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Effect of Intraocular Pressure Control on Visual Field Progression in the HORIZON Trial

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Purpose: To analyze the effect of intraocular pressure (IOP) characteristics on the 5-year rate of visual field mean deviation (MD) progression in the HORIZON trial.

Design: Post-hoc analysis of data from a randomized clinical trial.

Participants: Patients with glaucoma and visually significant cataract randomized to cataract surgery (CS) with or without the implant of the Hydrus Microstent (HMS).

Methods: One eye of each participant with at least 3 reliable visual fields (false positive errors ≤15%) over at least 1 year was included. We used a published Bayesian hierarchical model, designed to minimize the effect of perimetric noise and learning. We compared the mean rate of MD progression between the 2 arms and measured the effect of postoperative mean intraocular pressure (MIOP), peak washed-out intraocular pressure (WO-PIOP), mean washed-out intraocular pressure (WO-MIOP), and day-1 IOP. These IOP metrics were mean-centered and standardized (divided by their standard deviation) to allow a direct comparison of their effect.

Main Outcome Measures: Mean rate of MD progression.

Results: Data from 517 eyes (352 in the CS-HMS arm) were analyzed. The MD rate was −0.55 [−0.72,−0.39] dB/year (mean [95% credible intervals]) for the CS-only arm and −0.30 [−0.38,−0.22] dB/year for the CS-HMS arm (44.6% [18.0, 64.2] reduction, $P = 0.004$). Increase in all IOP metrics was significantly associated with a faster MD rate. MIOP, WO-MIOP, and WO-PIOP had similar proportional effects. Day-1 IOP had a considerably smaller effect. The difference in rate between the 2 arms remained significant after adjusting for MIOP ($P = 0.002$) but was largely eliminated after adjusting for WO-MIOP and WO-PIOP ($P = 0.396$). The MD rate in the CS arm remained significantly faster than CS-HMS ($P = 0.001$) after removing eyes with a day-1 IOP spike (IOP > 40 mmHg or 10 mmHg above the washed-out baseline IOP).

Conclusions: The MD rate was significantly slower in the CS-HMS arm in the HORIZON trial, compared to CS alone. This difference was not explained by day-1 IOP spikes or MIOP, but was largely accounted for by WO-IOP metrics.

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The main objective of glaucoma treatment is to prevent visual field (VF) deterioration. At present, the only modifiable risk factor to prevent progression is the reduction of intraocular pressure (IOP)[1–7] by means of medications (usually eye drops), laser procedures, surgery, or different combinations of these treatments. Drops are not always effective, require patients' compliance,[8] and can produce side effects. Minimally invasive laser treatments, such as selective laser trabeculoplasty, are effective but may not be sufficient in all patients.[7] Filtrating glaucoma surgery is usually the strongest form of IOP control and can reduce or eliminate drop-dependence[4,6] but carries a higher risk of sight-threatening complications and requires specialized surgical training.

In recent years, minimally invasive glaucoma surgery (MIGS) procedures have been developed to provide drop-independent IOP control without the risks of major incisional surgery. Minimally invasive glaucoma surgery procedures can target different outflow pathways, but many aim to improve outflow through the Schlemm's canal[9] and are often performed in combination with cataract surgery (CS). Despite their popularity, there is little evidence about their effect on disease progression.[10] This is particularly concerning[11] because the expected gains in terms of IOP reduction are, on average, modest[12,13] and difficult to translate to an expected effect on VF preservation.[14]

The HORIZON trial was a large randomized controlled trial comparing CS with or without the implantation of a

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Hydrus Microstent (HMS) (Alcon, Inc).[12,15,16] The main outcome of the trial was the difference in washed-out IOP, which was statistically significant. Since additional medical treatment was permitted where necessary, the average medicated IOP was, expectedly, very similar between the 2 arms. Despite this, at 5 years, patients receiving CS-HMS had a lower incidence of additional incisional surgery[12] and a slower rate of average pointwise VF progression.[17]

One hypothesis to explain these differences is better IOP control with the HMS, which might not be captured by sporadic in-clinic measurements. Worse VF prognosis might also arise from early postoperative IOP spikes, which were more common in the standalone CS arm.[18] In this analysis, we test these hypotheses by analyzing different IOP metrics available from the HORIZON trial and their association with VF progression. We use a novel Bayesian hierarchical model to more accurately estimate the "true" rate of mean deviation (MD) progression and the effect of IOP.[19,20]

Methods

Patient Cohort

The HORIZON trial was a multicenter randomized clinical trial in which one eye of patients with open angle glaucoma and visually significant cataracts were randomized 2:1 to receive either standalone CS or CS in conjunction with an HMS implant. The protocol was approved by the local governing institutional review boards, ethics committees, and national regulatory agencies for all centers. The study was conducted according to the principles in the Declaration of Helsinki and complied with the Health Insurance Portability and Accountability Act and local patient privacy protection regulations. All study participants provided written informed consent before any procedure. The trial is registered in the National Library of Medicine database (clinicaltrials.gov identifier, NCT01539239). All glaucoma drops were stopped after surgery and were reintroduced as deemed necessary by the treating clinician. The main outcome of the trial was the difference in washed-out (unmedicated) IOP at 12 and 24 months. The duration of the trial was 5 years. Intraocular pressure was recorded at screening, at baseline (after medication washout), and then postoperatively at 1, 7, and 30 days and at 3, 6, 12, 18, 24, 36, 48, and 60 months. Patients were included if their baseline unmedicated IOP was between 22 and 31 mmHg. Patients with previous incisional glaucoma surgery, secondary or angle closure glaucoma, VF MD < -12 dB, macular degeneration, proliferative diabetic retinopathy, and high risk of progression from medication wash-out were excluded. The washout period was a minimum of 4 weeks for prostaglandin analogs, beta adrenergic blockers, or combination medications; 2 weeks for alpha adrenergic agonists or carbonic anhydrase inhibitors; 7 days for cholinergic agonists.[15]

