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Intraocular Pressure Control and Long-term Visual Field Loss in the Collaborative Initial Glaucoma Treatment Study

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Abstract

Objective—To evaluate the impact of measures of intraocular pressure (IOP) control on progression of visual field (VF) loss during long-term treatment for open-angle glaucoma (OAG).

Design—Longitudinal, randomized clinical trial.

Participants—607 participants with newly-diagnosed OAG.

Methods—Study participants were randomly assigned to initial treatment with medications or trabeculectomy, and underwent examination at six-month intervals. Standardized testing included Goldmann applanation tonometry and Humphrey 24-2 full threshold VFs. Summary measures of IOP control during follow-up included the maximum, mean, standard deviation (SD), range, proportion less than 16, 18, 20, or 22 mmHg, and whether all IOP values were less than each of these four cut-points. Predictive models for VF outcomes were based on the mean deviation (MD) from VF testing, and were adjusted for age, sex, race, baseline VF loss, treatment, and time. Each summary IOP measure was included as a cumulative, time-dependent variable, and its association with subsequent VF loss was assessed from 3 to 9 years post-randomization. Both linear mixed models, to detect shifts in MD levels, and logistic models, to detect elevated odds of substantial worsening (3 dB or more), were used.

Main Outcome Measure—MD from Humphrey 24-2 full threshold VF tests.

Results—The effect of the summary IOP measures differed between the medicine and surgery groups in models that addressed the continuous MD outcome. After adjustment for baseline risk factors, in the medicine group larger values of three IOP control measures – maximum IOP ($p=0.0003$), standard deviation of IOP ($p=0.0056$), and range of IOP ($p<0.0001$) – were significantly associated with lower (worse) MD in the 3 to 9 year period. No IOP summary

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measure was significantly associated with MD over time in the surgery group. The same three IOP summary measures were also significantly associated with substantial worsening of MD; however, the effects were similar in both treatment groups. In models predicting inadequate IOP control, consistently significant predictors of higher maximum, SD, and range of IOP included black race, higher baseline IOP, and clinical center.

Conclusions—These results support considering more aggressive treatment when undue elevation or variation in IOP measures is observed.

Introduction

Open angle glaucoma (OAG) afflicts over 2 million people in the United States.¹ If untreated, it can result in progressive optic nerve damage that may lead to blindness, often without other symptoms. Treatments for OAG focus on reducing intraocular pressure (IOP). The specific role of IOP in glaucomatous progression remains under investigation. Recent reports indicate that higher mean IOP is a significant risk factor for incident glaucoma in people with ocular hypertension,² and higher mean IOP is predictive of progressive visual field (VF) loss in patients with newly diagnosed glaucoma,^{3–5} normotensive glaucoma,⁶ and advanced glaucoma.⁷ However, these studies differed in the types of patients enrolled, the treatment intervention, and the extent to which IOP was reduced. In addition, various measures of IOP reduction were used to characterize the effect of treatment, and the effect of fluctuating IOP levels over time on VF progression has not been conclusively addressed. With respect to preventing progressive VF loss, the relative importance of maintaining a low average or peak IOP value, a high percent IOP reduction, restricting IOP below a threshold, or limiting IOP fluctuation is not clear.

The Collaborative Initial Glaucoma Treatment Study (CIGTS), a randomized, multi-center, clinical trial of initial treatment approaches for 607 subjects with newly-diagnosed OAG,⁸ is in a unique position to address these IOP control measures. CIGTS patients exhibit a broad range of baseline VF severity and a range of IOP reduction during treatment and extended follow-up, both in absolute and relative terms. Therefore, we tested various functions of IOP control over time to determine the best predictor(s) of VF loss during the period from 3 to 9 years after treatment initiation.

