The Advanced Glaucoma Intervention Study, 8: Risk of Cataract Formation After Trabeculectomy

The AGIS Investigators

Objectives: To compare the risk of cataract formation in eyes with and without prior trabeculectomy and to assess other risk factors for cataract.

Methods: The Advanced Glaucoma Intervention Study (AGIS) has been following 789 eyes in 591 patients with medically uncontrolled open-angle glaucoma. From 1988 to 1992, these eyes were randomly assigned to either an argon laser trabeculoplasty (ALT)-trabeculectomy-trabeculectomy treatment sequence or a trabeculectomy-ALT-trabeculectomy sequence. Cox regression analyses were used to assess risk factors for cataract formation during 7 to 11 years of follow-up.

Main Outcome Measures: Cataract, defined as either having had cataract surgery or confirmed severe lens opacity with a best-corrected Early Treatment Diabetic Retinopathy Study visual acuity score less than 65 letters (worse than 20/50).

Results: Data are presented on the expected 5-year cumulative probability of cataract formation in each randomized sequence by age and presence of diabetes at study entry. Overall, approximately half of the eyes studied developed cataract. A first trabeculectomy, whether as the first or second AGIS intervention, increased the overall risk of cataract by 78% (risk ratio [RR] = 1.78; $P<.001$). Diabetes (RR = 1.47; $P=.004$) and age at study entry (RR = 1.07 per year of age; $P<.001$) were also risk factors for cataract. When postoperative complications of trabeculectomy were included in the analysis, the increased risk of cataract for eyes with a first trabeculectomy reduced to 47% when complications did not occur (RR = 1.47; $P=.003$) and increased to 104% when complications did occur (RR = 2.04; $P<.001$). Several specific postoperative complications of trabeculectomy were associated with increased risk of cataract, particularly marked inflammation (RR = 3.29; $P<.001$) and flat anterior chamber (RR = 1.80; $P=.004$). Trabeculectomy with complications was also significantly associated with an increased risk of cataract in each of 3 lens regions: nuclear, cortical, and posterior subcapsular.

Conclusions: In eyes of AGIS patients, after adjustment for age and diabetes, trabeculectomy increased the risk of cataract formation by 78%.

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IT HAS OFTEN BEEN reported and is widely accepted that cataract formation is a complication of full-thickness glaucoma filtering procedures[1,2] and trabeculectomy,[2-8] but the amount by which cataract risk is increased by these procedures has not been clearly assessed. The present article uses data from the ongoing Advanced Glaucoma Intervention Study (AGIS) to address this question for trabeculectomy by comparing the risk of cataract formation in eyes with and without prior trabeculectomy. We also assess other risk factors for cataract formation, including several complications of trabeculectomy. Additionally, risk factors for the formation of cataracts in 3 lens regions, nuclear, cortical, and posterior subcapsular, are evaluated.

RESULTS

More than half of the 746 eyes (54.3%, **Table 2**) in the present study developed cataract during follow-up, with the percentage being larger for eyes with (57.4%) than without (48.9%) a prior trabeculectomy. Type 1 cataracts accounted for 72.6% of all cataracts.

As an initial analysis, the cumulative probability of cataract occurrence was estimated in each intervention sequence, unadjusted for covariates. **Figure 2** shows that throughout the first 7 years of follow-up, the cumulative probability of cataract was higher for eyes in the TAT sequence than in the ATT sequence; in the TAT sequence, nearly all eyes (99.5%; 363/365) had a trabeculectomy on enrollment; whereas in the ATT sequence, only 35% of eyes (132/381) had a trabeculectomy by the time of database closure. At 7 years, the cumulative probability of cataract is 0.56 for eyes in the TAT sequence and 0.47 for eyes in the ATT sequence. A corresponding Cox regression analysis with intervention sequence as the only covariate indicates that eyes in the TAT sequence have a 34% increased cataract risk

PATIENTS AND METHODS

THE ADVANCED GLAUCOMA INTERVENTION STUDY

The design and methods of AGIS, detailed elsewhere,[9-11] are summarized in this section. Appropriate institutional review boards approved the AGIS protocol, and all patients provided informed consent to enroll in AGIS.

ELIGIBILITY

To be eligible for AGIS, patients had to be 35 to 80 years old, and eligible eyes had to be phakic and have either primary advanced open-angle glaucoma or open-angle glaucoma 4 weeks or more after laser iridotomy. We consider glaucoma in an eye to be advanced when, in the presence of at least some glaucomatous visual field loss, the disease cannot be adequately controlled by medications alone. Eligible eyes had to be receiving maximum medical therapy and meet 1 of 9 specified combinations of criteria for consistently elevated intraocular pressure (IOP), visual field defect due to glaucoma, and optic disc rim deterioration. The minimum required best-corrected visual acuity score for eligibility was 56 letters on the back-lit Early Treatment Diabetic Retinopathy Study[12] chart (approximate Snellen equivalent of 20/80). The current report excludes eyes that had a confirmed severe lens opacity (SLO) and visual acuity less than 65 letters (worse than 20/50) at baseline.