Visual field tests were collected at baseline and 6, 12, 24, 36, 48, and 60 months after surgery using a Humphrey field analyzer (Zeiss Meditec), 24-2 pattern, and Swedish Interactive Thresholding Algorithm-Standard strategy. Only postoperative VFs were considered to avoid any systematic influence from cataract.[17] We have used the main cohort selection defined in our previous analysis (at least 3 reliable VF tests over at least 1 year of follow-up). Note that 3 tests is the minimum required for the hierarchical model used for this analysis (see next Statistical Analysis). Reliability was defined as a false positive error rate $\leq$ 15%.[21] This selection included 517 patients (93% of the total 556). A detailed procedure and flowchart for VF data extraction, selection, and exclusions have been previously published.[17] Relevant summary statistics are reported in Table 1.

Statistical Analysis

Visual Field Data. Mean deviation values were manually collected during the trial. However, due to data protection constraints, some centers recorded the tests with deliberately altered dates of birth, differing from the actual dates by several decades. This affected the accuracy of all age-adjusted metrics, including the MD. To improve the accuracy of our reporting, we used the visuaFields package for R[22] to calculate the MDs using the raw sensitivity values, the package's internal normative database, and the correct patient age.

Intraocular Pressure Metrics. We considered 4 different IOP metrics for our analysis.

- **Mean IOP**: the average postoperative IOP, excluding the postoperative day-1 IOP and the washed-out IOP values at 12 and 24 months. This included patients who were treated or untreated with medications throughout the study. To prevent bias, we used a weighted average to account for the uneven spacing between visits, which were clustered at the beginning of the trial.[17]
- **Day-1 IOP and IOP spikes**: The unmedicated IOP measured 1 day after surgery. Following Zebardast et al,[18] we also defined an IOP spike as an IOP $>$ 40 mmHg or 10 mmHg above the washed-out baseline IOP.
- **Washed-out mean and peak IOP**: The average and the highest washed-out (unmedicated) IOP values from the 12-month and 24-month visits combined. At each washed-out visit, 3 measurements were taken in the morning, at noon, and in the afternoon. Washout data were missing for 9 patients in the CS + HMS arm and 8 patients in the CS arm. The washed-out metrics for these patients were imputed with predictions from a simple linear model, fitted on data from all the other patients. The linear model included the following covariates: baseline age, sex, race, screening IOP, baseline IOP, number of medications at baseline, central corneal thickness, treatment arm, day-1 IOP, and mean intraocular pressure (MIOP). A sensitivity analysis was performed excluding eyes without washed-out data.

A secondary analysis was performed to test the association between washed-out IOP variability, calculated as the standard deviation (SD) of the IOP values at 12 and 24

Table 1. Descriptive Statistics for the 2 Arms of the Trial, for the Patients Included in This Analysis

Characteristic	CS $n = 165$*	CS-HMS $n = 352$*	*P* Value†
Baseline			
Age (yrs)	71 (66, 76)	72 (67, 76)	0.4
Race			0.7
Asian	8 (4.8%)	21 (6.0%)	
Black or African American	14 (8.5%)	39 (11%)	
Other	7 (4.2%)	11 (3.1%)	
White	136 (82%)	281 (80%)	
Screening IOP (mmHg)	18.0 (16.0, 20.0)	18.0 (16.0, 20.0)	0.6
Screening medications (*n*)	1 (1, 2)	1 (1, 2)	0.7
Baseline IOP (mmHg)	24.7 (23.0, 27.0)	24.7 (23.2, 27.1)	0.6
CCT (μm)	551 (525, 576)	549 (527, 570)	0.5
Screening MD (dB)	−2.82 (−5.16, −1.40)	−3.23 (−5.22, −1.71)	0.4
Postsurgery			
Average medications (*n*)	0.56 (0.00, 1.00)	0.00 (0.00, 0.44)	<0.001
Final medications (*n*)			<0.001
0	84 (51%)	243 (69%)	
1	52 (32%)	60 (17%)	
2	18 (11%)	31 (8.8%)	
3 or more	11 (6.7%)	18 (5.1%)	
Eyes with day-1 IOP spike	36 (22%)	7 (2.0%)	<0.001
Day-1 IOP (mmHg)	25.0 (20.0, 33.5)	15.0 (12.0, 20.3)	<0.001
Mean IOP (mmHg)	17.1 (15.8, 18.7)	16.6 (15.0, 18.2)	0.005
Mean washed-out IOP (mmHg)	18.5 (16.5, 20.8)	17.0 (15.0, 19.0)	<0.001
Peak washed-out IOP (mmHg)	21.0 (19.0, 24.0)	19.0 (17.0, 22.0)	<0.001
Washed-out IOP CoV (%)	0.11 (0.07, 0.14)	0.10 (0.07, 0.14)	0.6
Tests (*n*)	6 (5, 6)	6 (5, 6)	0.9
Follow-up (yrs)	4.9 (4.8, 5.0)	4.9 (4.8, 5.0)	0.3