Methods

In the CIGTS, eligible subjects at 14 clinical centers in the United States provided informed consent and were randomized to initial treatment with either trabeculectomy (surgery) or topical medications. Follow-up visits occurred at months 3, 6, 12, and every 6 months thereafter. Visual fields were measured using the Humphrey Field Analyzer 24-2 full threshold test (Zeiss-Humphrey Systems, Dublin, CA). Visual field test results were summarized using both the mean deviation (MD) calculated by the Humphrey software and a visual field score developed by the CIGTS investigators (CIGTS VF score).⁹

Analyses reported herein were based on the MD of the study eye as the primary outcome measure, obtained from VF tests conducted 3 to 9 years after randomization (analysis of the CIGTS VF score gave similar results). We began the outcome assessment period at 3 years into follow-up to allow time for progression in VF loss and to accrue enough IOP history to permit calculation of reasonable summary measures for IOP control. We excluded the few (n=29) subjects with pseudoexfoliation glaucoma from our analyses, as these subjects were older and their IOP at baseline was substantially higher than that of the other two open-angle glaucoma diagnostic groups represented in the CIGTS enrollees (primary and pigmentary open-angle glaucoma). Data from all available follow-up visits through nine years after randomization were included in the analyses. Follow-up data were available through three,

six, and nine years for 495, 424, and 100 participants, respectively. University of Michigan institutional review board approval was granted for this study.

IOP in the CIGTS was measured at baseline and all follow-up examinations by Goldmann applanation tonometry. Certified technicians measured IOP under a standardized protocol that followed recommended guidelines.^{10,11} IOP summary measures were computed based on each participant's longitudinal IOP record. These measures included the mean IOP, mean percent reduction in IOP from the baseline IOP, maximum IOP value, percentage of IOP values that fell below a threshold value (e.g., percent less than 16, 18, 20, or 22 mmHg), an indicator of whether all IOP values fell below a given threshold value, and inter-visit variability in IOP over time as assessed by the standard deviation (SD) and the range. Two methods were used to calculate these IOP measures over time – cumulative and rolling. The cumulative IOP summary method made use of IOP values from the 3-month follow-up visit up to but not including the time point of VF assessment. For example, the IOP mean summary measure used to predict the VF outcome at five years was a mean of all IOPs available up to but not including 5 years (3 months to 4.5 years). In contrast, the rolling IOP summary method captured a summary of only the previous 3 years (not including the time point in question). For example, the 9 year mean summary measure was based on IOP data from years 5.5 to 8.5. Because the cumulative IOP summary measures related more closely with progressive VF loss, only those results are shown.

Statistical Methods

Descriptive statistics and Pearson's correlation coefficients were used. Both linear mixed models¹² to detect shifts in MD levels, and repeated measures logistic regression, based on generalized estimating equations¹³ to detect elevated odds of substantial worsening (3 dB or more), were used. For each of these models, adjustment was made for baseline factors previously identified as associated with progressive VF loss, including MD, diabetes, initial treatment, and time on treatment (except for range of baseline IOP, due to collinearity with time-dependent IOP measures).¹⁴ The IOP summary variables were added individually to these base models.

For the linear mixed models, we used a heterogeneous Toeplitz (banded) covariance structure to allow for increasing variance over time, and higher correlations between pairs of points closer together in time. Because of smaller variance of the MD in those with less VF damage, we allowed different variance estimates for those with baseline MD > -4 dB and MD ≤ -4 dB. For the repeated measures logistic regression models, the covariance structure was similar to the Toeplitz structure used for the linear model. SAS v.9.2 Proc Mixed and Proc Genmod (SAS Institute, Cary, NC) were used for these analyses. Rather than interpreting regression coefficients in terms of a one unit increase in the covariate, the IOP effects described below are given in terms of a substantial increase in each measure, one SD increase: SD (IOP range) = 4.5mmHg, SD (IOP SD) = 1.5 mmHg, SD (IOP maximum) = 5.5mmHg. These effects are obtained by multiplying the regression estimates by the SD.