ENROLLMENT, RANDOMIZATION, AND FOLLOW-UP

From April 1988 through November 1992, investigators at 11 AGIS clinical centers enrolled 789 eyes of 591 patients. Each eye was randomly assigned to be managed with a sequence of either argon laser trabeculoplasty (ALT)-trabeculectomy-trabeculectomy (ATT) or trabeculectomy-ALT-trabeculectomy (TAT). When both of a patient's eyes were eligible, 1 eye was randomly assigned to 1 of the 2 sequences, and the fellow eye was assigned to the other sequence. The first surgical intervention was performed soon after enrollment. The second and third interventions were offered only after failure of the preceding intervention. Failure occurs when an eye receiving maximum medical therapy again meets the study's eligibility criteria for elevated IOP, visual field defect, and optic disc rim deterioration. Argon laser trabeculoplasties were performed with a total of 90 to 110 burns in two 180° sessions at 1 to 6 weeks apart. Trabeculectomies were performed in accordance with Spaeth's description[13]; adjunctive antifibrotic use in AGIS has adhered to community standards in practice at the time of surgical interventions. Routine use in AGIS began in 1993 after all trabeculectomies as first interventions had been completed. For eyes at risk of cataract after trabeculectomy, antifibrotics were used in 2 (0.5%) of the 364 eyes that had an initial trabeculectomy, in 17 (16%) of the 108 eyes that had a trabeculectomy that followed a failed argon laser trabeculoplasty, and in 25 (96%) of the 26 eyes that had a second trabeculectomy.

Follow-up visits were scheduled 3 and 6 months after enrollment, and every 6 months thereafter. Although patients may be seen between study visits, these examinations need not be conducted according to AGIS protocol, and the data were not routinely collected by the study. Lenses were examined biomicroscopically after pupil dilation at baseline, at the first 6-month visit, and during all annual visits. These examinations are hereafter referred to as "AGIS-dilated lens examinations." Data on the presence or absence of each of 11 complications of first trabeculectomy were collected at postoperative visits.

CATARACT

Lens opacities found during AGIS-dilated lens examinations in 4 lens regions (nucleus, anterior cortex, posterior cortex, and posterior subcapsular) were classified as follows: nuclear opacities as (1) none, (2) mild, or (3) worse than mild; and anterior cortical, posterior cortical, and posterior subcapsular opacities as (1) no opacity, (2) opacity with center not involved, or (3) opacity with center involved. In this article, the anterior and posterior cortical regions are combined into a single region.

We define the following 5 terms essentially as they were defined in AGIS Report 6[14]:

1. *Severe lens opacity (SLO)* is the presence of one or more of the following: "worse than mild" nuclear opacity, cortical opacity with center involved, or posterior subcapsular opacity with center involved.
2. *Type 1 cataract* is an SLO in an eye for which the concurrent best-corrected visual acuity score is less than 65 letters on the back-lit ETDRS chart (Snellen equivalent, worse than 20/50), with the finding of SLO confirmed either by an SLO at the next AGIS-dilated lens examination or by cataract surgery before that visit. By definition, all eyes with Type 1 cataract had SLO in at least 1 lens region. Because the AGIS eligibility criteria for visual acuity only require an acuity of 56 letters (20/80) at entry, 20 eyes met the

over eyes in the ATT sequence at any given time during the entire follow-up period (RR=1.34; $P<.001$).

As **Table 3** presents, the expected 5-year cumulative probability of cataract in eyes of patients aged 55 to 75 years at study entry ranges from 0.16 to 0.83, depending on intervention sequence, age at study entry, and presence of diabetes. The probabilities were calculated from intervention sequence–specific Cox regression models for risk of cataract that included 2 covariates—age at study entry and diabetes (shown in analysis 1 to be significant risk factors for cataract). In each age-diabetes category, the probabilities of cataract were higher in the TAT sequence than the ATT sequence, and in both sequences, the probabilities increase with age at study entry and the presence of diabetes. The lowest risk occurs in the youngest patients, who did not have diabetes and were assigned to the ATT treatment sequence.

The multivariate risk-factor analyses (analysis 1, analysis 2, region-specific analyses) indicate that several patient characteristics were associated with the risk of cataract occurrence. In **Table 4**, the relative frequen-

criteria for Type 1 cataract at study entry. Data on these eyes are excluded from this article.

3. *Type 2 cataract* is cataract surgery without the lens having fulfilled the criteria for Type 1 cataract at the most recent AGIS-dilated lens examination before cataract surgery.
4. *The time of occurrence of a Type 1* cataract is the date of the visit at which the eye is first observed to have SLO plus a visual acuity less than 65 (ie, not the date of confirmation).
5. *The time of occurrence of a Type 2* cataract is the date of cataract surgery.

