



Impact of Intraocular Pressure Control on Rates of Retinal Nerve Fiber Layer Loss in a Large Clinical Population

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Purpose: To investigate the impact of intraocular pressure (IOP) control on rates of change of spectral-domain OCT (SD-OCT) retinal nerve fiber layer (RNFL) thickness in a large clinical population.

Design: Retrospective cohort study.

Participants: A total of 85 835 IOP measurements and 60 223 SD-OCT tests from 14 790 eyes of 7844 patients.

Methods: Data were extracted from the Duke Glaucoma Registry, a large database of electronic medical records of patients with glaucoma and suspected disease followed over time at the Duke Eye Center and satellite clinics. All records from patients with a minimum of 6 months of follow-up and at least 2 good-quality SD-OCT scans and 2 clinical visits with Goldmann applanation tonometry were included. Eyes were categorized according to the frequency of visits with IOP below cutoffs of 21 mmHg, 18 mmHg, and 15 mmHg over time. Rates of change for global RNFL thickness were obtained using linear mixed models and classified as slow if change was slower than $-1.0 \mu\text{m}/\text{year}$; moderate if between -1.0 and $-2.0 \mu\text{m}/\text{year}$; and fast if faster than $-2.0 \mu\text{m}/\text{year}$. Multivariable models were adjusted for age, gender, race, diagnosis, central corneal thickness, follow-up time, and baseline disease severity.

Main Outcome Measures: Rates of change in SD-OCT RNFL thickness according to levels of IOP control.

Results: Eyes had a mean follow-up of 3.5 ± 1.9 years. Average rate of change in RNFL thickness was $-0.68 \pm 0.59 \mu\text{m}/\text{year}$. Each 1 mmHg higher mean IOP was associated with $0.05 \mu\text{m}/\text{year}$ faster RNFL loss ($P < 0.001$) after adjustment for potentially confounding variables. For eyes that had fast progression, 41% of them had IOP < 21 mmHg in all visits during follow-up, whereas 20% of them had all visits with IOP < 18 mmHg, but only 9% of them had all visits with IOP < 15 mmHg.

Conclusions: Intraocular pressure was significantly associated with rates of progressive RNFL loss in a large clinical population. Eyes with stricter IOP control over follow-up visits had a smaller chance of exhibiting fast deterioration. Our findings may assist clinicians in establishing target pressures in clinical practice. *Ophthalmology* 2020;■:1–10 © 2020 by the American Academy of Ophthalmology



Supplemental material available at www.aaojournal.org.

Glaucoma is a progressive optic neuropathy estimated to affect approximately 80 million people worldwide and remains the leading cause of irreversible blindness.¹ Elevated intraocular pressure (IOP) remains the main and only modifiable risk factor in glaucoma, and understanding the impact of levels of IOP on risk of disease progression helps clinicians establish target pressures and individualize therapeutic approaches.^{2–4}

Several clinical trials have attempted to investigate the relationship between IOP and risk of glaucoma progression.^{5–11} The Early Manifest Glaucoma Trial estimated a 10% less risk of progression for each 1 mmHg reduction in IOP.⁸ In a post hoc analysis, the Advanced Glaucoma Intervention Study (AGIS) demonstrated that visual field loss was significantly more frequent in eyes with mean IOP above 17.5 mmHg compared with those with mean

IOP below 14 mmHg; those eyes with IOP less than 18 mmHg in 100% of visits during follow-up demonstrated no average change on visual fields, as measured by standard automated perimetry.⁵ However, such estimations of the impact of IOP lowering on glaucoma progression have mostly relied on studies with restrictive criteria and rigid treatment schemes, which do not necessarily represent how disease progresses under routine clinical care.^{12,13}

Recently, the widespread incorporation of electronic health records (EHRs) in clinical practice has allowed a rapid growth in the availability of clinical data. Use of EHR data may better reflect how the disease progresses in a practical setting, reducing issues of random selection and bias that can occur in patients enrolled in clinical research studies.^{14–16} In addition, although preservation of visual function is the primary goal of glaucoma management,

assessment of how IOP affects neural loss in glaucoma using standard automated perimetry may be confounded by the subjective nature of perimetry, as well as by nonlinearities in translating retinal ganglion cell loss to visual sensitivity thresholds.¹⁷⁻¹⁹ In that regard, analysis of imaging data from a large EHR database may have advantages when investigating the impact of IOP on glaucoma progression. By providing an objective and quantitative assessment of neural loss, spectral-domain OCT (SD-OCT) may be better able to capture the direct relationship between IOP and retinal ganglion cell losses in glaucoma.

In the present work, we used a large database of glaucoma patients and glaucoma suspects under routine clinical care to evaluate the impact of IOP control on rates of structural change over time, as measured by SD-OCT retinal nerve fiber layer (RNFL) thickness.

Methods

This was a retrospective cohort study of patients from the Duke Glaucoma Registry,²⁰ an EHR database developed by the Vision, Imaging, and Performance Laboratory. The database consisted of adults 18 years or older with glaucoma or glaucoma suspect diagnoses who were evaluated at the Duke Eye Center or its satellite clinics between January 2009 and September 2019. The Duke University Institutional Review Board approved this study with a waiver of informed consent because of the retrospective nature of this work. All methods adhered to the tenets of the Declaration of Helsinki for research involving human subjects and were conducted in accordance with regulations of the Health Insurance Portability and Accountability Act.

The database used for this study contained clinical information from baseline and follow-up visits, including patient diagnostic and procedure codes, medical history, best-corrected visual acuity, slit-lamp biomicroscopy, IOP measurement using the Goldmann applanation tonometry (GAT) (Haag-Streit, König, Switzerland), central corneal thickness (CCT), gonioscopy, ophthalmoscopy examination, stereoscopic optic disc photographs, and the results of all Spectralis SD-OCT (Heidelberg Engineering, GmbH, Dossenheim, Germany) scans during the study period.