Results

A total of 578 CIGTS subjects with either primary or pigmentary OAG were enrolled and randomized to initial treatment with either topical medications or incisional surgery. Participants had a mean age at randomization of 57.6 years (range 29 to 75), 56% were male, and 95% had primary OAG. Racial composition was 54% White, 40% Black, and 6% Asian and other. Approximately half (51%) had some education beyond high school, and 37% reported a history of glaucoma in their immediate family.

The mean IOP at baseline, prior to treatment initiation, was 27.6 ± 5.5 mmHg (mean $\pm$ SD) for medicine patients and 27.4 ± 5.7 mmHg for surgery patients. Table 1 presents descriptive information for the IOP cumulative summary measures obtained during treatment. For example, the mean IOP ranged from 17.1 to 18.3 mmHg in the medicine group, or 13.8 to 14.4 mmHg in the surgery group, based on all IOP measurements up to 3, 6, or 9 years. The percentage of participants whose IOP was always under 18 mmHg decreased over time, ranging from 18% at three years to 8% at nine years in the medicine group, and 59% at three years to 51% at nine years in the surgery group. Many of the continuous IOP summary measures were closely correlated, with *r*-values (using 6-year measures as an example) for the pairwise correlations between the maximum, range, and SD of IOP varying from 0.81 to 0.97 in the medicine group and from 0.69 to 0.96 in the surgery group. The correlations between the range of IOP and the SD of IOP in both groups were the highest. While the linear relationships between summary IOP measures are strong, each IOP summary measure provides some unique information.

The mean MD at baseline was -5.2 ± 4.3 dB in the medicine group and -5.7 ± 4.1 dB in the surgery group. Table 2 presents descriptive information on the MD values during treatment, and the percentage of participants who showed a 3 dB or greater worsening of their MD from baseline at 3, 6, and 9 years after treatment initiation. In the medicine group, MD mean values decreased from -5.1 ± 5.6 dB at 3 years to -6.2 ± 6.0 dB at 9 years. In the surgery group, MD mean values decreased from -5.3 ± 4.5 dB at 3 years to -7.9 ± 6.2 dB at 9 years. The percentage of participants who had a 3 dB or greater worsening from baseline increased from 11.5% to 17.4% to 23.1% in the medicine group, and from 9.4% to 10.9% to 34.1% in the surgery group, at 3, 6, and 9 years, respectively.

Results from an evaluation of each IOP summary measure's association with the MD from VF testing, stratified by initial treatment and adjusted for baseline factors previously shown to be predictive of the MD, are found in Table 3. This analysis provides average effects over follow-up time. In the medicine group, three continuous IOP summary measures showed significant associations with MD over time – the maximum IOP ($p=0.0003$), the range of IOP ($p<0.0001$), and the SD of IOP ($p=0.0056$). Estimates of meaningful effect (one SD increase) in each of these measures, based on the beta values from regression indicate that a 5.5 mmHg higher maximum IOP, a 4.5 mmHg wider range of IOP, and a 1.5 mmHg larger SD, are associated with lower (worse) mean MD of 0.61, 0.54, and 0.35 dB, respectively. In the surgery group, no IOP summary measure showed a significant association with MD over time.

The previous models assumed constant effects over follow-up time. Changing effects over time were further investigated. Figure 1 (top panel) shows an example of the effect that maximum IOP has on MD over time, by initial treatment. Those treated initially with medications whose maximum IOP was greater (at the 75th percentile, 24.0 mmHg) had a pattern of MD decrease over time that was much more dramatic than that observed in medically-treated subjects whose maximum IOP was at the 25th percentile or that found in either surgery group. These same patterns were observed for the SD and range measures [*p*-values for 3-way interactions (treatment $\times$ time $\times$ IOP summary measure) were 0.0001, 0.0004, and 0.0011, respectively]. The bottom panel of Figure 1 shows an example of the effect that the proportion <20 mmHg had on MD over time, by initial treatment (3-way interaction $p=0.0008$). In this example, medically treated subjects whose proportion of IOP values <20 mmHg was at the 25th percentile level (80% of their IOP values were <20 mmHg) had the worst predicted MD over time, followed by medically treated subjects in the 75th percentile (for whom 100% of IOP values were <20 mmHg). The two surgically-treated groups had similarly good predicted MD values over time that did not vary much by being at the 25th or 75th percentile of the proportion of IOP values <20 mmHg.