Some, perhaps many, of the Type 2 cataracts in the present study might have been classified as Type 1 had the AGIS protocol required routine dilated lens examinations to be performed and the data to be collected at each study visit.

The AGIS protocol does not require that the lens opacity be of any specified density before cataract surgery is performed; it requires only that the vision defect, with a visual acuity score less than 65 letters within 2 months before cataract surgery, be ascribed to cataract and adversely affect the patient's lifestyle. For 39 (35%) of 111 eyes with Type 2 cataract, the AGIS Operations Committee granted protocol exceptions to the visual acuity requirement. Generally, the exceptions were made in recognition of an adverse effect of the cataract on the patient's lifestyle and the reduced glare of AGIS visual acuity test conditions.

ANALYSIS DATA SET

The database for the present analysis was closed on December 31, 1999, by which time approximately 7 to 11 years had elapsed since enrollment. Of the 789 eyes enrolled, 43 were excluded from this report, leaving 746 eyes for analysis, including 314 eyes from 243 white patients, 421 eyes from 317 black patients, and 11 eyes from 8 patients of other races. Of the excluded eyes, 20 had already met the present investigation's criteria for Type 1 cataract at time of enrollment, 8 never had an AGIS glaucoma intervention, 8 were lost to follow-up prior to the first 6-month visit, and 7 had missing data on complications of the first trabeculectomy.

METHODS OF THE PRESENT INVESTIGATION

Patient and eye characteristics considered as covariates in the 3 risk-factor analyses, analysis 1, analysis 2, and lens region–specific analyses, are presented in **Table 1**. Analysis 2 differs from analysis 1 in that it includes information about whether or not any complications of trabeculectomy occurred. The lens region–specific analyses differ from analysis 2 in that their investigation of risk factors (for Type 1 cataracts only) is according to the location of the lens regions of the SLO.

Cox regression models[15] were used to explore the association between the hazard (risk) of developing cataract and the covariates in Table 1. When it was necessary to account for correlation between eyes in patients with both eyes enrolled, results of the Cox regression models were adjusted using the method of Wei et al[16]; the hazard ratio estimates are presented as risk ratios (RRs). For binary characteristics such as diabetes, the RR expresses the ratio of the risk of cataract occurrence in eyes or patients with the characteristic to the risk of cataract in eyes or patients without the characteristic. For the quantitative variable age, the RR expresses the increase in risk per year of age. In the risk-factor analyses, the final risk factors were selected from those in Table 1 by backward elimination, retaining variables with a P value less than or equal to .05 at the final step. In the lens region–specific analyses, if a covariate was retained in any specific region, it was included in the final analysis for each lens region.

Because multiple statistical tests have been conducted on the data in this article and on AGIS data in previous articles, we consider a P value less than .01, rather than the more conventional .05, to be statistically significant.

None of the eyes in this investigation met the criteria for Type 1 cataract at study enrollment, namely confirmed SLO with a visual acuity less than 65 letters, and all remained at risk of cataract either until cataract occurred or until the eye's last AGIS-dilated lens examination. Eyes were classified into 3 risk categories according to whether they received a trabeculectomy before cataract occurred, and if so, whether the trabeculectomy was the eye's first or second surgical intervention (**Figure 1**).

Because eyes whose initial intervention was ALT were moved from category 1 to category 3 when a first trabeculectomy was performed, "occurrence of first trabeculectomy" was a time-dependent variable in analysis 1 of risk factors. Similarly, "occurrence of first trabeculectomy with complications" and "occurrence of first trabeculectomy without complications" were time-dependent variables in analysis 2 of risk factors and in the lens region–specific analyses). Furthermore, age at first trabeculectomy was time-dependent in each of these analyses. Information on diabetes or systemic hypertension was collected at the baseline visit only; therefore, these variables were not time-dependent.

cies of these risk factors at baseline are presented according to whether or not the eye had a trabeculectomy prior to cataract occurrence. Of eyes without and with prior trabeculectomy, the percentages of patients with diabetes at study entry were 23.7% and 17.2%, respectively, and the percentages of patients at least 70 years old at study entry were 44.2% and 33.3%, respectively.

The analyses in **Table 5** evaluate risk factors for cataract. Analysis 1 indicates that the risk of cataract increases by 7% for a 1-year increase in age at study entry (RR=1.07; $P<.001$) and by 47% for eyes of patients with diabetes at study entry (RR=1.47; $P=.004$). Having a first trabeculectomy increases the overall risk of cataract by 78% (RR=1.78; $P<.001$).

