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The Rationale for Applying a Visual Field Rate of Progression Analysis Using a Hierarchical, Censored, Bayesian Model to the 5-Year HORIZON Data

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The Rationale for Applying a Visual Field Rate of Progression Analysis Using a Hierarchical, Censored, Bayesian Model to the 5-Year HORIZON Data

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KEY TAKEAWAY POINTS

- The clinical relevance of visual fields has progressed over time, and is a relevant functional indicator of the status of a patient's glaucoma
- Standardized automated perimetry has been an essential tool to help best guide disease management for glaucoma patients
- Several models beyond those found within standardized automated perimetry have attempted to better predict progression of visual field loss
- A hierarchical model that has the ability to describe the rates of progression between groups as well as at Garway-Heath clusters and point locations, and that accounts for censoring of 0 dB readings may provide practical advantages and can identify deeper insight into identified patterns of visual field loss
- A model by Montesano et al that was used in the Laser in Glaucoma and Ocular Hypertension Trial (LiGHT) and Treatment of Advanced Glaucoma Study (TAGS) was applied in a retrospective, post-hoc manner to the 5-year visual field data of the HORIZON Trial.
- This post-hoc analysis revealed a difference in the rate of progression between groups, but it was apparent that there were a greater number of fast progressors in the cataract surgery-alone group that could account for these differences.
- A number of limitations to this analysis must be understood to interpret these findings within context

HISTORY AND EVOLUTION OF VISUAL FIELDS

Open-angle glaucoma is a leading cause of irreversible blindness worldwide.[1] Glaucoma describes a group of progressive optic neuropathies characterized by retinal ganglion cell and nerve fiber layer degeneration that change the optic nerve head.[2] Achieving early IOP control may reduce progressive loss of vision,[3] and functions as the mainstay of current treatment modalities. Typically, the general rule is to exhaust optimal medical treatment prior to considering the need for procedural or surgical management. Data from the Laser in Glaucoma and Ocular Hypertension Trial (LiGHT) has challenged this assertion of primary medical treatment to achieve an intraocular pressure (IOP) goal. The use of focused energy treatments to increase aqueous outflow, such as Selective Laser Trabeculoplasty (SLT),[4,5] has shown success independent of medication.

On the surgical front, traditional glaucoma operations (trabeculectomy or glaucoma drainage devices) are very effective in reducing IOP. However, about 1 of every 3 patients develop some sort of early perioperative complication, with nearly 1 of every 5 requiring a reoperation.[6] The use of the trabecular bypass concept via trabeculectomy or aqueous shunts has advanced over time, with the goal of providing more reliable, less invasive control of intraocular pressure.[7] The behavior of delaying surgical treatment until the patient has definitive

progression on maximum medical therapy has, thankfully, been favorably altered with the introduction of multiple effective microinvasive glaucoma surgery (MIGS) options.[8] In a study evaluating the trends of glaucoma surgeries in Medicare Patients from 1994-2017, the use of MIGS procedures has rapidly increased, now accounting for a significant majority of glaucoma surgeries.[9]

The description of visual fields dates back to the time of Hippocrates (5th Century B.C.) when he described awareness of hemianopic visual field defects occurring with brain disease.[18] In 1668, Mariotte reported the correlation of the physiologic blind spot with the location of the optic disc. It was reported that Mariotte would optically "behead" individuals by closing one eye and fixate his open eye to the location of a person's head within his blind spot location.[19] Up until 1850, the nature of the visual field was slowly being discovered, to include its normal limitations, the functional capacities of its different components, as well as visual field changes that were associated with different disease processes. However, it was Albrecht von Graefe who many give credit to bringing perimetry and visual field testing to clinical ophthalmology in 1856. Perimetry was an indispensable part of von Graefe's clinical technique; he apparently complained that his colleagues did not perform visual field studies often enough to do a complete examination in order to improve their diagnostic acumen.[18]

Early perimetric studies included observations while a stimulus was moved around the subject's eye. Kinetic perimetry involves the movement of stimuli of constant size and luminance to determine the limits of the visual field. It suffers from variations in patient reaction time and speed of target movement: these may tend to produce unreliable results.

Over time, pioneers, such as Hans Goldman, standardized the measurement of visual fields. The basic principles that he proposed in 1945 with the development of his manual Goldman Perimeter are, essentially, still in use, today. With this standardization, it was possible to conceptualize automation of this process. Under the direction of Franz Fankhauser, the Octopus automated perimeter (the first commercially available automated perimeter) became available in 1974. The basic principles of interpretation have not changed, but software and hardware advances have shortened test-taking time and improved accuracy and reliability. Other perimeters, such as the Humphrey Automated visual field perimeter (Carl Zeiss, Meditech; Dublin, CA; USA) have also been developed. Currently, perimetry is commonly performed using the 24-2 Swedish Interactive Thresholding Algorithm (SITA) standard protocol. However, the subjective nature of the test makes it important to truly differentiate disease-related defects from artifact and noise abnormalities.