Figure 2 shows the estimates of a meaningful (one SD) increase in each IOP summary measure at seven years of follow-up. The regression estimates for those summary IOP measures that had a significant interaction with treatment (mean IOP, maximum IOP, SD of IOP, and range of IOP) are presented separately by treatment. For all but mean IOP, evidence of better IOP control (lower maximum IOP, less SD of IOP, and smaller range of IOP) had a significantly beneficial effect in the medicine group, but no significant effect in the surgery group. For example, in medically-treated subjects, those with an IOP range of 9 mmHg (2 SDs) would have a predicted decrease (worsening) in MD of 0.79 dB more than those with a range of 4.5 mmHg, and those with maximum IOP of 34 mmHg would have a predicted decrease (worsening) in MD of 0.96 dB more than those with a maximum IOP of 28.5 mmHg. Among all of the other IOP summary measures that lacked a treatment interaction, only the “All IOP < 20 mmHg” measure was associated with a significantly beneficial effect. Values represented in Figure 2 are presented in Table 4 (available at <http://aaojournal.org>).

Substantial VF loss (3 dB or greater worsening) was next evaluated as the outcome in a repeated measures logistic regression, with adjustment for all baseline factors. Three continuous IOP summary measures were significantly associated with substantial VF loss (Figure 3). Interpreting these results for a one SD increase in each summary measure shows that substantial VF loss was associated with: a larger range of IOP [odds ratio (OR)=1.39, 95% confidence interval (CI)=1.16 to 1.66], greater SD of IOP (OR=1.37, 95% CI = 1.15 to 1.64), and higher maximum IOP (OR=1.34, 95% CI = 1.09 to 1.64). No significant associations with substantial VF loss were found for any of the IOP threshold values (e.g., maintaining all IOP values below 16 or 18 mmHg) or any of the summary variables based on the percentage of time IOP was less than a specific value. Values represented in Figure 3 are presented in Table 5 (available at <http://aaojournal.org>), with additional information by treatment group.

Given that increasing range, SD, and maximum value of IOP during follow-up were consistently associated with more VF loss, we developed predictive models to identify baseline factors that were significantly associated with these three IOP summary measures. Greater IOP variability (increases in these three measures) was associated with black race (all p-values ≤ 0.016) and higher baseline IOP (all p-values < 0.0001). Significant differences in these summary IOP control measures were also observed across the 14 centers (all p-values ≤ 0.001). Also, the range of six IOP measurements taken at baseline was significantly correlated with the 7-year cumulative estimates of IOP range ($r=0.25$), SD ($r=0.26$), and maximum IOP ($r=0.25$), all p-values < 0.0001 .

Discussion

Controlling IOP in the management of patients with glaucoma has been the principal component of treatment paradigms throughout the past and present era of glaucoma treatment. An evidence base for its role has been challenged,¹⁵ and only recently has confirmatory evidence been obtained. Results from pivotal multi-center clinical trials have documented that measures of IOP control, such as mean IOP, are significantly associated with the risk of incident glaucoma and progressive VF loss.²⁻⁷ Some authors have suggested, though, that the extent of IOP variation that occurs during treatment may be a more important contributor to the risk of VF progression than mean IOP or other summary IOP measures. Caprioli reviewed evidence for this possibility.¹⁶

