of diabetes than patients with lower intraocular pressure. After adjustment for these disparities in baseline characteristics, the dose–response relationship between intraocular pressure and change in visual field defect score is maintained in both the Predictive Analysis and Associative Analysis, as described below.

When all visits are included in the Predictive Analysis, the model 1 adjusted estimates predict, over follow-up, an increase (worsening) in visual field defect score of one unit (95% confidence interval [CI] = 0.37, 1.62) for the highest group (greater than 17.5 mm Hg) relative to the lowest (less than 14 mm Hg). For example, an eye with mean intraocular pressure of 20 mm Hg over the first 18 months can expect, on average, an increase in visual field defect score that is one unit more than an eye with mean intraocular pressure of 13.5 mm Hg. The difference is larger in the model examining only the 84-month study visit, which predicts a nearly two-unit greater worsening of visual field defect score in the eye with elevated intraocular pressure (Table 5).

When all visits are included in the Associative Analysis, the adjusted estimates predict an increase in visual field defect score for the elevated intraocular pressure groups B, C, and D compared with group A (eyes with 100% of visits less than 18 mm Hg over 6 years), but one that is statistically significant for group C ($P = .016$, Table 6). The worsening of visual field is most evident at 84 months. For example, an eye with intraocular pressure greater than 18 mm Hg at seven or more of twelve 6-month visits can expect, on average, a worsening of visual field defect score at 84 months that is approximately two units greater than an eye with intraocular pressure less than 18 mm Hg at each of these twelve 6-month visits (Table 6).

An important finding of this study is that eyes in the lowest intraocular pressure group experienced, on average,

TABLE 6. Summary of Regression Analysis: Associative Analysis

Follow-up Visit	Group[†,‡]	Number of Eyes	Unadjusted			Adjusted*		
			Estimate of Change in VFDS	*P* Value	95% Confidence Limits	Estimate of Change in VFDS	*P* Value	95% Confidence Limits
All visits[§]	A	140	—	—	—	—	—	—
	B	152	0.62	.048	0.01, 1.24	0.47	0.104	−0.10, 1.03
	C	142	0.83	.022	0.12, 1.54	0.78	0.016	0.14, 1.41
	D	152	1.03	.005	0.31, 1.76	0.63	0.083	−0.08, 1.38
24-month	A	137	—	—	—	—	—	—
	B	151	0.35	.319	−0.34, 1.04	0.20	0.529	−0.42, 0.82
	C	140	0.47	.219	−0.28, 1.23	0.38	0.290	−0.32, 1.09
	D	149	0.71	.101	−0.14, 1.56	0.25	0.572	−0.62, 1.11
60-month	A	137	—	—	—	—	—	—
	B	149	0.86	.023	0.12, 1.61	0.73	0.047	0.01, 1.46
	C	134	1.03	.030	0.10, 1.95	1.10	0.011	0.26, 1.95
	D	147	1.23	.012	0.27, 2.19	0.93	0.062	−0.05, 1.91
84-month	A	111	—	—	—	—	—	—
	B	109	1.11	.023	0.16, 2.06	1.00	0.034	0.07, 1.92
	C	102	1.97	<.001	0.81, 3.12	2.05	<0.001	0.99, 3.12
	D	100	2.42	<.001	1.29, 3.56	1.93	<0.001	0.82, 3.05

Abbreviations as in Table 2.

*Models are adjusted for race, assigned intervention sequence, age at randomization, diabetes, gender, reference IOP, and reference visual field defect score.

[†]Percent of visits with IOP <18 mm Hg: Group A, 100%; Group B, 75 to <100%; Group C, 50 to <75%; and Group D, 0 to <50%.

[‡]The mean IOP over 6 years is 12.3 mm Hg for Group A, 14.7 mm Hg for Group B, 16.9 mm Hg for Group C, and 20.2 mm Hg for Group D.

[§]Data from the 6-month to 96-month visits are used in the analysis.

little visual field deterioration during follow-up. This finding is most striking in the Associative Analysis for eyes that maintained intraocular pressure less than 18 mm Hg at all study visits over 6 years. The average intraocular pressure for these eyes was 12.3 mm Hg over 6 years, and their mean change from baseline in visual field defect score ranged from −0.26 (improvement) at 2 years to 0.46 (worsening) at 4 years (Figure 3). Although the average change in visual field is close to zero, a proportion of eyes in this group experienced visual field loss despite having intraocular pressure at what is believed to be a safe level. To illustrate, a worsening of four or more units of visual field defect score from baseline was experienced by 13.1% of eyes at 2 years, 13.9% at 5 years, and 14.4% at 7 years. Although these instances of worsening were counterbalanced by improvements of four or more units of visual field defect score experienced by 8.8% of eyes at 2 years, 13.9% at 5 years, and 18.0% at 7 years, it is clear that maintaining intraocular pressure less than 18 mm Hg does not ensure the preservation of the visual field.