Glaucoma is a progressive disease requiring regular follow-up, and IOP, the only modifiable risk factor, is used to measure the efficacy of glaucoma treatment. However, the maximum clinic IOP measurements may underestimate mean daily maximum IOPs measured outside of clinic hours.[10] Furthermore, the Advanced Glaucoma Intervention Study showed that IOP fluctuations of ≥3 mmHg were consistently associated with VF progression.[11] It is, therefore, critical to determine the rate of disease progression during the treatment course of a glaucoma patient to gauge long-term treatment efficacy;[12] this is a fundamental aspect of glaucoma management.[13] Despite treatment, glaucoma oftentimes progresses, and because of this, monitoring these changes as well as the rates of change is important.[14] Some of the most common ways of performing this include observing the optic nerve head and measuring the visual fields.[15] However, the ability to detect the progression of visual field defects remains one of the most challenging aspects of glaucoma management, even by experienced observers.[14] The combination of both structural and functional optic nerve assessment may improve the ability to detect glaucoma progression over either modality alone.[16] Identifying test locations that are statistically different from prior tests as well as the emergence of rate-based progression assessment and event-based assessment via software can also aid in detection of visual field progression.[17] Effectively and accurately following the progression of glaucoma is, therefore, not a simple task.

Reliability indices found on the automated visual field printout may be subject to interpretation. False positives, indicating a trigger press when

no stimulus was present, is directly measured and may be the most significant indicator of reliability. Because false negatives are a derived value, they have lesser significance as a reliability indicator. Fixation losses, however, have little impact on reliability in patients with established glaucoma.[21] Furthermore, if fixation losses are identified during measurement in a clinical trial, protocol would likely dictate repeating the test.

It is important to note that for other than the raw sensitivities, the remaining visual field sensitivities of a test are compared to an age-matched "normal" patient. Grey-scale total deviation (TD) and pattern standard deviation (PSD) plots can provide direction of where visual fields exist at that particular point in time. PSD is helpful to discern the trend when factors that globally affect the visual field (i.e. cataracts) are present. Global indices, such as mean deviation (MD) are a convenient way to provide an overall snapshot of overall change in the visual field. Effectors of the global visual field, such as cataracts, have an effect on these global indices, and so preoperative comparisons for cataract surgery to that measured postoperatively would likely show an improvement. This is an important consideration for clinical studies that are attempting to evaluate the effect of a treatment on visual field preservation or loss. When treatment is applied to a population, the use of global indices such as MD may indicate a trend, but oftentimes, small changes withing the visual field cannot be adequately measured using global indices over time. Several studies have reported no changes in MD over time within a group of subjects, but does that mean that no visual field loss has actually occurred within that group? This question has led researchers to attempt defining a model that can more accurately describe visual field changes in groups of subjects undergoing different treatments. Loss of visual fields can be a rather slow process for some patients, or it can be a more rapid process for others.

EVOLUTION OF MODELS TO DESCRIBE PROGRESSION OF VISUAL FIELD LOSS

Over the last several years, efforts have been made to create hierarchical models that can account for different treatment groups as well as describe visual field loss progression within point and cluster locations (6 clusters, as defined by Garway-Heath, et al)[22] within these groups. Such a model may provide practical advantages and can identify deeper insight into any identified patterns of visual field loss (See Figure 1).