CCT = central corneal thickness; CoV = coefficient of variation; CS = cataract surgery; HMS = Hydrus Microstent; IOP = intraocular pressure; MD = mean deviation.
The baseline intraocular pressure (IOP) was preoperative, after wash-out. Day-1 IOP spikes were defined as IOP > 40 mmHg or >10 mmHg above the baseline IOP. The average number of medications per patient was calculated from month 1 onward.
*Median (Q1, Q3); n (%).
†Wilcoxon rank sum test; Pearson's χ^2 test.

months, and the MD rate of progression. However, IOP variability is positively correlated with the average IOP. To isolate the effect of IOP variability, we calculated the IOP coefficient of variation (CoV = SD/washed-out MIOP, Fig S1, available at www.ophthalmologyglaucoma.org) and included both the IOP-CoV and the washed-out MIOP as predictors in the model.

Hierarchical Model. The statistical methodology has been explained in detail previously and has been validated with large clinical data sets and data from clinical trials.[19,20] In brief, the longitudinal rate of progression is estimated through a Bayesian implementation of a hierarchical linear model (or linear mixed-effect model [LMM]). The model calculates the linear rate of change of the VF MD over time. Random intercepts and slopes model the progression in each eye. Different from standard LMMs, which assume a Gaussian distribution for the random effects, our implementation assumes that the "true" slopes for the rate of change follow a signed-reversed exponential distribution. This incorporates the assumption that glaucoma cannot really improve (i.e., true slopes cannot be positive). The observed slopes are measured in the presence of noise (test variability) and can therefore have positive values. This noise is assumed to be Gaussian. The resulting distribution for the observed slopes is therefore an *exGaussian*, which results when adding Gaussian noise to observations from an exponential distribution. The SD of the Gaussian noise is equal to the standard error of the individual slopes, estimated from the data. Moreover, the average observed rate of progression can be positively biased by a learning effect, which is captured by the mean of the Gaussian component.[19] The estimated exponential component is therefore a characterization of the distribution of the "true" rates of progression and is able to more reliably capture its typically long negative tail.[19] This is particularly relevant for the HORIZON trial, in which the difference in the average rate of progression was strongly influenced by fast progressing eyes.[17]

Note that here and throughout the manuscript, the term "true" rate refers to the rate estimated from the exponential component of the *exGaussian* distribution.

The learning effect is expected to be similar for the 2 arms because of randomization. However, a sensitivity analysis was performed with this constraint to exclude the possibility that the difference in the "true" rate could arise from randomly large differences in learning.

Modeling the Effect of Intraocular Pressure and Treatment Arm. The model can accommodate covariates to study the effect of specific variables on the "true" rate of progression. In a recent publication using data from the United Kingdom Glaucoma Treatment Study (UKGTS),[20] we modeled the effect of IOP with a logarithmic link function.

$$\mu_{IOP} = -\exp(\beta_0 + \beta_1 IOP)$$

Where μ_{IOP} is the mean rate of progression estimated for a value of average IOP. Note that this is a simple linear relationship in logarithmic scale, before sign inversion, but it models a proportional change in linear scale. This has been shown to more accurately describe the effect of IOP on VF progression.[20] It also prevents the model from predicting positive slopes for low IOP values, which would inevitably result from using a simple LMM. The coefficients β_0 and β_1 describe the effect of IOP and can be tested for significance. The covariates can also be changed to represent the effect of treatment allocation (CS or CS-HMS), modeled as a binary factor. When combined with IOP, this provides an IOP-adjusted effect of treatment.

To facilitate the interpretation of the results, the IOP metrics were centered and standardized. This means that, for each IOP metric, β_0 represents the rate of progression at its average value and the β_1 represents the effect of one SD change from the mean. This allows the comparison of IOP metrics with very different scales and ranges of variation. The standardized effect is reported as a percentage change in the linear rate of progression. For example, a $\beta_1 = 0.1$ translates to an 11% increase in the rate of progression for each unit of SD. Because the different IOP metrics were correlated with each other, a separate model was constructed to evaluate each one individually.

Model Fitting. All models were fitted using Just Another Gibbs Sampler (JAGS), via R (R Foundation for Statistical Computing), running 4 independent Markov Chain Monte Carlo chains, using noninformative priors. We ran the chains for 50 000 iterations, using a thinning interval of 10 iterations and discarding the first 5000 iterations for burn-in. The posterior distributions were therefore estimated using 18 000 samples. Convergence of the chains was confirmed with the Gelman-Rubin index[23] (<1.1) for the parameters of interest (fixed effects) and by visual inspection of the chains.

A Bayesian equivalent of the P value was calculated following Makowski et al,[24] similarly to our previous publications.[17,20,25] Statistical significance was defined as a Bayesian P value < 0.05.