In 1977, Werner et al.¹⁷ found no difference in the mean postoperative IOP between ten eyes that showed progressive VF loss after trabeculectomy and 14 eyes that did not progress. They reported that a measure of the quality of IOP control, the percentage of IOP

measurements that exceeded 21 mmHg, was the distinguishing factor predictive of progression. O'Brien et al.¹⁸ found three measures of IOP variation showed significant correlation with the rate of VF deterioration in 10 patients whose VF loss worsened during treatment - the standard error of the mean, the SD, and the range of IOP. Stewart et al.^{19,20} reported that the mean IOP and the variance and the average SD of individual IOP measurements significantly differed in subjects whose glaucoma progressed vs. those who were stable. Both the mean IOP and two measures of IOP variation – the range and peak value - were directly correlated with greater VF decay by Bergea et al.²¹ More recently, Hong et al.²² noted that larger long-term IOP fluctuation (an IOP SD >2 mmHg) was associated with progressive VF deterioration in 408 eyes that underwent phacoemulsification, intraocular lens implantation, and trabeculectomy. Lee et al.²³ evaluated IOP SD as a predictor for glaucoma progression in two cohorts of glaucoma patients. After controlling for age, mean IOP, VF stage, and other covariates, the authors found that each unit increase in IOP SD resulted in 4.2 to 5.5 times higher risk of glaucoma progression.

Evidence from large multicenter studies of glaucoma is mostly, but not uniformly, supportive of increased IOP variation as a factor to consider in the risk of glaucoma progression. The AGIS investigators²⁴ found larger IOP fluctuation, as measured by the SD of IOP values from all visits, to be significantly predictive of VF progression. Subsequently, Caprioli and Coleman²⁵ used pointwise linear regression to evaluate the effects of IOP fluctuation in the AGIS participants, and reported that IOP fluctuation was a risk factor for VF progression, but only within those with a low mean IOP. In the EMGT, Bengtsson et al.²⁶ reported that only mean IOP, not IOP fluctuation, was related to VF progression, in a time dependent Cox model that included both of these factors (which were highly correlated, $r=0.44$, $P<0.0001$). The authors note that they excluded post-progression IOP values from their data, to avoid the possibility that including these values may cause higher fluctuation after the fact. Most recently, in a multi-center study of three glaucoma medications (the Xalatan/Lumigan/Travatan Study), Varma et al.²⁷ found that inter-visit IOP range was associated with risk factors for glaucomatous change, such as African-American race and high baseline IOP.

Our analytical approach was unique in three ways. First, we treated measures of IOP control and variation as well as the primary outcome measure, mean deviation, as time dependent variables in repeated measures models, both linear and logistic. This approach differs from treating VF progression as a discrete survival event in a Cox regression model, which does not accommodate the often-observed reversal of VF progression that has supported recommendations that VF progression be confirmed by re-testing.^{28–30} Second, we addressed the role of each IOP measure in separate models, due to the fact that these measures are closely correlated with each other. Including correlated measures in one model can lead to errant estimates of their independent association with the outcome.³¹ Third, with one exception (IOP range at baseline), we adjusted for all baseline risk factors that we previously reported to be associated with the risk of VF progression,¹⁴ so that the effect of the IOP control or variation measure on VF progression could be interpreted as independent of those baseline factors. We did not adjust for the effect of IOP range at baseline because this factor was strongly associated with the summary measures of IOP control during follow-up.

Three approaches were used to deal with the potential influence that IOP-reducing interventions during follow-up, such as argon laser trabeculoplasty (ALT) or trabeculectomy, might have on estimates of variation (SD or range). First, we included an indicator variable in our mixed regression models to adjust for IOP data collected after ALT or trabeculectomy. Second, we truncated follow-up data after the first IOP-reducing

intervention (almost always ALT). Finally, we carried forward the last IOP measurement collected before the earliest IOP-reducing event. In all three approaches, the three IOP summary measures (range, SD, and maximum) remained significantly associated with progressive VF loss among those treated medically, but not among those treated surgically. We conclude that these summary measures of IOP control (or variation) are indeed predictive of subsequent VF loss.