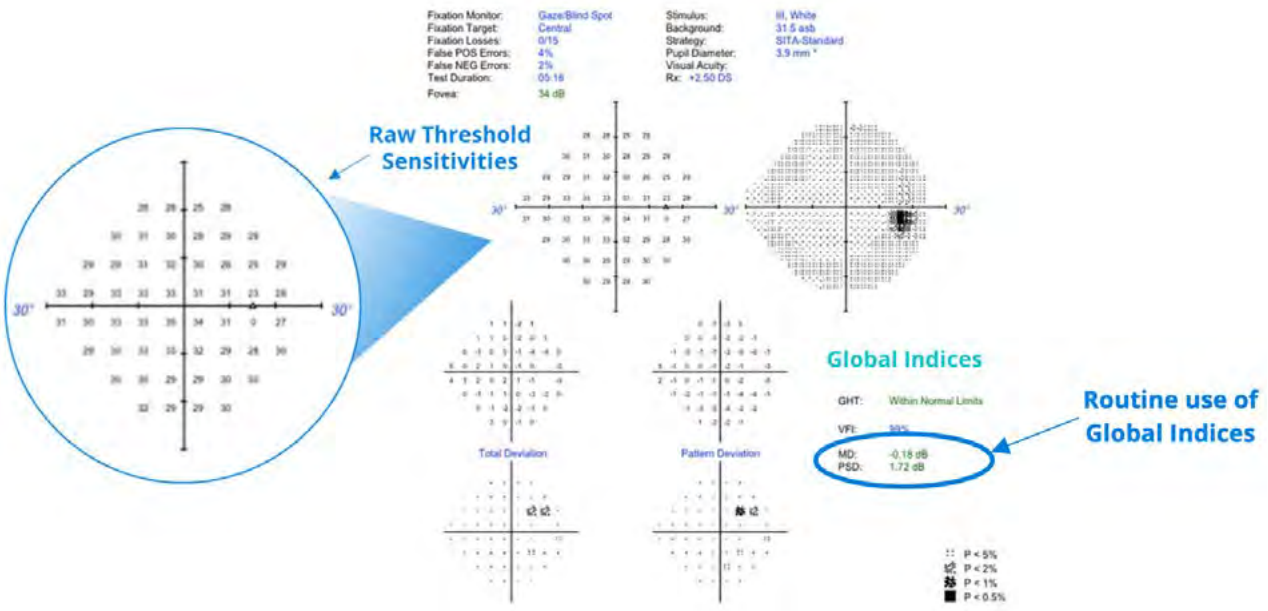


Figure 1: The use of raw threshold sensitivities in pointwise analysis as opposed to global indices, such as mean deviation (MD) or pattern standard deviation (PSD)

Zhu et al in 2014 described a Bayesian method, called Analysis with Non-Stationary Weibull Error Regression and Spatial enhancement (ANSWERS), which focused more on modeling the heteroskedasticity of VF data (the variability in measured sensitivity increases with the level of VF damage) by using a parameter to detect progression that combines the results at different locations to estimate the 'probability of no-deterioration'. This model relies on a combination of pointwise regression models fitted individually that are linked through spatial correlations and was able to detect VF deterioration significantly earlier than conventional linear regression methods at matched false positive rates. This model was also significantly better when using short time VF data series, for which the spatial correlation utilized may also have accounted for this improvement. In essence, ANSWERS used test-retest data to model the variability of observed responses, which in effect used estimated variability as a weighting method for the observations.[23]

One aspect of pointwise sensitivity data that was not addressed with models, such as the ANSWERS method, was the inherent limitation of what is measured by the testing method. VF sensitivity on the Humphrey field analyzer, one of the most commonly used devices, is measured over a limited range, with the scale ranging from 50 dB to 0 dB.[24] At points within the visual field that are expected to have slow progression (i.e. perimacular areas), the slope of VF loss is typically relatively flat with little loss (Figure 2).

In contrast, when the superior visual field point sensitivities are followed over time, the slope of VF loss can be steeper. When the sensitivity value reaches its lowest point (0 dB, representing the highest light stimulus during the test), an artifact of ceasing VF loss may become apparent. If this 0 dB point occurs before the last measured time point in years, the lowest reported value will remail at 0 db. Use of any linear regression method to approximate the slope of VF loss over time would bias a lower rate for the VF loss (Figure 3, Black regression line).

To address this issue, censoring of 0 dB sensitivity values in modelling could be a key improvement. This is represented by the red regression line in Figure 2, which may more closely represent the actual clinical sensitivity loss for this point of the visual field more accurately; the dotted red line is added for clarity. Other options, such as asymptotic modeling through exponential decay, have been proposed to deal with the 0 dB limits (Figure 4).[25] However, the limited stimulus range of the testing device and the underlying nature of the data do not support this methodology.[24]

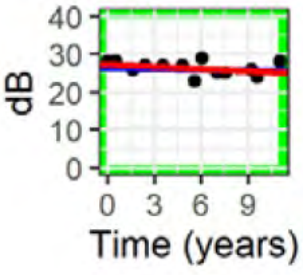


Figure 2: The slope of VF sensitivity loss at this perimacular point is relatively flat over time. From Montesano G, et al. Hierarchical censored Bayesian analysis of visual field progression. Transl Vis Sci Technol. 2021;10(12):4.[24]

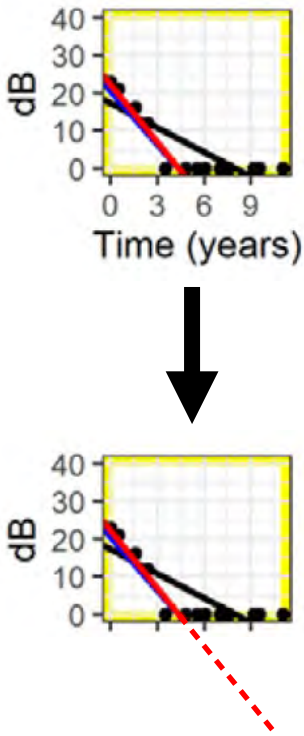


Figure 3: The slope of the regression line at this point over time for sensitivity loss biases a lower rate when the 0 dB sensitivities are included as a result of the lowest measured sensitivity (0 dB) for the test device. From Montesano G, et al. Hierarchical censored Bayesian analysis of visual field progression. Transl Vis Sci Technol. 2021;10(12):4.[24]