Results

Descriptive statistics of relevant variables for the selected sample are reported in Table 1. There were no significant differences in baseline characteristics, length of follow-ups, and number of VF tests per patient. Significant differences were present for the postoperative day-1 IOP, MIOP, and washed-out mean and peak IOPs. However, the mean (potentially medicated) IOP was very similar between the 2 arms, requiring more medications in the CS arm.

Group Analysis

The "true" MD rate was −0.55 [−0.72,−0.39] dB/year (mean [95% credible intervals]) for the CS arm and −0.30 [−0.38,−0.22] dB/year for the CS-HMS arm (44.6% [18.0, 64.2] reduction, $P = 0.004$). The estimated learning was 0.081 [−0.014, 0.182] dB/year in the CS-HMS arm and 0.23 [0.079, 0.386] dB/year in the CS arm ($P = 0.108$). The difference in the "true" rate remained significant when the learning effect was forced to be the same in both arms (−0.48 [−0.61,−0.36] dB/year in the CS arm, −0.32 [−0.40,−0.25] dB/year in the CS-HMS arm, $P = 0.011$). The results are shown in Figure 1 and Table 2.

Effect of Intraocular Pressure

Continuous Intraocular Pressure Modeling. We evaluated the effect of MIOP, day-1 IOP, and washed-out mean and peak IOP. These results are reported in Table 3 and Figure 2. Adjusting for the MIOP failed to account for the difference between the 2 arms, as indicated by the significant difference in the IOP-adjusted "true" rate of progression ($P = 0.002$). In contrast, there was no significant residual difference between the 2 arms after adjusting for the washed-out mean or peak IOP and for the day-1 IOP. Adjusting for washed-out peak IOP accounted for most of the treatment effect, providing the smallest and least significant difference between the 2 arms ($P = 0.396$). All IOP-adjusted rates are reported at the average value for each IOP metric in the whole cohort.

Because the IOP metrics are standardized, their proportional effects on the rate of MD progression can be compared despite their large differences in range and variability. All metrics had a statistically significant effect on the "true" rate of progression. The effect is reported as percentage change in the "true" rate of progression per SD or mmHg increase of each metric (more negative indicating faster progression, Fig 2). The standardized effect was very similar for the MIOP (−54.7 [−31.3, −86.6]%/SD or −19.8 [−11.9, −29.4]%/mmHg, $P < 0.001$), the washed-out MIOP (−39.0 [−16.9, −73.7]%/SD or −9.3 [−4.3, −16.1]%/mmHg, $P < 0.001$), and the washed-out peak IOP (−38.0 [−15.4, −79.0]%/SD or −7.5 [−3.3, −14.0]%/mmHg, $P < 0.001$). The smallest and least significant effect was from the postoperative day-1 IOP (−19.5 [−2.8, −38.9]%/SD or −1.8 [−0.3, −3.4]%/mmHg, $P = 0.022$). Plots of the overall prediction from the models (including the effect of learning) are provided in Figure S2 (available at www.ophthalmologyglaucoma.org).

The results for the washed-out metrics were similar after excluding eyes with imputed data: the estimates were −36.8 [−15.3, −69.5] %/SD or −8.8 [−3.9, −15.3] %/mmHg ($P < 0.001$) for the washed-out MIOP and −35.7 [−13.4, −79.2] %/SD or −7.1 [−2.9, −14.0] %/mmHg ($P < 0.001$) for the washed-out peak IOP. This analysis confirmed the lack of a significant difference between the 2 arms after adjusting for washed-out IOP metrics.

The effect of the washed-out IOP variability, quantified as the washed-out CoV (see Methods) and adjusted for the washed-out MIOP, was not significant ($P = 0.365$).

Effect of Day-1 Intraocular Pressure Spikes. In total, 43 patients (8.3%) had an IOP spike at postoperative day 1, 2% in the