These predictive associations were found only among medically-treated subjects in the mixed regression models. While it would be convenient to explain this finding as a result of less IOP variation during follow-up in the surgery group versus the medicine group, we found little indication that IOP variation differed substantially over time between the two treatment groups (Table 1). It may be that when the IOP level is low, as obtained using surgery, IOP fluctuation around that low level does not have as large an impact on MD as it does when the IOP is on average 3 to 4 mmHg higher (as observed in the medicine group). Another factor that may have contributed to the difference between medical and surgically-treated subjects is 24-hour pressure control, which we did not measure. Konstas et al.³² reported that the mean, peak, and range of 24-hour IOP in 30 medically-treated subjects with advanced OAG were significantly higher than these measures in 30 post-trabeculectomy subjects.

Our findings are consistent in identifying three measures of IOP control or variation during treatment – the range of IOP, the SD of IOP, and the maximum IOP – as important measures to consider in reviewing a patient's record of IOP measurements over time and considering their risk of progressive VF loss. We did not find that maintaining IOP below 16 or 18 mmHg on all visits resulted in less VF loss, which differs from the finding reported by the AGIS investigators.⁷ Mean IOP was also not significantly associated with risk of VF progression after adjustment for other risk factors. Reasons for the effects we observe may reflect the fact that most CIGTS subjects were aggressively treated for IOP, resulting in average IOPs of 16 mmHg. The AGIS findings²⁵ have provided some evidence that measures of IOP fluctuation are related to VF progression among subjects who had lower IOP during follow-up. Caprioli¹⁶ speculates that long-term variability, including irregular and large IOP fluctuations, may disrupt the homeostasis required to protect retinal ganglion cells.

Our findings support the hypothesis that increased IOP fluctuation (SD or range of IOP) as well as high IOP (maximum IOP) are important predictors of progressive visual field loss. In clinical practice, this would be easiest to measure by observing the inter-visit range of IOP over time, as advocated by Varma et al.^{27,33} and commented on by Katz and Myers.³⁴ Of course, doing so requires having regular examinations and access to data on a patient's IOP over an extended period. If routine follow-up of a patient with OAG results in IOP measurements every six months, for example, it would take at least two years to obtain an initial idea of that patient's IOP fluctuation.

With this in mind, it would be helpful to predict which patients are more likely to show higher levels of these summary IOP variables, with the goal to prevent this from happening and thereby reduce the likelihood of progressive VF loss. We previously reported that observing a wide range of IOP prior to initiating treatment, on the order of 8.5 mmHg or greater, upon taking repeated measures over two visits, was predictive of long-term progression of VF loss.¹⁴ Subjects who were younger, male, black, and those who presented with pseudoexfoliation glaucoma or a pupillary defect tended to have a wider range of baseline IOP. For the three measures of IOP variation during follow-up that we identified as predictive of worse MD, the strongest consistently predictive factors included a higher baseline IOP, black race, and a center effect. Varma et al.²⁷ recently reported that black

race, longer time since diagnosis, and a higher mean pre-treatment IOP were associated with high (> 6 mmHg) post-treatment inter-visit range of IOP.

Our evaluation was limited by the fact that IOP and MD measurements were available from visits conducted at six month intervals, and so we have no way to assess inter-visit fluctuations. While IOP was measured in a standardized manner, the time of its measurement was not controlled, and so a participant's IOP could have been measured in the morning or afternoon of a scheduled follow-up visit. The fact that we uncovered consistent associations of measures of IOP control during treatment with measures of progressive VF loss, even though we did not have data on inter-visit IOP fluctuation nor did we control for diurnal variation, speaks to the likely import of these IOP control measures. Another limitation was the lack of collecting central corneal thickness information on all of the CIGTS participants. The subset on which we had CCT information was insufficient to address its potential association with progressive VF loss, as suggested in the EMGT findings.⁵

In summary, three measures of IOP fluctuation over extended time, the range of IOP, the SD of IOP, and the maximum IOP, appear to play an important role in visual field progression, particularly among those treated medically. Monitoring for IOP fluctuation and considering more aggressive treatment to limit it seems advisable. Monitoring and timely intervention would be facilitated by use of simple software algorithms that provide clinicians with summary IOP information from accumulating IOP data.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Model-based estimates of the mean deviation over follow-up for low and high values of two cumulative IOP summary measures (maximum IOP and proportion <20 mmHg), by initial treatment. Results are presented for the 25th and 75th percentile values of each IOP summary measure: (a) maximum IOP: 17.5 & 24.0 mmHg, respectively; (b) proportion of IOP values that were < 20 mmHg: 80% & 100%, respectively.