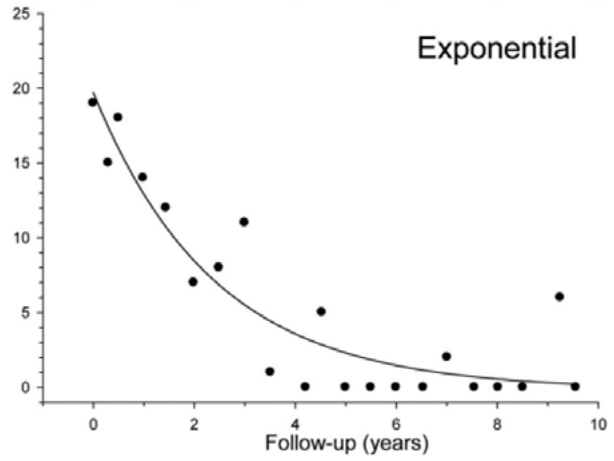


Figure 4: Fitting the sensitivity data using an exponential model to account for the "bottoming-out" of the VF data. From Caprioli J, et al. A method to measure and predict rates of regional visual field decay in glaucoma. Invest Ophthalmol Vis Sci. 2011 Jul 1;52(7):4765-73.[25]

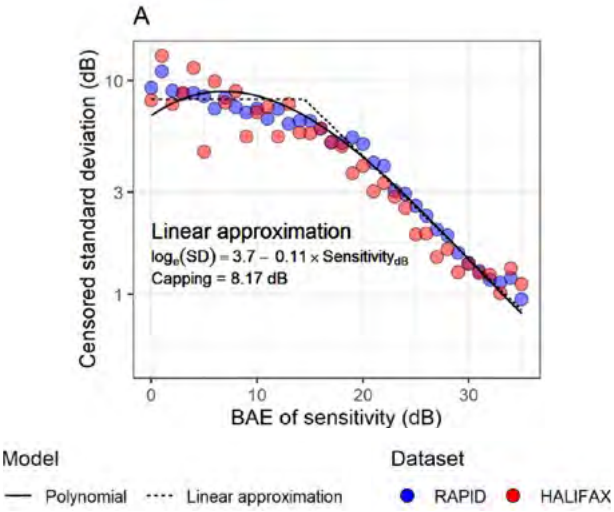


Figure 5: Changes in the censored standard deviation for test-retest variability at different sensitivity levels and the corresponding predictions from the polynomial model and the bi-linear approximation. BAE - best available estimate. From Montesano G, et al. Transl Vis Sci Technol. 2021;10(12):4.[24]

Montesano et al in 2021 published on the development of a model that incorporated several of these above-mentioned elements to define the visual field loss from a clinical database of visual field data. Their approach differs from previous attempts in its modeling of spatial correlations within the VF; in their model, a full hierarchical approach allowed VF clusters to be represented as an intermediate level in the hierarchy. Their model also accounted for censoring of 0 dB sensitivity levels. Three Bayesian models were proposed and tested: a linear regression of pointwise values over time (Hi-linear); an identical model to the Hi-linear that included a normal error distribution censored at 0 dB (Hi-censored); a model that also used a censored normal error distribution for sensitivity, but the Standard Deviation of the error distribution was heteroskedastic and linked to the estimated sensitivity using linear approximation (Hi-HSK).[24]

With these elements in mind, the model was constructed using the longitudinal VF data extracted from the electronic medical records of 5 UK glaucoma clinics. This clinic dataset included all patients with at least 10 VFs recorded over at least four years with a mean deviation worse than −2 dB in at least two VFs. This aggregated database was composed of 576,615 VFs from 71,361 people over a time span from April 2000 and March 2015. It becomes clear as to why Bayesian models, which have the capability to address the size and complexity of these data sets, was chosen as the tool for the analysis.[24]

To address the need to correlate response variability at each point with sensitivity, a model was created using the first of 2 test-retest data sets with values from stable eyes with primary open angle glaucoma (the RAPID dataset). The value of using this short-term database is that little VF progression is expected, and the variability within this group can be tested accurately. Test repeats were performed in 146 eyes of 75 subjects undergoing a mean of 10 test repeats per eye over an average time period of 9 weeks, with a minimum of 3 tests for inclusion. The second test-retest data set (the HALIFAX Dataset) was used to create a stable series through permutations to quantify the false-positive discovery rate (FPR = 1 – specificity). This dataset is composed of 12 VF test repeats from 30 eyes of patients with glaucoma over 12 weeks. Fitting of the variability based on the RAPID database with a broken-stick linear approximation as well as a polynomial fit is shown in Figure 5.[24]