Participant Selection

Patients were included in the study if they had glaucoma or suspicion of glaucoma based on International Classification of Diseases (ICD) codes at baseline. Subjects were also required to have at least 2 good-quality SD-OCT scans and 2 IOP measures with GAT in different days over a minimum follow-up period of 6 months. Tests performed after any diagnosis of retinal detachment, retinal or malignant choroidal tumors, nonglaucomatous disorders of the optical nerve and visual pathways, uveitis, and venous or arterial retinal occlusion according to ICD codes were excluded. In addition, tests performed after treatment with panretinal photocoagulation, according to Current Procedural Terminology (CPT) codes, were also excluded. The ICD and CPT codes used for inclusion and exclusion in the study are further described in [Table S1](#) (available at www.aaojournal.org). Tests were further censored after any filtration procedure (i.e., trabeculectomy or tube shunt surgery) happening during follow-up. The baseline characteristics and demographics were drawn from the date when the first valid SD-OCT test for each eye was performed.

Spectral-Domain OCT Testing

Thickness measurements of RNFL were obtained from a 12-degree (for single circle scans) or a 3.45-mm-diameter peripapillary circle scan (for scans from the Glaucoma Mode Premium Edition) acquired using the Spectralis SD-OCT, as described in detail previously.²¹ Tests were acquired using the latest available software version at the time of the scan and exported using the latest available version at the time of the analysis (Software Version 6.8). For each scan, the global average RNFL thickness was calculated as the average of thicknesses of all points from the 360 degrees around the optic nerve head. This parameter was used to assess rates of change in RNFL thickness over time.

The device's eye-tracking capability was used during image acquisition to adjust for eye movements. All scans that had a quality score lower than 15 were excluded from this analysis. Furthermore, because manual review of all tests was impractical, scans that had average global RNFL thickness measurements with implausible values were excluded (i.e., lower than 20 and greater than 150 μm). Those cutoffs represent measurements above the higher range of reported RNFL thickness for normal controls and below the lower range for glaucoma subjects²²⁻²⁴ and may indicate the presence of acquisition or segmentation errors in the presence of otherwise good quality scores.²⁵ From the total of 136 322 eligible circle scans from the database (i.e., after exclusions for ICD and CPT codes), 6337 (4.6%) tests were excluded because of low-quality score, and 1678 (1.2%) were further excluded because of implausible average RNFL thickness values. When more than 1 good-quality test was available for the same date, the mean global RNFL thickness of all tests from that date was used in the analyses. Remaining tests were excluded when eyes had less than 6 months of follow-up or because of the unavailability of complete IOP or CCT data.

Data Analyses

Linear mixed models (LMMs) were used to evaluate the effect of IOP parameters on the rates of change in SD-OCT global peripapillary RNFL thickness over time for each group while adjusting for potential correlations between both eyes from the same individual. This standard technique has been described in detail.²⁶ In brief, mixed models take into account the natural correlation of such data over time, as well as the fact that each patient may contribute with 2 eyes for the analyses. Differences in rates of change between eyes and subjects are taken into account by introducing random slopes and random intercepts. Multivariable LMMs were also adjusted for baseline age, gender, race, glaucoma diagnosis, CCT, follow-up time, and baseline disease severity (as defined by the baseline RNFL thickness). Best linear unbiased prediction was used to estimate individual slopes of change for each eye.²⁷⁻²⁹

Individual slopes were then classified into groups according to pre-established cutoffs for rates of global RNFL thickness loss: slow, if change was slower than $-1.0 \mu\text{m}/\text{year}$; moderate, if between -1.0 and $-2.0 \mu\text{m}/\text{year}$; and fast, if faster than $-2.0 \mu\text{m}/\text{year}$.²⁰ For each RNFL slope from the LMM, a mean IOP value was calculated as the average measurement for a given eye during the corresponding follow-up. Peak IOP was determined as the highest value during follow-up. Eyes were also categorized in 4 groups according to the frequency of IOP measurements below 18 mmHg at each visit over time, previously proposed by the AGIS investigators:⁵ (A) 100% of visits, (B) 75% to less than 100% of visits, (C) 50% to less than 75% of visits, (D) less than 50% of visits. We also evaluated eyes classified according to looser and stricter levels of IOP control of 21 mmHg and 15 mmHg, respectively.

All statistical analyses were completed in Stata (version 16, StataCorp LP, College Station, TX) within the Protected Analytics Computing Environment, a highly protected virtual network space developed by Duke University for analysis of identifiable protected health information.

Results

In this study, we included a total of 60 223 SD-OCT tests acquired over 56 153 SD-OCT visits from 14 790 eyes of 7844 patients. Of these patients, 4502 (57.4%) were female, and 2240 (28.6%) were self-identified as Black or African American. A total of 4509 eyes (30.5%) had a diagnosis of primary open-angle glaucoma, 7007 eyes (47.4%) were glaucoma suspect, and 3274 eyes (22.1%) had “other glaucoma,” according to ICD codes from the baseline visit. [Table 2](#) summarizes the demographic and clinical characteristics of the eyes included in the study according to their baseline diagnosis. There was a large variation in baseline characteristics ([Fig S1](#), available at www.aajournal.org) comprising the whole spectrum of the disease. Of note, mean \pm standard deviation (SD) age of subjects at baseline was 65.3 ± 13.1 years, and eyes had a mean \pm SD follow-up time of 3.5 ± 1.9 (range, 0.5–9.5) years, with a mean \pm SD number of 3.8 ± 1.7 SD-OCT visits, ranging from 2 to 14. The dataset had a total of 85 835 valid visits where IOP was measured with GAT, with an average of 5.8 ± 3.6 visits per eye.