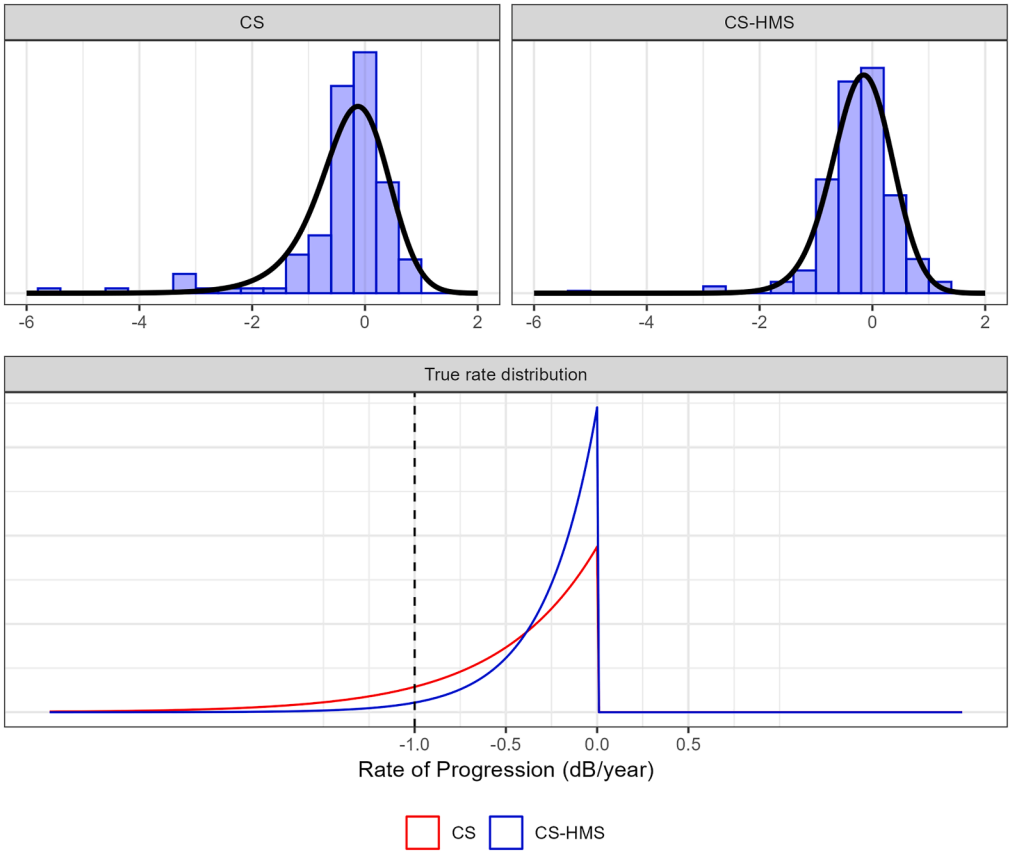

Figure 1. The top panels show the histograms for the distribution of the observed linear rates for the 2 arms of the trial. The black line shows the probability density function of the estimated *exGaussian* distribution. The histograms are normalized to represent probability densities rather than counts. The bottom panel shows a comparison of the distribution of "true" rates estimated for the 2 arms of the trial. The exponential component captures the longer negative tail in the distribution of rates for the cataract surgery arm. The vertical dashed line shows the cut-off for fast progressors. CS = cataract surgery; HMS = Hydrus microstent.

CS-HMS arm and 21.8% in the CS arm ($P < 0.001$). We compared the rate of progression between patients who did and did not spike at day 1. The "true" MD rate was −0.59 [−0.89,−0.37] dB/year in those who had an IOP spike at day 1 and −0.35 [−0.42,−0.27] dB/year in those who did not ($P = 0.029$). The learning effect was set to be equal between the 2 groups, due to the small sample size of the patients who had a day-1 IOP spike.

The main analysis was also repeated by excluding patients who had an IOP spike at postoperative day 1 from both arms (Fig S3, available at www.ophthalmologyglaucoma.org). Data from 474 eyes (345 in the CS-HMS arm) were analyzed. The "true" MD rate was −0.57 [−0.77,−0.40] dB/year for the CS arm and −0.28 [−0.36, −0.20 dB/year for the CS-HMS arm (50.4% [24.5, 68.8] reduction, $P = 0.001$). The results were confirmed when the learning effect was forced to be the same between the 2 groups. This confirmatory analysis was performed because of the statistically significant difference in the parameter associated with learning between the 2 arms in this subset. With this constraint, the "true" MD rate was −0.46 [−0.62,−0.33] dB/year for the CS arm and −0.31 [−0.39,−0.23] dB/year for the CS-HMS arm (31.5% [4.8, 52.5] reduction, $P = 0.026$). These results are reported in Table 4.

Table 2. Parameters Estimates [95% Confidence Intervals] From the Model

	CS-HMS	CS	*P* Value
Intercept (dB)	−2.61 [-2.89, −2.33]	−2.66 [−3.07, −2.24]	0.875
Rate (dB/yr)	−0.30 [−0.38, −0.22]	−0.55 [−0.72, −0.39]	0.004
Learning (dB/yr)	0.081 [−0.014, 0.182]	0.23 [0.079, 0.386]	0.108

CS = cataract surgery; HMS = Hydrus Microstent.

Discussion

Our results showed a significantly faster rate of MD progression in the CS arm compared to CS-HMS in the HORIZON trial, which appeared to be largely explained by differences in postoperative washed-out IOP. We used a novel and validated Bayesian model to estimate the "true" average rate of MD progression, minimizing the effect of

Table 3. Estimated "True" Rate of Progression [95% Credible Intervals] in the 2 Arms Adjusted for Each IOP Metric

IOP Adjustment	True Rate of Progression (dB/yr)		
	CS-HMS	*CS*	*P Value*
At mean IOP: 16.8 mmHg	−0.20 [−0.11, −0.31]	−0.43 [−0.30, −0.58]	0.002
At day 1 IOP: 20.3 mmHg	−0.31 [−0.23, −0.40]	−0.46 [−0.32, −0.64]	0.085
At washed-out peak IOP: 20.4 mmHg	−0.25 [−0.16, −0.35]	−0.32 [−0.14, −0.54]	0.396
At washed-out mean IOP: 17.8 mmHg	−0.25 [−0.16, −0.34]	−0.34 [−0.18, −0.53]	0.236

CS = cataract surgery; HMS = Hydrus Microstent; IOP = intraocular pressure.
A significant difference in rate between the 2 arms persisted after adjusting for the mean IOP. The values represent the estimated "true" rate at the sample average value for each IOP metric.