To compare the progression models fairly, all methods were based on sensitivity values or their aggregate measurement (i.e. mean sensitivity) to correctly model censoring and heteroskedasticity at the VF point level in the Bayesian models. Using various software packages to run these models, the data for point sensitivity and cluster sensitivity progression rates were achieved and a display of a representation of the three pointwise progression model predictions is displayed on Figure 6.[24]

All Bayesian models performed similarly when detecting global progression; compared to the other hierarchical models, the Hi-HSK model was slightly superior for shorter series, but less so for longer series. When further applied to cluster and location progression (a further benefit to this modelling scheme), the Bayesian hierarchical models performed much better than simple linear regression, with the Hi-HSK model outperforming the other two hierarchical models for both clusters and locations. However, there were minimal differences between the Hi-censored and the Hi-linear models. Regarding predictions, the mean absolute error was generally better for the hierarchical models compared to simple pointwise linear regression (one of the several models compared) as well as the prediction of no change, with minimal differences among the three hierarchical models.[24]

A description of the limitations of these hierarchical Bayesian models is beyond the scope of this summary. However, within these

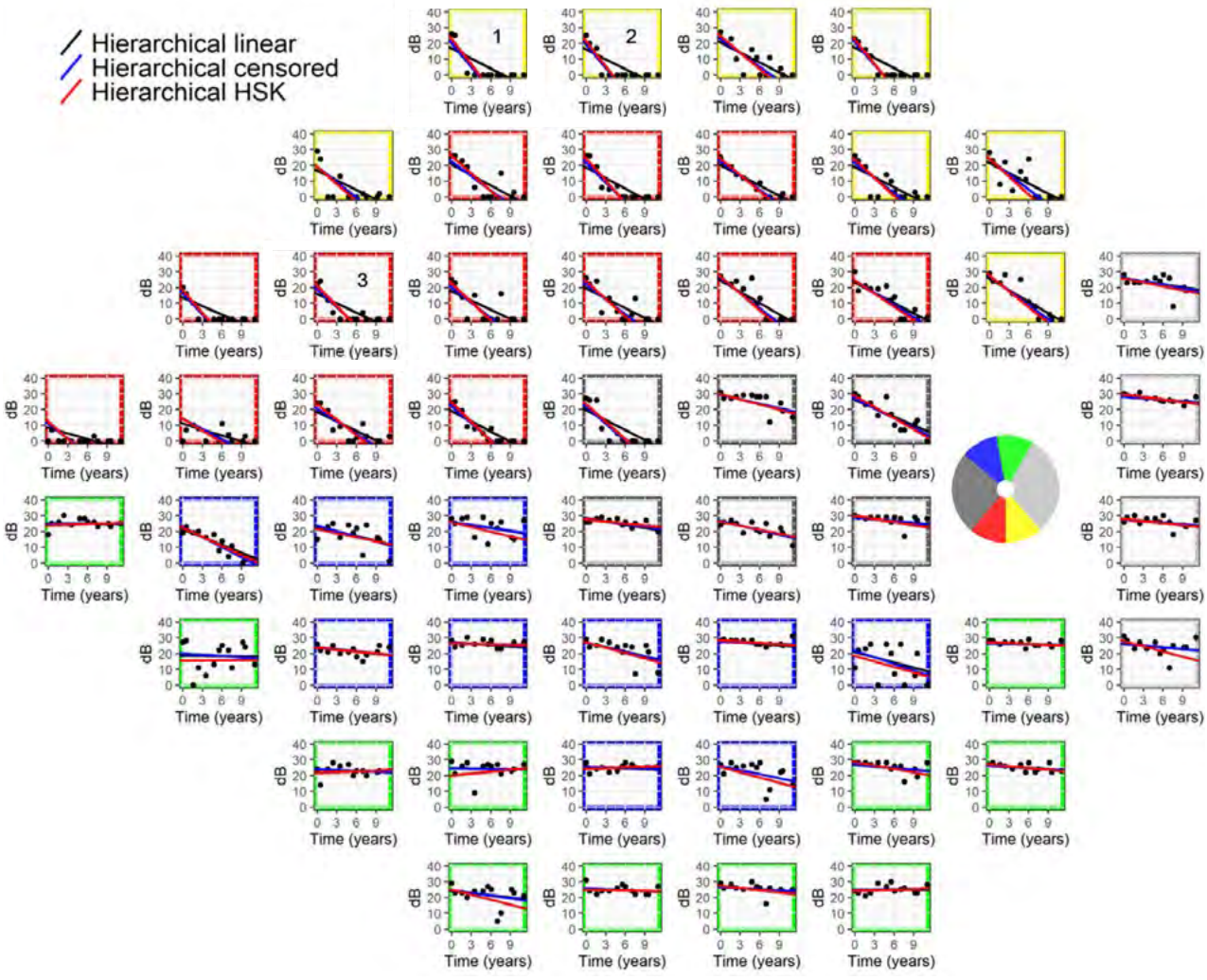


Figure 6: A visual field series, fitted with the 3 different hierarchical models indicated in the left upper corner. In the superior hemifield, it is evident how the censored models are less affected by the floor effect. The borders of the subplots are color-coded to indicate the cluster corresponding to different optic nerve head sectors. From Montesano G, et al. Transl Vis Sci Technol. 2021;10(12):4.[24]