The mean \pm SD rate of change for global RNFL thickness in the overall population was -0.68 ± 0.59 $\mu\text{m}/\text{year}$ (median, -0.64 ; interquartile range, -0.88 to -0.42). [Table 3](#) details the distribution of the rates of RNFL change according to each diagnostic group. Patients with primary open-angle glaucoma had faster rates of change than glaucoma suspects but slower than other glaucoma types, on average. Results of univariable and multivariable analysis for the effect of each variable of interest on the rates of RNFL thickness loss over time are detailed in [Table 4](#). Each 1 mmHg higher mean IOP was associated with 0.051 $\mu\text{m}/\text{year}$ faster loss of RNFL, and each 1 mmHg higher of peak IOP was associated with 0.038 $\mu\text{m}/\text{year}$ faster RNFL loss, after adjustment for potentially confounding variables.

[Figure 2](#) shows average rates of global RNFL loss for groups of eyes according to the percentage of visits with IOP <18 mmHg. The proportions of eyes in each of the 4 categories of IOP control (IOP <18 mmHg at each visit for (A) 100% of visits, (B) 75%–100% of visits, (C) 50%–75% of visits, (D) $<50\%$ of visits) were 40%, 14%, 19%, and 27%, and they had mean \pm SD IOP values of 13.1 ± 2.0 , 15.2 ± 1.4 , 17.1 ± 1.3 , and 20.3 ± 2.4 mmHg, respectively. Corresponding mean \pm SD rates of RNFL thickness change for each group were -0.61 ± 0.53 , -0.68 ± 0.60 , -0.71 ± 0.63 , and -0.75 ± 0.62 $\mu\text{m}/\text{year}$, respectively. [Figure 2](#) also shows a similar analysis for eyes divided by the cutoffs of 15 mmHg and 21 mmHg.

[Figure 3](#) shows the proportion of eyes classified according to the rates of RNFL loss as slow (slower than -1 $\mu\text{m}/\text{year}$), moderate (between -1 and -2 $\mu\text{m}/\text{year}$), or fast progressors (faster than -2 $\mu\text{m}/\text{year}$) for groups of eyes according to the percentage of visits with IOP <21 mmHg ([Fig 3A](#)), <18 mmHg ([Fig 3B](#)), and <15 mmHg ([Fig 3C](#)). [Figure S4](#) (available at www.aajournal.org) displays additional plots according to glaucoma diagnosis at baseline. Overall, eyes progressing at fast rates had a relatively lower frequency of visits with “satisfactory” IOP measures. For example, for eyes that had fast progression, 20% of them had IOP <18 mmHg in all visits, whereas in 40% of them, the IOP was above that cutoff in more than half of the visits. For a stricter cutoff of 15 mmHg, only 9% of the eyes with fast progression had all visits with IOP

below that cutoff. As expected, for a looser cutoff of 21 mmHg, 41% of fast progressors had IOP below this level in all visits.

We also investigated the relationship between levels of mean IOP during follow-up and rates of RNFL loss. Rather than looking at the proportion of visits with IOP below a certain cutoff, this additional analysis investigates the proportion of eyes with slow, moderate, and fast progression according to predefined levels of mean IOP during follow-up, as proposed by the AGIS study.⁵ Twenty-seven percent of the eyes had mean IOP below 14 mmHg, 42% had mean IOP between 14 and 17.5 mmHg, and 31% had mean IOP above 17.5 mmHg during follow-up. The results are illustrated in [Figure 5](#). Of note, of eyes with fast RNFL progression, 18% had mean IOP below 14 mmHg, 35% had mean IOP between 14 and 17.5 mmHg, and 47% had mean IOP above 17.5 mmHg.

Discussion

In this large integrated study of EHR and structural imaging data, we assessed the effect of IOP control on rates of RNFL thickness change from a population of patients followed at a tertiary care center. We present the largest analysis of longitudinal SD-OCT results to date, with 14 790 eligible eyes undergoing routine clinical care over a follow-up period that extended up to 9.5 years. Although most patients under routine clinical care had relatively slow rates of progression and satisfactory IOP control, eyes with higher IOP over follow-up had significantly faster rates of change. Most important, by investigating the relationship between the frequency of visits with IOP below certain cutoff levels and the risk for fast progression, our results may assist clinicians in establishing target IOP levels in clinical practice.

In our study, for each 1 mmHg increase in mean IOP during follow-up, global RNFL thickness declined at a 0.05 $\mu\text{m}/\text{year}$ faster rate. This effect was of similar magnitude even after adjusting for other relevant covariates such as age, sex, race, CCT, baseline disease severity, and follow-up time and is similar to that found in previous studies from smaller populations.^{30–32} Such estimate, however, offers little guidance on how clinicians should think about target IOP levels to prevent RNFL loss over time. We therefore conducted analyses investigating the relationship between rates of progression and the frequency of visits in which IOP levels would be below a certain cutoff. This more closely replicates how clinicians set target IOP levels in clinical practice. We investigated a cutoff of 18 mmHg based on the AGIS study,⁵ but also stricter and looser cutoffs of 15 mmHg and 21 mmHg, respectively. In the AGIS, eyes with IOP consistently lower than 18 mmHg in all visits did not show apparent visual field progression as measured by the AGIS score, a summary metric of visual field damage that behaves similarly to mean deviation. In our study, we found that although having a higher frequency of visits with IOP <18 mmHg translated into slower RNFL change over time, it was not sufficient to prevent moderate or fast progression. In eyes with moderate progression, still 33% had all their visits with IOP <18 mmHg. In eyes with fast progression, 20% had all their visits below such cutoff. These findings may