IOP: intraocular pressure; mmHg: millimeters of mercury; dB: decibels

Figure 2.

Forest plot of the difference in MD associated with substantial changes in individual IOP summary measures. Panel (a) presents the difference in MD (estimate, 95% CI) resulting from a 1 SD increase in the IOP summary measure for measures that showed differences by initial treatment; Panel (b) presents the difference in MD (estimate, 95% CI) resulting from a 1 SD increase in the IOP summary measure for measures that had no significant treatment effect; for the percent-based measures (e.g., percent of IOP measurements that were <18 mmHg), differences are presented in terms of a 20% increase (e.g., difference in MD between having 60% vs. 80% of IOP measurements <18 mmHg). Note: all estimates are

adjusted for baseline MD, age at baseline, cataract, diabetes, age, and interactions. Estimates in Panel (b) are also adjusted for initial treatment.

MD: mean deviation; IOP: intraocular pressure; CI: confidence interval; mmHg: millimeters of mercury; dB: decibels

Figure 3.

Forest plot of ORs and 95% CIs for the association of individual IOP summary measures with a worsening of mean deviation (3 dB or more decrease) from baseline. ORs are shown for a one SD increase in the mean, maximum, SD, and range summary measures. For measures of percent IOP < 16, 18, 20, 22 mmHg, or percent of baseline IOP, ORs are shown for a 20% increase (e.g., OR for having 80% vs. 60% of IOP measurements <18 mmHg). Note: all ORs are adjusted for baseline MD, initial treatment, age at baseline, cataract, diabetes, age, and interactions.

OR: odds ratio; CI: confidence interval; IOP: intraocular pressure; dB: decibels; SD: standard deviation; mmHg: millimeters of mercury; MD: mean deviation

Cumulative intraocular pressure summary measures over the time period from 3 months to 3, 6, and 9 years after treatment initiation

Table 1

IOP Summary Measures	Medicine			Surgery		
	3 year (n=256)	6 year (n=223)	9 year (n=53)	3 year (n=239)	6 year (n=239)	9 year (n=47)
Continuous Measures	Mean (SD)			Mean (SD)		
Mean IOP	18.3 (2.7)	17.7 (2.6)	17.1 (2.4)	14.4 (4.3)	14.4 (3.8)	13.8 (3.8)
Maximum IOP	22.3 (4.4)	23.0 (4.6)	23.5 (5.2)	17.9 (5.6)	19.0 (5.5)	18.8 (5.9)
Range IOP	7.1 (4.2)	9.1 (4.6)	11.1 (6.1)	6.7 (4.0)	8.7 (4.3)	9.5 (4.5)
Standard Deviation IOP	2.8 (1.8)	2.8 (1.4)	3.0 (1.7)	2.6 (1.6)	2.7 (1.3)	2.6 (1.2)
Proportion < 16 mmHg	0.3 (0.3)	0.4 (0.3)	0.4 (0.3)	0.7 (0.4)	0.7 (0.3)	0.7 (0.3)
Proportion < 18 mmHg	0.6 (0.3)	0.6 (0.3)	0.7 (0.3)	0.8 (0.3)	0.8 (0.3)	0.9 (0.2)
Proportion < 20 mmHg	0.8 (0.3)	0.8 (0.2)	0.9 (0.2)	0.9 (0.2)	0.9 (0.2)	0.9 (0.1)
Proportion < 22 mmHg	0.9 (0.2)	0.9 (0.2)	0.9 (0.1)	0.9 (0.2)	0.9 (0.1)	1.0 (0.1)
Proportion of Baseline IOP	0.7 (0.1)	0.7 (0.1)	0.7 (0.1)	0.6 (0.2)	0.5 (0.2)	0.5 (0.2)
Categorical Measures	Frequency (Percent)			Frequency (Percent)		
All IOP < 16 mmHg	7 (2.7)	1 (0.5)	0 (0.0)	105 (43.9)	69 (34.3)	18 (38.3)
All IOP < 18 mmHg	45 (17.6)	27 (12.1)	4 (7.6)	140 (58.6)	98 (48.8)	24 (51.1)
All IOP < 20 mmHg	96 (37.5)	69 (30.9)	16 (30.2)	169 (70.7)	131 (65.2)	32 (68.1)
All IOP < 22 mmHg	150 (58.6)	120 (53.8)	25 (47.2)	192 (80.3)	150 (74.6)	37 (78.7)