perimetric noise and learning.[19,20] Our analysis showed 43% slower MD progression in the CS-HMS arm, very similar to our results from point-wise data (47% in the same cohort[17]). These findings are also corroborated by the reduced incidence of incisional glaucoma surgery in the CS-HMS arm compared to the CS arm.[12]

The methodology used for this analysis has several advantages over standard LMMs. A direct estimation of the "true" rate of progression provides more generalizable estimates across different populations, because it reduces the bias introduced by perimetric learning. Most of the patients in HORIZON would not be newly diagnosed, and the learning is expected to be smaller than other trials recruiting naive patients. Indeed, the learning effect was smaller than the one estimated in UKGTS.[20] However, learning can persist for many tests and affect even relatively long VF series.[19,26] In the main analysis, the learning effect was not significantly different between the

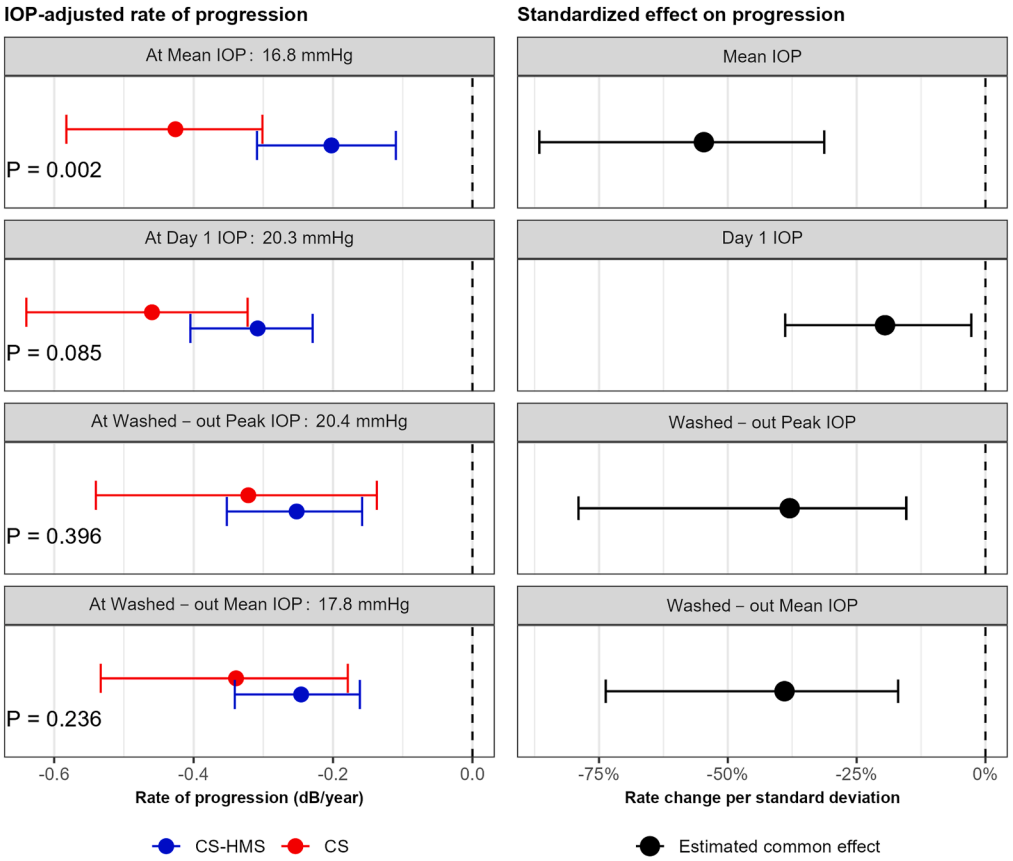

Figure 2. Estimates (dots) and 95% credible intervals (error bars) for the IOP-adjusted "true" rate of progression in each arm, at the average IOP metric (left panels) and for the proportional effect of each standardized IOP metric on the "true" rate of progression (the negative sign indicates faster deterioration per SD increase). CS = cataract surgery; HMS = Hydrus microstent; IOP = intraocular pressure; wo = wash-out; SD = standard deviation.

Table 4. Parameters Estimates [95% Confidence Intervals] from the Models Comparing the 2 Arms after Removing Eyes with Day-1 IOP Spikes and Comparing the Eyes Which Did or Did Not Experience a Day-1 IOP Spike

	Day-1 IOP Spike			Eyes with IOP Spikes Excluded		
	No IOP Spike at day 1	*IOP Spike at day 1*	*P Value*	*CS-HMS*	*CS*	*P Value*
Intercept (dB)	−2.65 [−2.89, −2.40]	−2.41 [−3.22, −1.61]	0.581	−2.60 [−2.89, −2.31]	−2.77 [−3.24, −2.31]	0.539
Rate (dB/yr)	−0.35 [−0.42, −0.27]	−0.59 [−0.89, −0.37]	0.029	−0.28 [−0.36, −0.20]	−0.57 [−0.77, −0.40]	0.001
Learning (dB/yr)	0.12 [0.041, 0.208]			0.069 [−0.027, 0.167]	0.29 [0.12, 0.47]	0.027

CS = cataract surgery; HMS = Hydrus Microstent; IOP = intraocular pressure.
For the latter model, the learning was set to be the same across both groups given the small number of eyes with an IOP spike (N = 43).