Table 2. Demographics and Clinical Characteristics of Subjects Included in the Study

| Characteristic | Overall | Diagnosis at Baseline | | |
|------------------------------------------------------------|------------------|-----------------------|------------------|------------------|
| | | GS | POAG | Other |
| Subject-specific | | | | |
| No. of patients, n (%) | 7844 (100.0) | 3691 (47.0) | 2468 (31.4) | 1821 (23.2) |
| Age (yrs), Mean ± SD | 65.3 ± 13.1 | 62.9 ± 12.6 | 68.8 ± 12.2 | 65.6 ± 13.8 |
| Sex, female (%) | 4502 (57.4) | 2214 (60.0) | 1319 (53.4) | 1040 (57.1) |
| Race, (%) | | | | |
| White | 4822 (61.5) | 2265 (61.4) | 1505 (61.0) | 1124 (61.7) |
| Black or African American | 2240 (28.6) | 1037 (28.1) | 771 (31.2) | 482 (26.5) |
| Other | 782 (9.9) | 389 (10.5) | 192 (7.8) | 215 (11.8) |
| Eye-specific | | | | |
| No. of eyes, n (%) | 14 790 (100.0) | 7007 (47.4) | 4509 (30.5) | 3274 (22.1) |
| Follow-up, yrs Mean ± SD | 3.5 ± 1.9 | 3.6 ± 1.9 | 3.3 ± 2.0 | 3.5 ± 1.8 |
| CCT, μm Mean ± SD | 549.5 ± 41.8 | 554.7 ± 41.2 | 544.0 ± 40.8 | 546.0 ± 43.0 |
| SD-OCT | | | | |
| No. of visits, n (%) | 56 153 (100.0) | 25 971 (46.2) | 17 147 (30.6) | 13 035 (23.2) |
| No. of visits per eye, Mean ± SD [range] | 3.8 ± 1.7 [2–14] | 3.7 ± 1.6 [2–12] | 3.8 ± 1.9 [2–12] | 4.0 ± 1.9 [2–14] |
| Baseline mean RNFL thickness, μm | | | | |
| Mean ± SD | 82.4 ± 17.0 | 89.2 ± 13.6 | 74.7 ± 17.0 | 78.5 ± 17.9 |
| Median (IQR) | 84.0 (72.0–94.0) | 90.0 (81.0–98.0) | 75.0 (63.0–87.0) | 79.8 (66.0–91.0) |
| Baseline mean SD-OCT quality, | | | | |
| Mean ± SD | 24.6 ± 4.3 | 24.7 ± 4.3 | 24.5 ± 4.3 | 24.4 ± 4.2 |
| Median (IQR) | 25.0 (22.0–28.0) | 25.0 (22.0–28.0) | 25.0 (21.0–28.0) | 25.0 (21.0–27.0) |
| IOP | | | | |
| No. of visits, n (%) | 85 835 (100.0) | 33 661 (39.2) | 29 647 (34.6) | 22 527 (26.2) |
| No. of visits per eye, n (%) Mean ± SD [range] | 5.8 ± 3.6 [2–34] | 4.8 ± 2.9 [2–24] | 6.6 ± 3.9 [2–28] | 6.9 ± 3.9 [2–34] |
| Average IOP during follow-up, mmHg | | | | |
| Mean ± SD | 16.1 ± 3.5 | 16.6 ± 3.4 | 15.5 ± 3.6 | 15.9 ± 3.5 |
| Peak IOP during follow-up, mmHg | | | | |
| Mean ± SD | 19.4 ± 5.5 | 19.2 ± 4.8 | 19.2 ± 6.0 | 19.9 ± 6.1 |
| Visits with IOP <21 mmHg during follow-up, n (%) | | | | |
| 100% | 9911 (67.0) | 4756 (67.8) | 3062 (67.9) | 2093 (63.9) |
| 75%–100% | 2050 (13.9) | 742 (10.6) | 720 (16.0) | 588 (18.0) |
| 50%–75% | 1664 (11.2) | 824 (11.8) | 455 (10.1) | 385 (11.8) |
| <50% | 1165 (7.9) | 685 (9.8) | 272 (6.0) | 208 (6.3) |
| Visits with IOP <18 mmHg during follow-up, n (%) | | | | |
| 100% | 5959 (40.3) | 2799 (40.0) | 1926 (42.7) | 1234 (37.7) |
| 75%–100% | 2131 (14.4) | 746 (10.7) | 794 (17.6) | 591 (18.1) |
| 50%–75% | 2783 (18.8) | 1279 (18.2) | 832 (18.5) | 672 (20.5) |
| <50% | 3917 (26.5) | 2183 (31.1) | 957 (21.2) | 777 (23.7) |
| Visits with IOP <15 mmHg during follow-up, n (%) | | | | |
| 100% | 2182 (14.7) | 947 (13.5) | 778 (17.3) | 457 (14.0) |
| 75%–100% | 1305 (8.8) | 406 (5.8) | 549 (12.2) | 350 (10.6) |
| 50%–75% | 2464 (16.7) | 1067 (15.2) | 827 (18.3) | 570 (17.4) |
| <50% | 8839 (59.8) | 4587 (65.5) | 2355 (52.2) | 1897 (58.0) |

CCT = central corneal thickness; GS = glaucoma suspect; IOP = intraocular pressure; IQR = interquartile range; POAG = primary open-angle glaucoma; RNFL = retinal nerve fiber layer; SD = standard deviation; SD-OCT = spectral-domain OCT.