Analysis 2 expands analysis 1 by subdividing the occurrence of first trabeculectomy according to whether or not complications of trabeculectomy occurred. Compared with risk in eyes that have not had a trabeculectomy, the risk of cataract was 47% greater if the trabeculectomy was without complications (RR=1.47; $P=.003$) and approximately doubles if there were complications (RR=2.04, $P<.001$). As in analysis 1, older age at study entry and dia-

Table 1. Covariates Considered in Risk Factors Regression Analyses

Core baseline covariates*†
Race (black, nonblack)‡
Educational achievement (some college or more, high school graduation or less)
Age at study entry
Sex
Hypertension at study entry§
Diabetes at study entry§
Iris color (brown, nonbrown)
Prescribed systemic beta-blockers at study entry
Prescribed topical beta-blockers at study entry
Prescribed topical miotics at study entry
Time-dependent covariates
Occurrence of first trabeculectomy*
Occurrence of first trabeculectomy without complications†
Occurrence of first trabeculectomy with complications†
Age at first trabeculectomy*†

*Analysis 1 (see Table 5).
†Analysis 2 (see Table 5) and lens region–specific analyses (see Table 8).
‡Nonblack includes white, Hispanic, and other.
§Some patients may have developed diabetes or systemic hypertension during the study; this information has not been systematically collected and is not included.

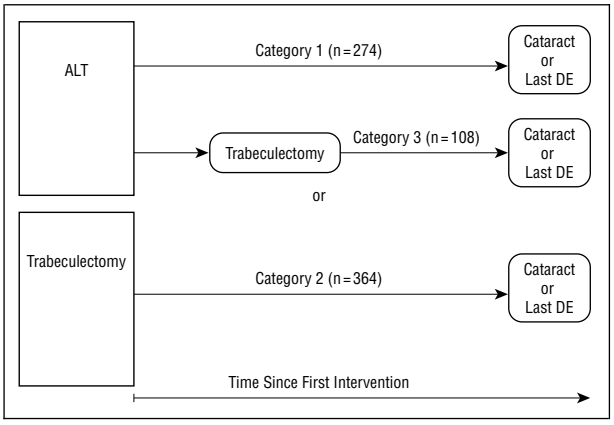

Figure 1. Time lines for cataract risk categories 1, 2, and 3. "Cataract," indicates cataract occurrence; DE, dilated lens examination; and ALT, argon laser trabeculoplasty.

betes increased the risk of cataract in analysis 2 (RR per year of age = 1.07, $P<.001$; RR for diabetes = 1.47, $P<.005$).

To investigate the association between each of 11 reported complications of first trabeculectomy and risk of cataract (**Table 6**), we analyzed the data from the 472 of 746 eyes that had at least one trabeculectomy followed by either cataract or an AGIS-dilated lens examination. Time at risk in this analysis began at the date of first trabeculectomy; therefore, the occurrence of each complication was a baseline (not a time-dependent) covariate. The multiple regression analysis presented in Table 6 evaluates the risk associated with a specific complication after adjusting for age at study entry, diabetes at study entry, and the other listed complications.

Peripheral anterior synechiae, shallow anterior chamber, encapsulated bleb, anterior chamber bleeding, and flat anterior chamber were the 5 most frequent complications of first trabeculectomy (Table 6). Table 6 lists the

Table 2. Eyes Developing Cataract, by Type of Cataract and Prior Trabeculectomy Status

	No. (%)		
	Total	No Prior Trabeculectomy	Prior Trabeculectomy
No. of eyes	746 (100.0)	274 (100.0)	472 (100.0)
Eyes not developing cataract	341 (45.7)	140 (51.1)	201 (42.6)
Eyes developing cataract	405 (54.3)	134 (48.9)	271 (57.4)
Eyes developing cataract	405 (100.0)	134 (100.0)	271 (100.0)
Type 1 cataract	294 (72.6)	96 (71.6)	198 (73.1)
Type 2 cataract	111 (27.4)	38 (28.4)	73 (26.9)

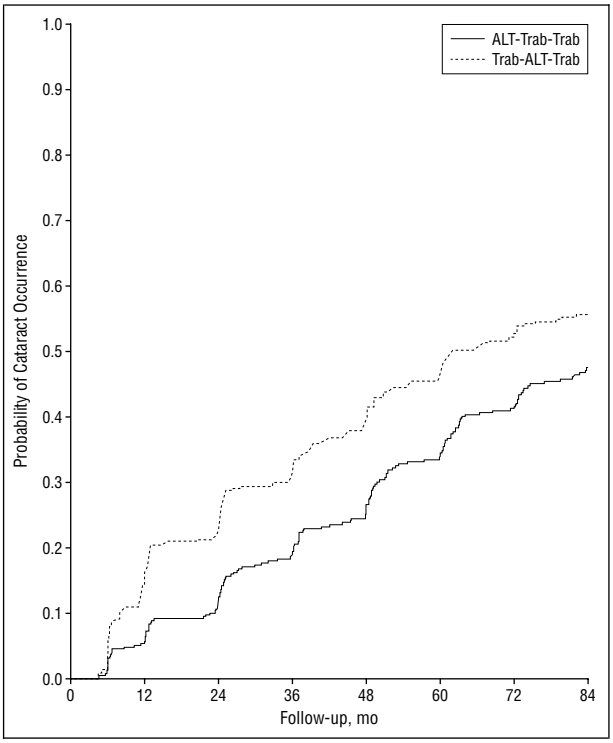

Figure 2. Cumulative probability of cataract occurrence, by randomized intervention sequence. In the trabeculectomy (Trab) –argon laser trabeculoplasty (ALT) –trabeculectomy sequence, nearly all eyes (99.5%; 363/365) had a trabeculectomy on enrollment; whereas in the ALT –trabeculectomy–trabeculectomy sequence, only 31% of eyes (119/381) had a trabeculectomy during the first 7 years after enrollment, and only 35% of eyes (132/381) had a trabeculectomy by the time of database closure.