The regression analyses presented in Tables 5 and 6 contain interval-scaled predictor variables (intraocular pressure as less than 14 mm Hg, 14 to 17.5 mm Hg, and greater than 17.5 mm Hg in the Predictive Analysis; percent of visits as 100% [group A], 75% to less than 100% [group B], 50% to less than 75% [group C], and 0% to less than 50% [group D] in the Associative Analysis). Statistical tests in these analyses compare each level of the variable to a reference level, with intraocular pressure less than 14 mm Hg being the reference in the Predictive Analysis, and 100% of visits for which eyes presented with intraocular pressure less than 18 mm Hg (group A) in the Associative Analysis. Although we have not made pairwise statistical tests between other intraocular pressure groups within models (for example, the greater than 17.5 mm Hg group versus the 14 to 17.5 mm Hg group in the Predictive Analysis), the large overlaps in the confidence intervals of the estimates indicate that the estimates are not statistically significantly different from one another.

The positive association between the prevalence of diabetes and the level of postintervention intraocular pressure is intriguing. It suggests that the presence of diabetes in glaucoma patients may reduce their responsiveness to intraocular pressure–lowering treatments. This possibility will be examined in a more focused analysis in a future article.

The inverse association between reference visual field defect score and level of follow-up intraocular pressure may be artifactual, in that it could be a function of the inverse relationship between the Advanced Glaucoma Interven-

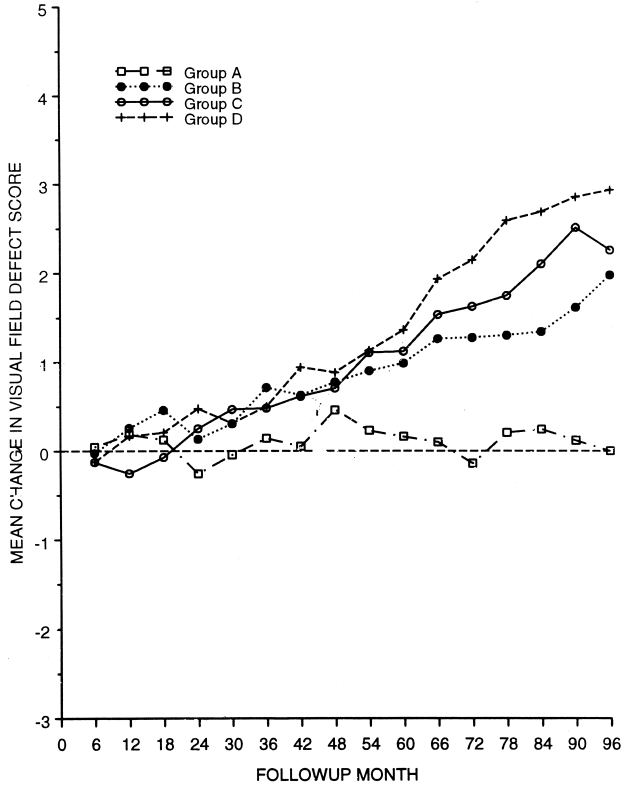

FIGURE 3. Associative Analysis. Mean change in visual field defect score by percent of visits over 6 years at which an eye presented with intraocular pressure less than 18 mm Hg (group A is 100%, group B is 75% to less than 100%, group C is 50% to less than 75%, and group D is 0% to less than 50%).

tion Study eligibility criteria for intraocular pressure and visual field defect score[16] coupled with a modest positive correlation between reference and follow-up intraocular pressure (Table 3). The following example illustrates the inverse relationship between intraocular pressure and visual field defect score in eligibility criteria: for entry into Advanced Glaucoma Intervention Study, an eye with intraocular pressure of 21 mm Hg had to have a visual field defect score of at least 11, whereas an eye with intraocular pressure of 30 mm Hg could enter with a defect score of as little as 1 (all eyes had to be on maximum medical therapy).