indicate a relative lack of sensitivity of the AGIS criteria to assess visual field progression, as found by other authors.^{33–35} It may also reflect the fact that structural change may often be seen in the absence of detectable visual field change.^{17–19} In fact, rates of RNFL change have been shown

to be predictive of future visual field loss and decline in quality of life in glaucoma.^{36–38} In addition, studies such as the AGIS rely on very restrictive criteria and rigid treatment schemes, which do not necessarily represent how glaucoma progresses under routine clinical care.^{14,16,39}

Table 3. Rates of Change for Spectral-Domain OCT Retinal Nerve Fiber Layer Thickness According to Glaucoma Diagnosis at Baseline for All Subjects Included in the Study

| Diagnosis | Rates of Global RNFL Change ($\mu\text{m}/\text{Year}$) 14 790 Eyes of 7844 Subjects | | | | | | |
|-----------|-------------------------------------------------------------------------------------------|------|--------|-------|-------|-------|-------|
| | Mean | SD | Median | IQR | $p5$ | $p15$ | |
| GS | -0.60 | 0.55 | -0.57 | -0.78 | -0.36 | -1.42 | -0.94 |
| POAG | -0.68 | 0.53 | -0.67 | -0.88 | -0.48 | -1.46 | -1.03 |
| Other | -0.84 | 0.70 | -0.79 | -1.07 | -0.52 | -1.85 | -1.30 |
| Overall | -0.68 | 0.59 | -0.64 | -0.88 | -0.42 | -1.56 | -1.06 |

GS = glaucoma suspect; IQR = interquartile range; POAG = primary open-angle glaucoma; RNFL = retinal nerve fiber layer; SD = standard deviation.

The contrast between results using cutoffs of 21 mmHg and 15 mmHg as shown on Figure 3 gives further insight into the relationship between IOP control over time and progression. Only 9% of the eyes with fast progression had IOP <15 mmHg in all visits, whereas 41% of eyes with fast progression had IOP <21 mmHg in all visits. These results suggest that a target IOP of 15 mmHg would make it less likely to have fast progression, whereas a target of 21 mmHg would still be insufficient for a large number of eyes in preventing fast deterioration. On average, eyes with fast progression had an IOP of 17.5 ± 3.8 mmHg during follow-up, with 82% of them with mean IOP of 14 mmHg and above (Fig 5). However, it should be noted that the association between levels of IOP control over time and rates of RNFL thickness change was not perfect and many eyes continued to progress despite relatively low IOP levels. Likewise, many eyes had slow progression despite having at least some of their visits with IOP >21 mmHg, as Figure 3 indicates. Ultimately, the required target pressure for each eye will depend on full consideration of risks and benefits of more aggressive therapy, including risk of disability, side effects of therapeutic options, disease severity at baseline, life

expectancy, and the patient's perceptions about treatment.^{40,41} In addition, pretreatment levels of IOP may need to be considered when assessing target IOP levels. Because many of the patients included in our study were already under treatment at baseline and most did not undergo washout, it was not possible to determine the impact of percent reductions in IOP in risk of progression over time. This, however, replicates common scenarios seen in practice.

The assessment of the true relationship between IOP and progression can be affected by the variability in IOP and RNFL measurements over time as well as by possible effects of treatment. In our study, patients were treated at the discretion of the attending ophthalmologists, and each attending may have had a different way of setting target IOP values. Overall, it is likely that patients with more severe stages of the disease underwent more aggressive treatment, which led to lower IOP values, whereas mild cases were allowed higher IOP values. Ultimately, the effect of treatment is expected to translate into changes in IOP over time and would therefore be captured by our analyses. However, it is possible that the limited office measurements acquired over time may not have fully captured the true IOP behavior

Table 4. Univariable and Multivariable Linear Mixed Models of the Effect of Each Clinical Characteristic on the Rate of Change of Spectral-Domain OCT Retinal Nerve Fiber Layer Thickness Over Time

| Characteristic | Univariable Model | | Multivariable Model 1 | | Multivariable Model 2 | |
|-------------------------------------------------------------------|-------------------|------------------|-----------------------|------------------|-----------------------|------------------|
| | Coefficient | P Value | Coefficient | P Value | Coefficient | P Value |
| Diagnosis, | | | | | | |
| GS | 0 (base) | | 0 (base) | | 0 (base) | |
| POAG | -0.084 | 0.005 | -0.148 | <0.001 | -0.124 | 0.001 |
| Other | -0.242 | <0.001 | -0.241 | <0.001 | -0.205 | <0.001 |
| Age at baseline, per 10 yrs older | -0.028 | 0.006 | -0.063 | <0.001 | -0.055 | <0.001 |
| Sex, female | 0.041 | 0.116 | 0.053 | 0.089 | 0.046 | 0.132 |
| Race, Black or African American | -0.055 | 0.056 | -0.028 | 0.451 | -0.019 | 0.594 |
| Follow-up, yrs | -0.011 | 0.092 | -0.038 | <0.001 | -0.034 | <0.001 |
| Baseline mean global RNFL thickness, per 10 μm thicker | -0.045 | <0.001 | -0.050 | <0.001 | -0.063 | <0.001 |
| CCT, per 40 μm thinner | 0.007 | 0.551 | -0.019 | 0.262 | -0.012 | 0.431 |
| Average IOP during follow-up, per 1 mmHg higher | -0.054 | <0.001 | -0.051 | <0.001 | — | — |
| Peak IOP during follow-up, per 1 mmHg higher | -0.049 | <0.001 | — | — | -0.038 | <0.001 |

Boldface indicates statistical significance ($P < 0.05$).