complications in order of decreasing significance. The 2 complications that had a statistically significant relationship with increased cataract risk were marked inflammation (RR = 3.29; $P<.001$) and flat anterior chamber (RR = 1.80; $P=.004$).

In multiple regression analyses (not shown in the tables) of other possible risk factors for cataract in the above 472 eyes, a previous ALT was not a significant risk factor (RR = 1.11; $P=.44$ adjusting for age and diabetes). However, after adjusting for age at study entry, diabetes, and complications of first trabeculectomy, an eye with a second trabeculectomy has nearly 3 times the risk of cataract compared with an eye with only 1 trabeculectomy (RR = 2.91; $P<.001$).

Table 3. Expected 5-Year Cumulative Probability of Cataract, by Intervention Sequence, Diabetes, and Age

Cox Regression Analyses*	5-Year Expected Probability of Cataract	95% Confidence Limits	
		Lower	Upper
Analysis for eyes in TAT sequence†			
Diabetes			
Age, y			
55‡	0.38	0.26	0.49
60	0.49	0.36	0.59
65	0.60	0.47	0.71
70	0.72	0.58	0.82
75	0.83	0.68	0.91
No diabetes			
Age, y			
55‡	0.25	0.19	0.31
60	0.33	0.27	0.38
65	0.42	0.36	0.48
70	0.53	0.47	0.59
75	0.65	0.57	0.72
Analysis for eyes in ATT sequence§			
Diabetes			
Age, y			
55	0.20	0.13	0.27
60	0.27	0.19	0.35
65	0.36	0.26	0.45
70	0.47	0.35	0.56
75	0.59	0.45	0.70
No diabetes			
Age, y			
55	0.16	0.11	0.21
60	0.22	0.17	0.27
65	0.29	0.24	0.34
70	0.39	0.32	0.44
75	0.50	0.41	0.57

*The covariates in each intervention sequence–specific Cox regression analysis are diabetes and age at study entry. TAT indicates trabeculectomy–argon laser trabeculoplasty (ALT)–trabeculectomy; ATT, ALT-trabeculectomy-trabeculectomy.

†Diabetes (risk ratio for cataract [RR] = 1.69; $P = .003$), age at study entry (RR = 1.07 per year; $P < .001$).

‡The 5-year expected probability of cataract in an eye of a 55-year-old patient without diabetes is 0.25, and the risk ratio for diabetes in the TAT sequence is 1.69 (see footnote†). Therefore, the 5 year expected probability of cataract in an eye of a 55-year-old patient with diabetes in the TAT sequence is $1 - (1 - 0.25)^{1.69} = 0.38$.

§Diabetes (RR = 1.30; $P = .13$), age at study entry (RR = 1.07 per year; $P < .001$).

Table 4. Baseline Characteristics of Eyes at Risk of Cataract, by Prior Trabeculectomy Status*

	No Trabeculectomy Prior to Cataract (ALT Only) Category 1	Trabeculectomy Prior to Cataract		
		Total	Trabeculectomy as First Intervention, Category 2	Trabeculectomy as Second Intervention, Category 3
No. of eyes	274†	472	364‡	108
% Of eyes in patients with diabetes at study entry	23.7	17.2	15.7	22.2
Median age at study entry, y	68	66	66	65
% Of eyes in patients 70 y or older at study entry	44.2	33.3	34.3	29.6
% Of eyes in black patients	63.9	52.1	53.6	47.2

*Categories 1, 2, and 3, are illustrated in Figure 1. ALT indicates argon laser trabeculoplasty.

†Includes 2 eyes randomized to the trabeculectomy-ALT-trabeculectomy sequence that did not have the initial trabeculectomy.

‡Includes 1 eye randomized to the ALT-trabeculectomy-trabeculectomy sequence that did not have the initial ALT.

Table 5. Results of Regression Analyses of Risk of Cataract Related to Trabeculectomy and Patient Characteristics at Study Entry

Analyses and Risk Factors	Risk Ratio	95% Confidence Limits		*P* Value
		Lower	Upper	
Analysis 1				
Occurrence of first trabeculectomy*	1.78	1.46	2.16	<.001
Age at study entry	1.07†	1.05	1.08	<.001
Diabetes at study entry	1.47	1.13	1.92	.004
Analysis 2‡				
Occurrence of first trabeculectomy without complications*	1.47	1.14	1.89	.003
Occurrence of first trabeculectomy with complications*	2.04	1.65	2.52	<.001
Age at study entry	1.07	1.05	1.08	<.001
Diabetes at study entry	1.47	1.12	1.92	.005

*Time-dependent covariate.