IOP: intraocular pressure; SD: standard deviation; mmHg: millimeters of mercury

Table 2

Descriptive information on mean deviation values and percentage showing a 3 dB or greater loss from baseline during follow-up

Follow-up Time in years	Medicine			Surgery		
	Number of Subjects	MD mean (SD) in decibels	% (n) with $\geq$ 3dB loss of MD from baseline	Number of Subjects	MD mean (SD) in decibels	% (n) with $\geq$ 3dB loss of MD from baseline
0	293	-5.2 (4.3)	--	285	-5.7 (4.2)	--
3	252	-5.1 (5.6)	11.5 (29)	233	-5.3 (4.5)	9.4 (22)
6	218	-5.7 (5.9)	17.4 (38)	193	-5.2 (4.6)	10.9 (21)
9	52	-6.2 (6.0)	23.1 (12)	44	-7.9 (6.2)	34.1 (15)

MD: mean deviation; SD: standard deviation; dB: decibels

* Sample sizes differ from Table 1 due to missing MD values

Table 3

Main effects from mixed linear models of the association of intraocular pressure summary measures with mean deviation

IOP Summary Measure	<u>Medicine</u>		<u>Surgery</u>	
	Estimate (SE)	P-value	Estimate (SE)	P-value
Mean IOP	−0.02 (0.06)	0.7127	−0.05 (0.04)	0.2037
Max IOP	−0.11 (0.31)	0.0003	−0.02 (0.03)	0.5173
Range IOP	−0.12 (0.03)	<0.0001	−0.00 (0.03)	0.9128
SD IOP	−0.23 (0.08)	0.0056	−0.10 (0.09)	0.2432
Proportion IOP < 16 mmHg	0.62 (0.49)	0.2045	0.29 (0.43)	0.4946
Proportion IOP < 18 mmHg	−0.33 (0.47)	0.4472	0.35 (0.52)	0.5037
Proportion IOP < 20 mmHg	−0.14 (0.58)	0.8070	0.74 (0.69)	0.2854
Proportion IOP < 22 mmHg	−0.78 (0.73)	0.2854	1.41 (0.97)	0.1460
All IOP < 16 mmHg	0.77 (0.59)	0.1895	0.03 (0.24)	0.8867
All IOP < 18 mmHg	0.08 (0.29)	0.7712	−0.12 (0.24)	0.6180
All IOP < 20 mmHg	0.61 (0.26)	0.0187	0.21 (0.27)	0.4412
All IOP < 22 mmHg	−0.09 (0.28)	0.7553	0.17 (0.28)	0.5497
Proportion of Baseline IOP	0.65 (1.42)	0.6461	−1.29 (0.97)	0.1868

* models adjusted for time, time2, MD0, (MD0)2, age, race, cataract, diabetes and interactions

note: no interaction between IOP measure and time (the plots include this interaction and are at the 7 year period) IOP: intraocular pressure; SE: standard error; SD: standard deviation; mmHg: millimeters of mercury; MD: mean deviation