CCT = central corneal thickness; GS = glaucoma suspect; IOP = intraocular pressure; POAG = primary open-angle glaucoma; RNFL = retinal nerve fiber layer; SD = standard deviation.

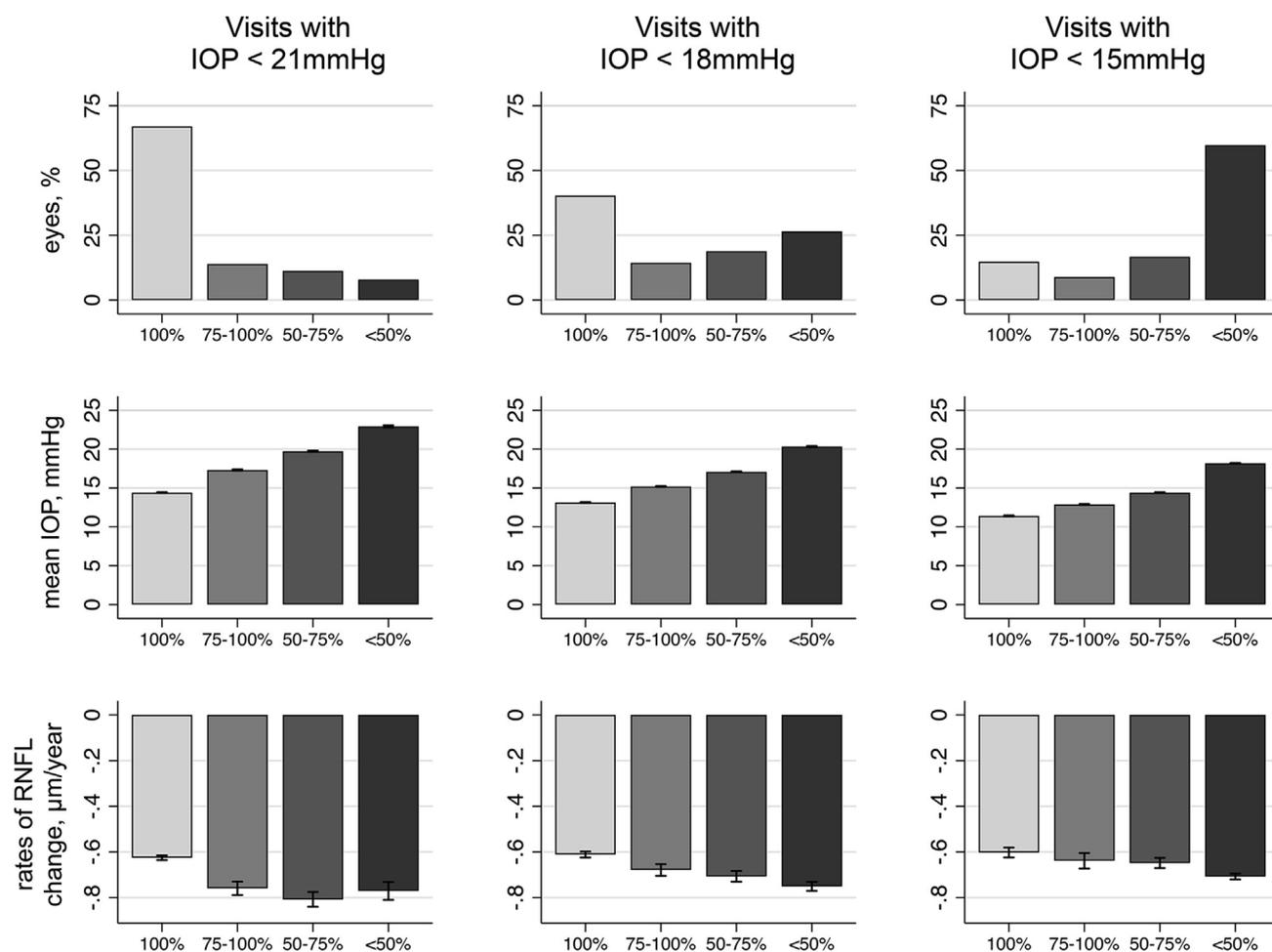


Figure 2. Proportion of eyes, mean intraocular pressure (IOP), and mean rates of change of spectral-domain (SD)-OCT retinal nerve fiber layer (RNFL) thickness according to the percentage of visits with IOP below 21 mmHg, 18 mmHg, and 15 mmHg during follow-up. Capped spikes represent 95% confidence intervals.

in many eyes.⁴² In fact, large variations of IOP outside office hours have been reported in glaucoma patients, and in-office measurements may not fully reflect a patient's medication-taking behavior or adherence to treatment at home.^{12,43} Nevertheless, office IOP measurements remain the most commonly applied metric for both deciding on appropriate therapy and defining the success of a given intervention.⁴¹ Therefore, our results are relevant to common clinical practice.