2 arms. This is expected as a result of randomization. However, because the learning effect is front-loaded, average differences can arise, for example, when one arm has a shorter follow-up. This was not the case, on average, in our cohort (Table 1). We have also previously shown that, despite being front-loaded, modeling learning as an average effect over the whole VF series allows a consistent estimation of the distribution of "true" rates of progression.[19] The treatment effect estimates are also more generalizable because they are defined as proportional changes of the exponential distribution of "true" rates.[20] This proportionality, enforced by the choice of the exponential distribution, could be more directly translated to other populations with different expected average rates of progression. Finally, our improved model is better suited to capture the typically negatively skewed distribution of rates of progression.[19,27] This is particularly relevant in HORIZON because we have shown that the average difference between the 2 arms was greatly influenced by fast progressors.[17] The use of the exponential distribution also allows a direct estimate of the proportion of eyes whose "true" rate of MD progression is faster than a specified threshold. For example, in the main analysis, the estimated proportion of fast progressors (RoP < -1 dB/year) was 3.6% [1.0, 7.2] in the CS-HMS arm and 16.0% [7.7, 25.1] in the CS arm (Fig 1).

It should be noted that, by reducing the bias due to learning, the estimated "true" rate is expected to be more negative than commonly reported average rates of progression. However, estimates similar to a standard LMM can be easily calculated by adding the estimated average "true" rate to the estimated learning: −0.21 dB/year for CS-HMS and −0.32 dB/year for CS. The average overall rate for the CS group is therefore consistent with commonly reported average rates in treated glaucoma populations with mild to moderate glaucoma[19,28] and in glaucoma patients after CS.[29]

The model is also particularly well adapted to capture the nonlinear effect of IOP on the rate of perimetric loss.[20,30] These results address important questions regarding the preservation of VF in HORIZON. In Montesano et al,[17] the MIOP alone failed to account for the difference between the 2 arms of the trial; that is, the significant difference persisted after adjusting for the MIOP, which included patients who were medicated or unmedicated throughout the study. This finding was replicated in the current analysis (Table 3 and Fig 2). This is both reassuring, since we would expect clinicians to treat to target IOP postoperatively by adding medications as needed, and unsurprising, since the difference between the 2 groups in MIOP (medicated or unmedicated) was modest in the first place, although statistically significant in the cohort we analyzed (Table 1). We speculated that such an unexplained difference in the rate of VF progression could be due to a protective effect offered by the HMS against undetected episodes of elevated IOP outside clinic hours. These IOP fluctuations could be due to the natural variability in glaucoma patients, increased IOP fluctuations with medications,[31] or gaps in compliance with medications.[8] For this analysis, we hypothesized that washed-out mean and peak IOP could serve as surrogates of such fluctuations, because they recorded the unmedicated IOP at multiple timepoints during the day. Indeed, adjusting for these IOP metrics greatly reduced the difference in the average "true" rate of progression between CS and CS-HMS, making it not significant. Importantly, their standardized effect was very similar to that of the MIOP (Table 3 and Fig 2). Taken together, these results provide evidence to support that the HMS preserves VF by achieving better drop-independent IOP control. Similar results were found, for example, when analyzing the VF outcomes in the Laser in Glaucoma and Ocular Hypertension Trial,[32] showing a slower rate in the selective laser trabeculoplasty-first arm. We have recently analyzed the 6-year VF MD data with the same methodology used for this analysis and confirmed these results.[28] It is interesting to note that the estimated effect for the washed-out mean (−9.3% [−4.3, −16.1]/mmHg) and peak (−7.5% [−3.3, −14.0]/mmHg) IOP were both within the confidence intervals estimated for the effect of the average IOP in UKGTS [−7.38% [−4.10,−10.97]/mmHg].[20] The washed-out IOP would be the most similar metric to the average IOP in UKGTS because it would not be affected by treatment escalation and would cover a comparable range. These similarities give confidence in the generalizability of our findings and further support the idea of washed-out IOP as a valid and robust surrogate for the effect of IOP of VF progression.

Analyses of data from landmark clinical trials such as the UKGTS and the Early Manifest Glaucoma Trial have shown little effect of IOP SD after adjusting for the

MIOP,[33,34] suggesting that fluctuations are relevant to the extent that they contribute to increasing the overall exposure to high IOP. It is important to note that such an analysis was possible in the UKGTS and the Early Manifest Glaucoma Trial because they observed patients without treatment modification for an extended period of time. This is profoundly different from trials in which treatment is escalated according to clinical practice: patients with unstable disease (because of uncontrolled IOP and/or progression) will have their treatment escalated more frequently, which results in larger intervisit IOP variation. This would introduce a spurious association between IOP variability and VF progression, biasing the results. However, in HORIZON, patients had multiple measurements during 2 postoperative wash-out sessions, which would be independent of treatment escalation. Our analysis of the IOP-CoV did not show any significant association between IOP variability and the rate of MD progression ($P = 0.365$), confirming previous results. Analyzing the impact of intervisit IOP change using a time-varying model will be the objective of future work.