The Advanced Glaucoma Intervention Study data support the suggestive evidence from earlier studies[4–10] that achieving low levels of intraocular pressure slows the progression of glaucomatous optic neuropathy. The Normal Tension Glaucoma Study investigators reported that the effect of the reduction of intraocular pressure on progression of visual change in normal-tension glaucoma was found only when the impact of cataract was removed.[9] To what extent do cataracts in eyes of Advanced Glaucoma Intervention Study patients affect the results in this article? To answer this question, we used the findings of a previous Advanced Glaucoma Intervention Study report to adjust the visual field defect scores in the present analysis for the presumed effect of cataract. As described in detail elsewhere,[22] this adjustment was accomplished by first estimating the expected change in visual field defect score from before to after cataract surgery. Then for eyes with cataract not removed (based on clinical gradings of lenses viewed through a slit-lamp biomicroscope), we used the estimates of expected change to remove analytically the presumed effect of cataract on visual field defect when cataract is present. Table 7 presents the mean change from baseline in visual field defect score, unadjusted and adjusted for the effect of cataract, at annual visits based on the intraocular pressure groupings defined in the Predictive Analysis. As expected, the mean changes from baseline in visual field defect score are lower when adjustments are made for cataract, although the differences are small and similar across intraocular pressure groups. Thus, the adjustments for cataract do not affect the conclusions presented in this article.

The present analyses assess intraocular pressure during follow-up without taking into account the glaucoma management employed to achieve intraocular pressure control. An Advanced Glaucoma Intervention Study goal is to maintain intraocular pressure less than 18 mm Hg. For eyes with sustained elevation of intraocular pressure 18 mm Hg or greater, the Advanced Glaucoma Intervention Study protocol requires escalation of medical management. Eyes with sustained intraocular pressure 18 mm Hg or greater while on maximum medical therapy are candidates for the next glaucoma intervention in the assigned intervention sequence if the level of intraocular pressure, visual field defect, and/or optic disk deterioration again meet the study eligibility criteria. The declining mean intraocular pressure in the highest (greater than 17.5 mm Hg) group in the Predictive Analysis (Figure 1) as follow-up lengthens may be a consequence of additional surgical procedures to lower intraocular pressure.

The focused attention given to the intraocular pressure level of 18 mm Hg in the Advanced Glaucoma Intervention Study protocol was instrumental in our selection of greater than 17.5 mm Hg in defining the high intraocular pressure group in the Predictive Analysis and of less than 18.0 mm Hg as a defining level in the Associative Analysis. We chose the intraocular pressure level of 14 mm Hg to define the low intraocular pressure group in the Predictive Analysis because eyes with intraocular pressure less than 14 mm Hg are usually believed to be at a safe level of pressure. Fortuitously, these cut-off points provide relatively equal numbers of eyes for the three intraocular pressure groups of the Predictive Analysis.

A limitation of the present study and of previous studies of the association between intraocular pressure reduction and visual field damage is that the comparison between groups of eyes achieving low and high levels of intraocular pressure is not based on a random allocation. Although in our analyses we have adjusted for potential confounding

TABLE 7. Mean Change From Baseline in Visual Field Defect Score, by Intraocular Pressure Group, Not Adjusted and Adjusted for Cataract: Predictive Analysis

	IOP Averaged Over the Three 6-Month Visits								
	<14 mm Hg			14–17.5 mm Hg			>17.5 mm Hg		
Follow-up Visit	Mean	Adjusted Mean	Difference*	Mean	Adusted Mean	Difference*	Mean	Adjusted Mean	Difference*
24-month	−0.09	−0.35	0.26	0.03	−0.19	0.22	0.87	0.63	0.24
36-month	0.40	0.24	0.16	0.36	0.12	0.24	0.97	0.69	0.28
48-month	0.77	0.58	0.19	0.41	0.16	0.25	1.19	0.91	0.28
60-month	0.45	0.30	0.15	0.85	0.63	0.22	1.72	1.55	0.17
72-month	0.33	0.25	0.08	1.11	0.96	0.15	2.60	2.52	0.08
84-month	0.63	0.51	0.12	1.42	1.29	0.13	3.11	3.13	−0.02
96-month	0.71	0.64	0.07	1.97	1.82	0.15	2.97	2.92	0.05

*Difference = mean − adjusted mean.