Of note, our inclusion criteria required a minimum of 2 SD-OCT tests over a follow-up period of at least 6 months. It could be argued that eyes with only 2 or a few SD-OCT tests would not have a sufficient number of datapoints to reliably estimate a rate of change. However, in a large cohort study such as ours, estimates of rates of change in eyes with few observations can be improved by making use of data from the whole population sample.²⁹ For example, it is reasonable to assume that the best estimator of the rate of change in a patient in whom we have no follow-up measurements collected over time is the average rate of change in the subgroup of the population that shares similar baseline

characteristics as those of the patient. As more measurements are acquired for this patient, however, his/her rate of change will most likely deviate from the population average. For patients with few measurements, the precision of the estimates can be increased by "borrowing strength" from the population, whereas for patients with large number of measurements, precise estimates can be obtained relying almost only on the individual data and the need to borrow strength from the population decreases. These estimates correspond to empirical Bayes estimators (i.e., the best linear unbiased predictions) from LMMs used in our study. We and others have previously shown that best linear unbiased predictions improve the precision of slopes of change in glaucoma and result in improved prediction of future observations.^{27,30,44} Of note, this approach also reduces the potential for selection bias that may occur from throwing away data from eyes with few observations. For example, eyes with very fast progression occurring over a relatively short period of time could be inadvertently excluded if one were to keep only eyes with a large number of tests during follow-up. Of note, the inclusion of eyes with few

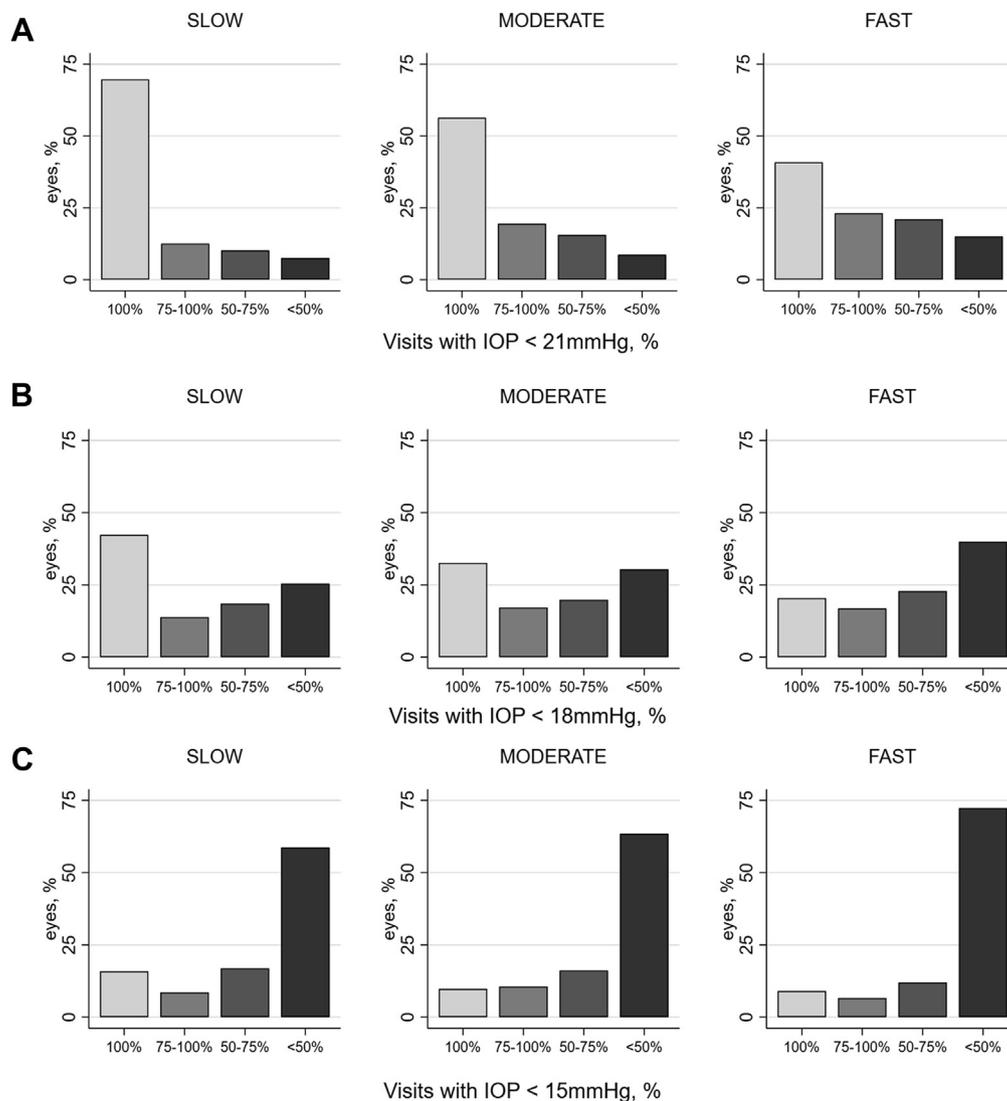


Figure 3. Proportion of eyes classified as slow, moderate, and fast progressors according to the rates of change of spectral-domain (SD)-OCT retinal nerve fiber layer (RNFL) thickness. Eyes are grouped according to the percentage of visits with intraocular pressure (IOP) below (A) 21 mmHg, (B) 18 mmHg, and (C) 15 mmHg during follow-up. Rates of SD-OCT global RNFL thickness change: slow, if slower than $-1.0 \mu\text{m}/\text{year}$; moderate, if between -1.0 and $-2.0 \mu\text{m}/\text{year}$; fast, if faster than $-2.0 \mu\text{m}/\text{year}$.

IOP measurements could lead to difficulties in properly categorizing these eyes according to the percentage of visits with IOP below cutoff points, a main outcome measure in our study. We therefore repeated the analysis using only eyes with at least 4 measurements, but the results remained essentially unchanged (Fig S6, available at www.aajournal.org).