limitations, an important application of this class of models would be for the analysis of visual field outcomes in clinical trials evaluating different glaucoma treatments. Primary outcomes for such a trial would need to be sensitive enough to detect glaucoma progression over the short time span of a trial. The described hierarchical structure could be extended such that individual subjects would constitute an additional level within the random effect structure, furthermore having fixed effects used to model the differences in the rate of progression between two trial arms. This approach could overcome the limitations from comparing survival curves of VF progression between the two trial arms, better utilizing the data to directly test the change in the rate of progression.[24]

APPLYING THE REVISED MODEL TO CLINICAL DATASETS, INCLUDING THE 5-YEAR HORIZON DATA

Application of a more complex hierarchical structure using the available pointwise data was analyzed by Montesano's group in the post-hoc evaluation of the Laser in Glaucoma and Ocular Hypertension Trial (LiGHT) data. The findings from applying this complex methodology to the 4-year data in that trial showed that naïve glaucoma patients initially treated with medication experienced a slightly larger proportion of rapid VF progression when compared to those initially treated with Selective LASER Trabeculoplasty.[26] This model was also recently applied in a post-hoc fashion to the 2-year results of the Treatment of Advanced Glaucoma Study (TAGS). Findings included more eyes progressing in the medication-first arm as compared to the trabeculectomy-first arm, but this difference was not significant. The cluster-specific rates of progression were also evaluated, but at 2 years, outcomes in the trabeculectomy-first group clusters were favored in 5 of 6 clusters, but the differences were, again, not significant.[27]

This hierarchical mixed effect model was also applied in a post-hoc manner to the 5-year visual field data collected during the HORIZON trial. The HORIZON trial was a prospective, randomized clinical registration trial of 556 patients (369 in the HYDRUS Microstent (Alcon, Fort Worth, TX; USA) with concurrent cataract surgery group and 187 in the cataract surgery-alone group) with mild to moderate primary open angle glaucoma. This trial compared the ≥20% IOP reduction success as well as the IOP reduction from a medication washed-out baseline between the groups at 2 years; 5-year safety data as well as the efficacy outcomes in the medication-free subgroup of patients were also assessed, as medication wash-out was not continued after 2 years.[28,29]

Findings from the HORIZON trial included 77.3% of the HYDRUS group eyes and 57.8% of the cataract surgery-alone group eyes (difference = 19.5%, $P < 0.001$) showing a ≥20% IOP reduction. Two-year mean unmedicated IOP reduction was -7.6 ± 4.1 mmHg in the HYDRUS group and -5.3 ± 3.9 mmHg in the cataract surgery-alone group (difference = -2.3 mmHg; $P < 0.001$). Furthermore, the mean number of medications was reduced at 2 years from a baseline of 1.7 ± 0.9 down to 0.3 ± 0.8 in the HYDRUS group, and from 1.7 ± 0.9 down to 0.7 ± 0.9 in the cataract surgery-alone group (difference = -0.4 medications; $P < 0.001$). The rate of medication-free patients at 2 years was 78% in the HYDRUS group and 48% for the cataract surgery-alone group. The rate of adverse events was comparable between groups, although there were more eyes with peripheral anterior synechiae (PAS) in the HYDRUS group as compared to the cataract surgery-only group.[28] Five-year data showed no sight-threatening adverse events in either group with 3.5% of eyes in the HYDRUS group and 4.3% of eyes in the cataract surgery-alone group with serious adverse events. There was no significant difference in safety outcomes from 2 to 5 years except for PAS, in which a significant difference between groups was found (14.6% in the HYDRUS group and 3.7% in the cataract surgery-alone group); however, a majority of eyes with PAS (8.7%) in the HYDRUS group were not device obstructing, and there was no difference in IOP control between HYDRUS patients with and without PAS. There was also a greater than 50% relative reduction rate of incisional secondary surgical interventions (to include trabeculectomy, tube shunt, gel stent, ECP/TSCP, non-penetrating) in the HYDRUS group (2.4%; 9/369) as compared to the cataract surgery-alone group (5.3%; 10/187).[30] The efficacy outcomes at 5 years showed that in the subgroup of medication-free eyes (wash-out was not continued after 2 years), 54.2% of HYDRUS group eyes as compared to 32.8% of cataract surgery-