Our analysis did not explicitly account for the number of medications used because such a metric would be correlated with the average potentially medicated IOP. Moreover, because treatment was escalated as clinically required in HORIZON, patients with uncontrolled glaucoma and potentially progressing VF were more likely to be prescribed additional medications. Any association between increased treatment and faster progression would be, therefore, biased by design. Specific medications could have different direct effects on glaucoma deterioration, besides their intended effect on IOP.[35] Unfortunately, the study design of HORIZON does not allow an unbiased investigation of the effect of individual medications, which would require a randomized allocation to different individual IOP-lowering treatments.

There is also a chance that medication wash-outs might have directly caused harm and determined faster VF deterioration in a subset of patients. This is unlikely because the wash-out periods were of relatively short duration (4 weeks). The likelihood of the observed difference being a consequence of direct harm from wash-out is further reduced by the fact that only 3 patients of those on medications at 12 and 24 months in the selected cohort had a peak washed-out IOP $\geq$ 35 mmHg. The difference in the rate of progression remained significant after excluding these 3 patients ($P = 0.033$). Like for the intervisit IOP change, estimating the direct impact of short wash-out periods would require carefully modeling the time-varying effect of IOP and will be the objective of future work.

Another possible explanation for the differences in rate of progression in HORIZON was a knock-on effect from IOP "spikes" at day 1 after surgery. These were more than 10 times more common in the CS arm[18] (Table 1) and conceivably might have affected the long-term health of the optic nerve during the trial. This is an important hypothesis to explore because it would greatly change the interpretation of the VF outcomes in HORIZON. When analyzed as a continuous variable, the postoperative day-1 IOP was significantly associated with the "true" average rate of progression (Table 3 and Fig 2). However, it also had the smallest standardized effect of all the IOP metrics (less than half that of MIOP and approximately half that of the WO IOP metrics). Adjusting for the day-1 IOP also resulted in a nonsignificant difference between the 2 arms, but the residual difference was much larger in magnitude compared to the washed-out metrics and the P value much smaller. It should be noted that instances of elevated day-1 IOP were promptly treated[18] and this would have further reduced the likelihood of a direct impact on VF deterioration.

One key limitation of these analyses is that, without a dedicated, carefully designed study, the contributions of individual IOP metrics are impossible to fully disentangle because of their correlations. For example, the postoperative day-1 IOP was significantly correlated with all other IOP metrics (range of $\rho = 0.30-0.32$, $P < 0.001$). This means, for example, that a mediated statistically significant effect of day-1 IOP on the rate of progression could result from the direct causal effect of other IOP parameters. For the same reason, the individual IOP metrics could not be combined as predictors in the same model. However, the subgroup analysis of eyes with day-1 IOP spike provides additional important information on this issue. These 43 eyes progressed at a significantly faster rate (Table 4). Nevertheless, the significant differences in the rate of progression between the CS and CS-HMS arms persisted after removing these eyes from the analysis (Table 4). The learning effect was significantly different after this selection, which is expected because such a selection would not affect the 2 arms evenly (i.e., it is not expected to preserve randomization). However, the results were confirmed when assuming the same learning for both arms. Taken together, these results make the postoperative day-1 IOP an unlikely candidate to explain the differences in the rate of progression between 2 arms of the HORIZON trial, but it remains possible that these spikes are in themselves of pathophysiological significance. Alternatively, day-1 IOP spikes may be a marker for eyes that are subject to larger upward IOP fluctuations (whether on treatment or during episodes without treatment, or both), that is, a provocative test of risk of progression. However, differently from the washed-out IOP measurements at 12 and 24 months, day-1 IOP spikes are often influenced by other factors related to the surgery itself (such as bleeding, inflammation, or retained viscoelastic material) and would therefore be an imperfect predictor.

It should be borne in mind that, despite being obtained in the context of a randomized controlled trial, these findings are the result of a post-hoc analysis. The HORIZON trial was not powered to detect differences in the rate of VF progression. However, the detailed characterization of washed-out IOP, the long follow-up, and the large number of patients, 93% of whom were retained in the current analysis, make these data valuable to understand the mechanisms by which MIGS procedures can help prevent VF progression. The slightly different cohort also explains the small differences observed in the washed-out IOPs compared to previous reports.[15]

Conclusions

This analysis used an improved statistical methodology to characterize the distribution of "true" rates of MD progression in the HORIZON trial. In addition to confirming previous findings, we provide important insights into how the quality of IOP control with a MIGS procedure can achieve better disease control despite seemingly similar medicated IOP measured in the clinic. Our findings underscore the importance of evaluating the effect of interventions on disease progression rather than IOP alone. This is relevant not only for randomized clinical trials but crucially also for retrospective analyses of data from clinical practice, in which washed-out IOP data are generally not available. Future work could explore the effect of baseline predictors of treatment effects, both in terms of VF preservation and IOP control, to help refine the indication for MIGS procedures in glaucoma patients.

Footnotes and Disclosures

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Abbreviations and Acronyms:
CoV = coefficient of variation; **CS** = cataract surgery; **HMS** = Hydrus Microstent; **IOP** = intraocular pressure; **LMM** = linear mixed-effect model; **MD** = mean deviation; **MIGS** = minimally invasive glaucoma surgery; **MIOP** = mean intraocular pressure; **SD** = standard deviation; **VF** = visual field; **WO** = washed-out.

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