Study Limitations

Although the size of our study is a major strength, working with EHR data also imposes limitations. Retrospective data may have missing values or be inaccurately coded. Coding for glaucoma diagnosis was done by the attending physicians, without following prespecified guidelines other than general billing coding guidelines, and thus may differ from physician to physician. As such, many eyes classified as

suspects may have had glaucomatous damage. Conversely, many eyes with glaucoma may have received such diagnosis based on history or other factors, without necessarily having confirmed optic nerve damage. In fact, although one would expect the effect of increased IOP to be different in glaucoma suspect eyes versus those with confirmed damage, we found similar effects of IOP on rates of RNFL loss when we performed analyses separately according to diagnostic groups (Fig S4, available at www.aajournal.org). As another limitation of our study, we assumed that the effect of treatment on the rate of RNFL loss was mediated by the IOP-lowering effect and not by any other potential mechanism of action that may be particular to a specific class of drugs. However, this assumption is not unreasonable because no class of medication has been clearly demonstrated to exert effects on glaucoma progression by mechanisms other than IOP.

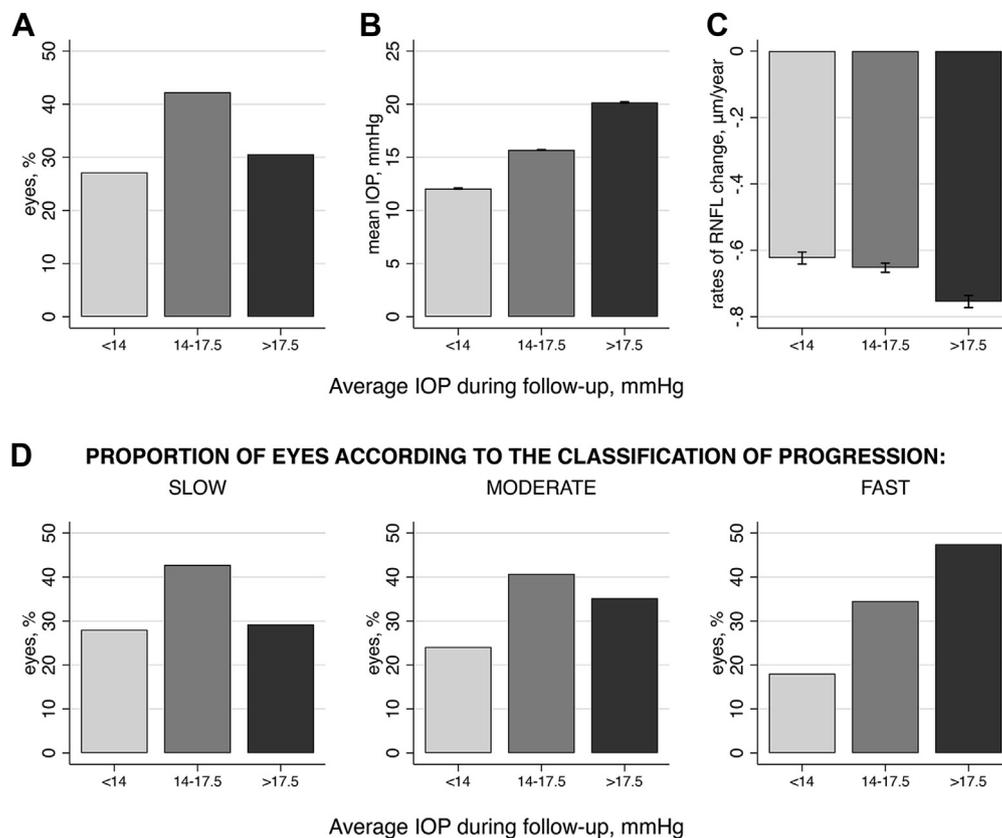


Figure 5. Proportion of eyes (A), mean intraocular pressure (IOP) (B), and mean rates of change (C) for each category of average IOP during follow-up, and (D) the proportion of eyes classified as slow, moderate, and fast progressors within each category according to the rates of change of spectral-domain (SD)-OCT retinal nerve fiber layer (RNFL) thickness. Capped spikes represent 95% confidence intervals. Rates of SD-OCT global RNFL thickness change: slow, if slower than $-1.0 \mu\text{m}/\text{year}$; moderate, if between -1.0 and $-2.0 \mu\text{m}/\text{year}$; fast, if faster than $-2.0 \mu\text{m}/\text{year}$.

Given the large number of therapeutic options and the frequent changes in treatment scheme during a patient follow-up, it would be difficult to obtain reliable estimates of individual drug effects on rates of RNFL change. Finally, adjustment for confounders in our study was obviously limited by the availability of EHR data. For example, refractive error, which has been shown to potentially affect SD-OCT measurements, was only available for a subset of the patients (13 393 eyes, 90.5% of the sample). For those eyes, spherical equivalent had no statistically significant effect on rates of RNFL change over time ($\beta = 0.006 \mu\text{m}/\text{year}$ for each diopter lower, $P = 0.346$) in multivariable analysis. Future studies assembling even larger samples of data might be able to address issues of related to the effect of different classes of medications or other potential confounding factors.

In conclusion, our results indicate that IOP was significantly associated with rates of progressive RNFL loss in a large clinical population. Most important, we were able to quantify the impact of different levels of IOP control on rates of RNFL change over time, showing that eyes with stricter IOP control over follow-up visits had a smaller chance of exhibiting fast deterioration. Our findings may assist clinicians in establishing individualized target pressures in clinical practice.

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Data collection: Jammal, Mariottoni, Estrela, Shigueoka

Analysis and interpretation: Jammal, Thompson, Berchuck, Medeiros

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Abbreviations and Acronyms:

AGIS = Advanced Glaucoma Intervention Study; **CCT** = central corneal thickness; **CPT** = Current Procedural Terminology; **EHR** = electronic health record; **GAT** = Goldmann applanation tonometry; **ICD** = International Classification of Diseases; **IOP** = intraocular pressure; **LMM** = linear mixed models; **RNFL** = retinal nerve fiber layer; **SD-OCT** = spectral-domain OCT.

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