†Risk ratio per year of age at study entry.

‡Analysis 2 differs from Analysis 1 by including information about complications of trabeculectomy. The covariate "occurrence of first trabeculectomy" is subdivided into 2 parts depending on whether or not there were complications.

Table 7 presents the regional distribution of SLO observed at the time of Type 1 cataract occurrence. Because the location of opacities is not reported for Type 2 cataracts, this analysis is limited to Type 1 cataracts. Nearly half the eyes with Type 1 cataract had SLO in more than one region (Table 7). The percentage of Type 1 cataracts with severe nuclear, cortical, or posterior subcapsular lens opacities was 80.3%, 45.6%, and 28.9%, respectively. Eyes with and without prior trabeculectomy had similar proportions of cataracts with SLO in the nuclear region (80%) and similar proportions in the cortical region (about 46%); eyes with prior trabeculectomy were more likely to have a cataract with an SLO in the posterior subcapsular region (32.8%) than those without prior trabeculectomy (20.8%).

In **Table 8**, we present the covariates associated with cataract risk in any lens region and in each specific lens region at the time of Type 1 cataract occurrence. If a covariate was associated with cataract in any of the lens region–specific analyses, it was kept in the analysis for each region to facilitate comparisons across lens regions. In the analysis of Type 1 cataract in specific lens regions, eyes that had a trabeculectomy with complications were at increased risk of cataract compared with eyes with ALT only

Table 6. Results of Regression Analyses of Risk of Cataract Related to Complications of First Trabeculectomy, Adjusted for Age and Diabetes*

Complication of First Trabeculectomy	No. (%)		Multiple Complication Analysis	
	No Cataract Development	Cataract Development	Risk Ratio†	*P* Value
No. of eyes with a trabeculectomy while at risk of cataract (N = 472)	201 (100.0)	271 (100.0)	. . .	. . .
Marked inflammation	2 (1.0)	19 (7.0)	3.29	<.001
Flat anterior chamber (either peripheral iridocorneal or lens-corneal touch)	13 (6.5)	41 (15.1)	1.80	.004
Anterior chamber bleeding	18 (9.0)	38 (14.0)	1.34	.103
Elevated intraocular pressure (increase of at least 10 mm Hg more than pretrabeculectomy level)	10 (5.0)	20 (7.4)	1.49	.118
Peripheral anterior synechiae	26 (12.9)	55 (20.3)	1.31	.14
Corneal dellen	14 (7.0)	10 (3.7)	0.63	.146
Choroidal detachment	8 (4.0)	30 (11.1)	1.38	.18
Wound leakage	12 (6.0)	21 (7.7)	1.17	.492
Encapsulated bleb	32 (15.9)	44 (16.2)	1.12	.502
Posterior synechiae	6 (3.0)	19 (7.0)	1.14	.634
Shallow anterior chamber	27 (13.4)	52 (19.2)	1.04	.815

*Complications are fixed baseline covariates (non–time-dependent) because in these analyses the period of risk begins at the time of trabeculectomy. Multiple complications may have been reported for an eye. Ellipsis indicate not applicable.

†The risk of cataract in eyes with the given postoperative complication relative to eyes without the given complication adjusted for age at study entry, diabetes at study entry, and each of the listed complications.

Table 7. Location of SLO in Eyes With Type 1 Cataract, by Prior Trabeculectomy Status and Lens Region*

	No. (%)		
	Total	No Prior Trabeculectomy	Prior Trabeculectomy
Eyes with type 1 cataract	294 (100.0)	96 (100.0)	198 (100.0)
Opacity location†‡			
Nuclear only	111 (37.8)	39 (40.6)	72 (36.4)
Cortical only	31 (10.5)	13 (13.5)	18 (9.1)
PSC only	15 (5.1)	4 (4.2)	11 (5.6)
Nuclear and cortical only	65 (22.1)	24 (25.0)	41 (20.7)
Nuclear and PSC only	33 (11.2)	9 (9.4)	24 (12.1)
Cortical and PSC only	11 (3.7)	2 (2.1)	9 (4.5)
All 3 regions	26 (8.8)	5 (5.2)	21 (10.6)
Regions of SLO§			
Any nuclear‖	236 (80.3)	77 (80.2)	159 (80.3)
Any cortical¶	134 (45.6)	44 (45.8)	90 (45.5)
Any PSC‡	85 (28.9)	20 (20.8)	65 (32.8)

*Lens opacities in this analysis are limited to Type 1 cataracts because opacity locations in Type 2 cataracts are not reported. SLO indicates severe lens opacity; PSC, posterior subcapsular.