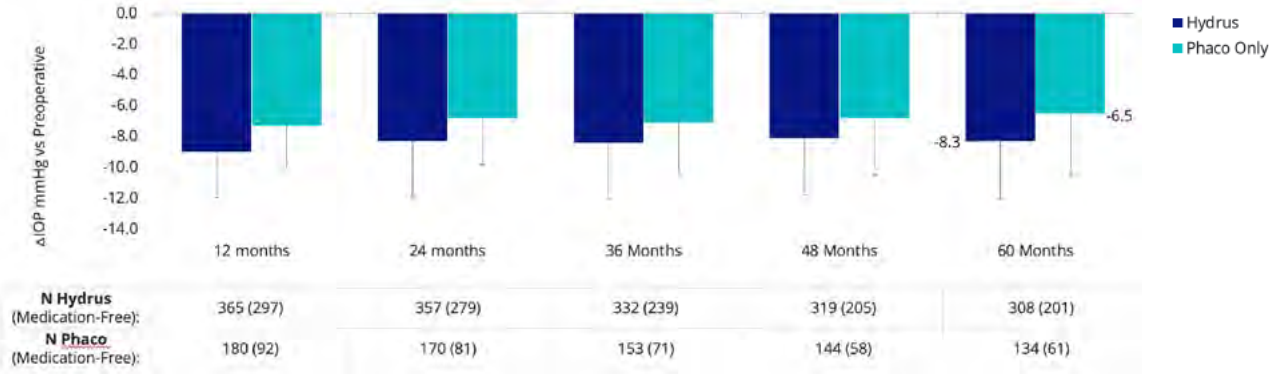


Figure 7: IOP Reduction from baseline over time in medication-free eyes between the HYDRUS and cataract surgery-alone groups.[29]

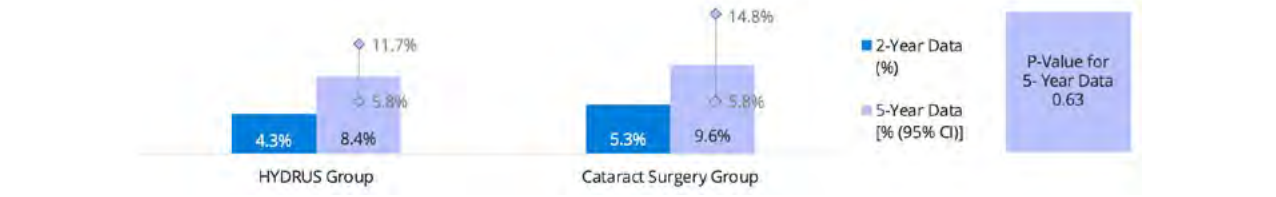


Figure 8: Mean Deviation visual field safety outcomes.[29]

alone group eyes achieved a ≥20% IOP reduction, and a total of 66% of HYDRUS group eyes and 46% of cataract surgery-alone eyes were medication-free. The HYDRUS group eyes consistently had a greater IOP reduction from baseline throughout the trial when compared to the cataract surgery-alone group, medication-free eyes (Figure 7). It is, however, important to recall that when all patients were included in the 5-year final IOP reported between groups, the HYDRUS group IOP was 16.8 ± 3.1 mmHg and the Cataract surgery-alone group IOP was 17.2 ± 3.2 mmHg (P=0.24).[29]

With regards to visual field data, the HORIZON trial used the Mean Deviation (MD) partially as an inclusion criterion (MD ≥-12 dB) as well as an adverse event defined as a MD loss at any time ≥2.5 dB from baseline; two additional tests were performed per protocol if this worsening was observed. The adverse event rate with regard to MD loss of ≥2.5 dB at 2 and 5 years is displayed on Figure 8.[29]

When comparing the HYDRUS group to the cataract surgery-alone group in the HORIZON trial, the IOP reducing outcomes with medication wash-out or medication-free subgroup analysis were significantly different at both 2 and 5 years. However, as stated above, the 5-year mean IOP was 16.8 ± 3.1 mmHg in the HYDRUS group and 17.2 ± 3.2 mmHg in the CS group (P = 0.24) for all patients, medicated and unmedicated. The Advanced Glaucoma Intervention Study did stipulate that IOP fluctuation of ≥3 mmHg compared to IOP fluctuations of <3 mmHg was consistently associated with VF progression.[11] Furthermore, De Moraes et al did some relevant work to help define clinically meaningful progression in clinical trials. Clinically meaningful progression corresponds to a slope worse than −0.5 dB/yr in ≥5 abnormal test locations; decreasing the rate of visual field progression by 30% in a trial lasting 12–18 months is also clinically meaningful.[31] Since the HORIZON protocol planned visual field measurements using Humphrey automated perimetry with the 24-2 SITA Standard at six postoperative timepoints (6, 12, 24, 36, 48 and 60 months), there was interest in performing a post-hoc analysis using the methodology as described by Montesano et al. It is important to note that the HORIZON trial did not include any prospectively defined statistical comparisons on MD worsening between groups. Table 1 shows the baseline as well as 2-year and

Table 1: Global VF Indices from the HORIZON Trial over time.[32]