factors, the adjustment is limited, as are all such adjustments, to factors for which recorded observations are available. There may be factors related to the progression of glaucoma that, in these studies, have not been observed and for which, therefore, no corrections were made. Randomization tends to create groups that are similar with respect to all factors, whether observed or not. Thus, while the present study strengthens the evidence linking reduced intraocular pressure to reduced progression of optic neuropathy, conclusive evidence must await the results of specifically designed and well-conducted randomized clinical trials.[11,12]

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ADVANCED GLAUCOMA INTERVENTION STUDY CENTERS AND INVESTIGATORS: PARTICIPATING INSTITUTIONS, CURRENT INVESTIGATORS, AND FORMER INVESTIGATORS WHO PARTICIPATED FOR TWO OR MORE YEARS

STUDY CO-CHAIRMEN: Douglas E. Gaasterland, MD; Fred Ederer, MA, FACE

• **CLINICAL CENTERS**: Abbreviations: CD = Clinic Director; CI = Co-Investigator; CC = Clinic Coordinator; CM = Clinic Monitor; SD = Satellite Director; SC = Satellite Coordinator; T = Technician.

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Ohio State University, Columbus, OH: Paul A. Weber, MD (CD); Robert Derick, MD (CI); Kathryne McKinney, COMT (CC, CM); Diane Moore, COA (T); Tammy Lauderbaugh (T). Satellite facility: N. Douglas Baker, MD (SD); Fred Kapetansky, MD (CI); David Lehmann, MD (CI); Lori Black, COA (SC). Past participating personnel: Becky Gloeckner, COT (SC); Kris Coleman, COT; Mary Cassady, COA; Lisa J. Sharf, COA; Billi Romans; Yvonne Satterwhite; Lori Simmons.

Piedmont Hospital, Atlanta, GA: M. Angela Vela, MD (CD); Thomas S. Harbin, Jr., MD (CI); Laura Brannon, COMT (CC, CM); Julie Wright, COT (T); June LaSalle, COA (T); Gail Degenhardt (T); Stephanie Ann Bridgman (T); Johnny Gunsby, COT (T). Past participating personnel: Randall R. Ozment, MD (CI); Montana Hooper, COT (CC); Stacy Goldstein, COMT (SC); Linda Butler, COT; Marianne Perry, COT; Anne Eckel, COA; Anja

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Sinai Hospital/Detroit, Southfield, MI: Marshall N. Cyrlin, MD (CD); Holly Dubay (CC, CM). Past participating personnel: Roselyn Fazio, BS, COT (CC); Patricia S. Corbin (CC).

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• **COORDINATING CENTER**: The EMMES Corporation, Potomac, MD: Paul C. VanVeldhuisen, MS (Director, Coordinating Center); Fred Ederer, MA, FACE (Epidemiologist); L. G. Dally, MS (Statistician); Beth Blackwell, ScD (Statistician); Pam Inman (Data Manager); Susan Raitt, MA (Administrative Coordinator). Past participating personnel: Anne S. Lindblad, PhD (Deputy Director); James D. Knoke, PhD (Deputy Director), E. Kenneth Sullivan, PhD, (Director); Lie-Ling Wu, MS (Statistician); Gary Entler, COT (Protocol Monitor); Pamela Phillips, MHS (Protocol Monitor); Carol Smith, MPH (Protocol Monitor), Marline Bradford (Data Manager), Marsha Denekas, MLT (Data Coordinator); Elizabeth L. Wagner, MPH (Data Coordinator); Elaine Stine (Alternate Interviewer); Katherine L. Tomlin, MA (Administrative Coordinator); Tamara Voss, BA (Administrative Coordinator).

• **SPONSORS**: National Eye Institute and the Office of Research on Minority Health: Mary Frances Cotch, PhD (NEI Representative); William W. Darby, (Grants Management Specialist). Past participating personnel: Richard L. Mowery, PhD (NEI Representative); Frances Goff (Grants Management Specialist); Carolyn Grimes (Grants Management Specialist); Gaye Lynch (Grants Management Specialist).

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Training and Certification Faculty: Fred Ederer, MA, FACE; Douglas E. Gaasterland, MD; Aaron Kassoff, MD (Consultant); L. Jay Katz, MD; Donna Leef, MMSc, COMT; Gregory L. Skuta, MD; Carol Standardi, RN CRNO; Fillis Samuel, COT. Past participating personnel: Anne S. Lindblad, PhD; Cathy Reed, COMT; Coleen C. Beckershoff; Gary Entler, COT; Elizabeth L. Wagner, MPH.

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