†The 7 categories in this section are mutually exclusive; an eye with cataract is counted only once.

‡Excludes 1 eye with data on nuclear opacity but missing data on cortical and PSC opacities, and 1 eye with data on cortical opacity but missing data on nuclear and PSC opacities.

§Categories in this section are not mutually exclusive; a Type 1 cataract may occur simultaneously in more than one lens region.

‖Excludes 1 eye with missing data on nuclear opacity.

¶Excludes 1 eye with missing data on cortical opacity.

(nuclear region RR=2.50, $P<.001$; cortical region RR=2.92, $P<.001$; posterior subcapsular region RR=4.56, $P<.001$). Additionally, in the nuclear lens region, eyes that had a trabeculectomy without complications had an increased cataract risk compared with eyes with ALT only (RR=1.77; $P=.001$). The 95% confidence interval for the covariate "trabeculectomy with complications" overlaps the 95% confidence interval for the covariate "trabeculectomy without complications" within each of the 3 region-specific analyses, particularly in the nuclear region.

Several baseline characteristics were significantly associated with cataract risk in the lens region–specific analyses. Age at study entry was a significant factor for increased cataract risk in each analysis, and diabetes at study entry was a significant risk factor in all but the cortical region. Black race was significantly associated with increased risk of cataract in all but the posterior subcapsular region. Also, because sex was kept as an important covariate at the 0.05 level in some regions, each lens region–specific analysis adjusts for patient sex.

COMMENT

The main findings of the present study must be understood in the context of the characteristics of the patients and the methods of the study. The eyes enrolled in AGIS,

Table 8. Results of Regression Analyses for Type 1 Cataract, by Region of SLO*

Region of SLO and Risk Factors	Risk	95% Confidence Limits		*P* Value
		Lower	Upper	
Any region				
Occurrence of first trabeculectomy without complications†	1.60	1.19	2.17	.002
Occurrence of first trabeculectomy with complications†	2.49	1.93	3.23	<.001
Age at study entry	1.07	1.05	1.09	<.001
Diabetes at study entry	1.56	1.16	2.10	.003
Race (black)	1.71	1.29	2.26	<.001
Sex (female)	1.31	1.01	1.70	.04
Nuclear‡				
Occurrence of first trabeculectomy without complications†	1.77	1.28	2.46	.001
Occurrence of first trabeculectomy with complications†	2.50	1.85	3.38	<.001
Age at study entry	1.08	1.07	1.10	<.001
Diabetes at study entry	1.80	1.30	2.50	<.001
Race (black)	1.61	1.17	2.21	.003
Sex (female)	1.38	1.02	1.86	.04
Cortical‡				
Occurrence of first trabeculectomy without complications†	1.26	0.77	2.05	.36
Occurrence of first trabeculectomy with complications†	2.92	2.01	4.25	<.001
Age at study entry	1.08	1.05	1.10	<.001
Diabetes at study entry	1.39	0.90	2.16	.14
Race (black)	2.52	1.64	3.88	<.001
Sex (female)	1.20	0.81	1.76	.359
Posterior subcapsular§				
Occurrence of first trabeculectomy without complications†	1.94	0.99	3.81	.05
Occurrence of first trabeculectomy with complications†	4.56	2.71	7.68	<.001
Age at study entry	1.06	1.03	1.08	<.001
Diabetes at study entry	2.08	1.23	3.52	.006
Race (black)	1.73	1.08	2.78	.02
Sex (female)	1.66	1.04	2.65	.03

*In this analysis, lens opacities are limited to Type 1 cataracts because opacity locations in Type 2 cataracts are not reported. SLO indicates severe lens opacity.
†Time-dependent covariate.
‡Regression analysis on 745 of 746 eyes, with 1 eye excluded due to incomplete data on location of opacity.
§Regression analysis on 744 of 746 eyes, with 2 eyes excluded due to incomplete data on location of opacity.

all after failure of maximum medical therapy for glaucoma, were randomized to either the ATT or the TAT sequence. The initial glaucoma intervention in each sequence was administered on enrollment, and subsequent interventions were performed only after failure of the preceding intervention. The median age of AGIS patients at enrollment was 67 years, and 20% had diabetes. Both older age and diabetes are shown in this article to be risk factors for cataract development.

The AGIS provides a rich database for exploratory studies related to vision outcomes in glaucoma patients, such as the analyses presented here. Because AGIS was designed to study glaucoma outcomes rather than cataract development, lens examinations with a dilated pupil, after the first follow-up year, were scheduled not more frequently than annually. Moreover, during the planning stages of AGIS in 1986 through 1987, methods of grading lens opacities according to standard lens photographs, such as the Lens Opacities Classification System II[17] and the Wisconsin System,[18] were not yet available. Undoubtably, these semiobjective methods are more highly reproducible than the subjective grading of lenses viewed through slitlamp biomicroscopes by AGIS ophthalmologists at 12 clinical centers. A measure of confirmation for Type 1 cataracts was built into this analysis by the requirement that the occurrence of a potential Type 1 cataract (ie, an SLO accompanied by a visual acuity score less than 65 letters [20/50]) was followed by either an SLO at the next annual lens examination, or by cataract extraction before the next annual examination.

It has long been accepted that glaucoma filtering surgery, both the full-thickness procedure[1,2] and trabeculectomy,[2-8] accelerate cataract formation. Analysis 1 (Table 5) of the present article quantifies the increased risk after a single trabeculectomy relative to risk without trabeculectomy at 78% (RR=1.78). This 78% increase in risk after a single trabeculectomy decreases to 47% when the operation was without complications, and increases to 104% (ie, approximately doubles) when there was at least one complication. Age and diabetes, which were associated with cataract in our analyses, are well-known risk factors for lens opacities or cataract.[19-24] In the AGIS data, information on diabetes is only routinely collected at baseline, not during follow-up. Therefore, the risk associated with diabetes must be interpreted as the risk associated with having diabetes at study entry. A subset analysis, in which risk of cataract began at time of first trabeculectomy, found the increased risk after 2 trabeculectomies relative to 1 trabeculectomy to be 191% (RR=2.91) (ie, that the risk was nearly tripled by a second trabeculectomy relative to eyes with only one trabeculectomy).

Our primary analyses for this article do not compare eyes in the 2 randomly assigned intervention sequences, but rather before and after trabeculectomy. An

analysis of the probability of cataract by the AGIS randomized intervention sequence (Figure 2 and Table 3) does not fully assess the effect of trabeculectomy because of the eyes in the ATT sequence initially treated with ALT (and while they were still at risk of cataract), as many as 28% (108/380, Table 4) had trabeculectomy as the second glaucoma intervention.

During the 7- to 11-year follow-up interval in AGIS, 49% of the eyes developed cataract after ALT but before possible need of trabeculectomy, and 57% developed cataract after trabeculectomy (Table 2). Because we found that prior ALT did not significantly increase the risk of cataract formation in eyes that had a trabeculectomy (prior ALT RR=1.11; $P=.43$), we combined the 364 eyes in category 2 (trabeculectomy as the first glaucoma intervention) with the 108 eyes in category 3 (trabeculectomy as the second glaucoma intervention after initial ALT). The analyses comparing these 472 eyes with the 274 eyes without a trabeculectomy prior to cataract include the covariates to reduce the possibility of bias from confounding.

After trabeculectomy with complications, the risk of cataract significantly increased in all 3 lens regions, and the increased risk associated with age was similar in all 3. We found that diabetes was significantly associated with nuclear or posterior subcapsular cataract, but not with cortical cataract. In other studies, diabetes has been found to be associated with each of these regional opacities or cataracts, although not with all 3 types in any one study.[21-23,25-27]

Race was not a significant risk factor in the overall analysis ($P>.05$); however, in the analyses by lens region, black patients were significantly more likely than nonblack patients to develop nuclear and cortical cataracts; posterior subcapsular cataracts showed a borderline significant relationship to race ($P=.02$). Consistent with our finding, some epidemiological studies have found that black patients were at increased risk of having cortical lens opacities,[28] cortical cataracts,[25] and nuclear cataracts[25]; in contrast, 2 studies have found that white, not black patients, were at increased risk of nuclear opacities.[28,29]

In these analyses of Type 1 cataract, an eye with more than one type of SLO was classified as having each type of opacity that was present; in other studies, an eye with more than 1 type of opacity was classified as a "mixed opacity"[23,27] or was not included in the analyses.[25]

Long-term use of steroids is well-known to be cataractogenic. Steroids were generally applied topically after trabeculectomy for a limited time (usually no more than several months). Some eyes, such as eyes that had surgical complications, may have received steroids after trabeculectomy for a longer duration. Unfortunately, from our data, we were unable to determine to what extent steroid application contributes to the increased cataract risk after trabeculectomy.

In the 472 eyes at risk of cataract after first trabeculectomy, the use of antifibrotics was not statistically associated with an increased risk of cataract ($P>.10$, data not shown). It is important to note that antifibrotics were only used in a small number of these first trabeculectomies (19/472).

Clinicians recognize that older age, diabetes, and filtration surgery for glaucoma increase the risk of cataract development. The current article quantifies the extent to which these factors and the complications of glaucoma surgery increase the risk. Additionally, the study quantifies the increased risk of Type 1 cataract in specified lens regions. It is important to recognize that a substantial proportion of eyes do not develop cataract during the years after trabeculectomy or ALT (slightly less than half of the eyes did not develop cataract), and that the risk of developing cataract exists no matter which first intervention is chosen. Although these AGIS data do not provide information on how the risk of cataract compares with that in patients who do not have advanced glaucoma, they do indicate that ALT before trabeculectomy does not alter the risk of subsequent cataract and that the risk is greater after trabeculectomy than after ALT only.

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