	Baseline		2-Year		5-Year	
	HYDRUS	*CS-Only*	*HYDRUS*	*CS-Only*	*HYDRUS*	*CS-Only*
Mean Deviation	-3.611 ± 2.494	-3.611 ± 2.602	-2.863 ± 3.121	-3.281 ± 3.896	-3.511 ± 3.946	-3.313 ± 3.732
Pattern Standard Deviation	3.183 ± 2.176	3.131 ± 1.853	3.359 ± 2.572	3.464 ± 2.352	3.847 ± 2.995	3.609 ± 2.745

5-year global visual field metric data from the HORIZON trial; both groups were comparable regarding these metrics at the indicated time points.[32]

The previous discussion regarding the methodology of hierarchical modelling, above, is important. Some of the potential benefits of using the hierarchical methodology as compared to an analysis of global indices, such as mean deviation, include:

- Analysis of global indices may not be as sensitive as a pointwise analysis
- Focal VF loss is clinically characteristic of glaucomatous damage
- Hierarchical Methodology provides the spatial information to monitor glaucoma progression
- Rate of Progression (RoP) method can look at the VF progression at each cluster and/or location
- Rate of change can identify more rapidly-progressing patients who may need more intensive intervention

With this in mind, a study design for this post-hoc analysis of the 5-year HORIZON visual field data was undertaken. The primary endpoint was defined as the entire group Rate of Progression for the HYDRUS and cataract surgery-alone arms. The secondary endpoint was to repeat this analysis looking at the results from the Garway-Heath clusters as well as point locations in both groups. Observations were then grouped by location, VF cluster and eye in a hierarchical nested manner using hierarchical mixed effect models as described previously. The measurement floor at 0 dB was addressed by censoring the observations where no response was recorded (< 0 dB on the VF printout).[33,34] The authors reported P-values in their analysis, and are provided for information, as the relevance of P-values in a retrospective analysis is unclear.

Hard copies of the Humphrey visual field report printouts were digitized, taking special attention to identify the time since surgery at which the test results were obtained for each patient. These printouts and the digitized raw sensitivity values were compared for accuracy. After all available visual field data were obtained, those with a greater than 15% false positivity rate were excluded; this was the only metric used to establish the reliability of the VF test since, as stated previously, fixation losses and false negative errors may be poor indicators of reliability.[21] Furthermore, the presence of cataract increases visual field variability using both global and pointwise analysis, and changes in visual field caused by cataract removal may be blunted by this increased variability.[35] As a result, only postoperative visual field data were used and the preoperative baseline visual field data were excluded. Finally, the VFs of subjects with at least 3 VF measurements, with the last one at least one year after the date of surgery, were included. Figure 9 shows the flow of the selection steps for the data used in the analysis, with a final number of 2025 VFs from 352 subjects in the HYDRUS arm and 941 VFs from 165 subjects in the cataract surgery-alone arm.[33,34] Recall

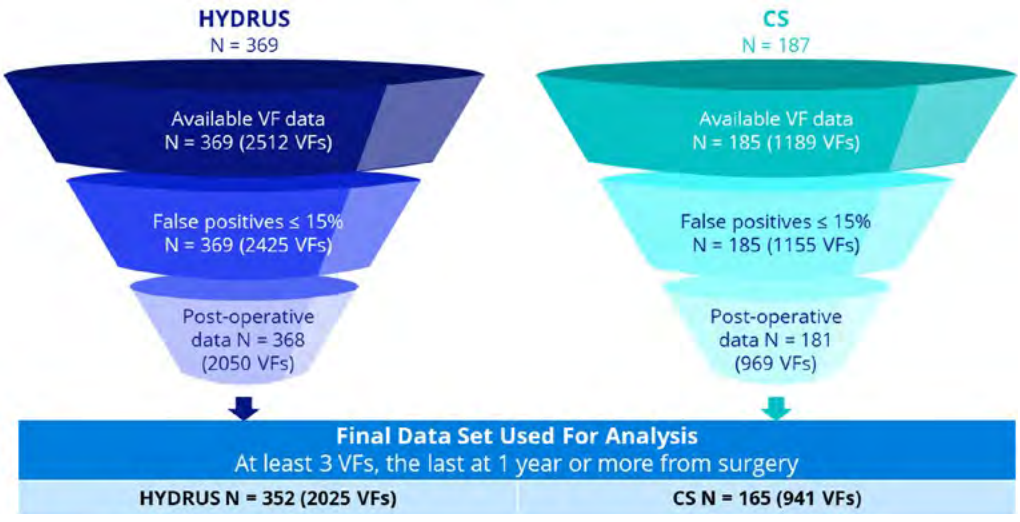


Figure 9: Flow of the data selected for use in the Rate of Progression Analysis.[33,34]

Table 2: Demographics of the data for the Rate of Progression analysis.The authors reported P-values for this retrospective analysis.[33,34]

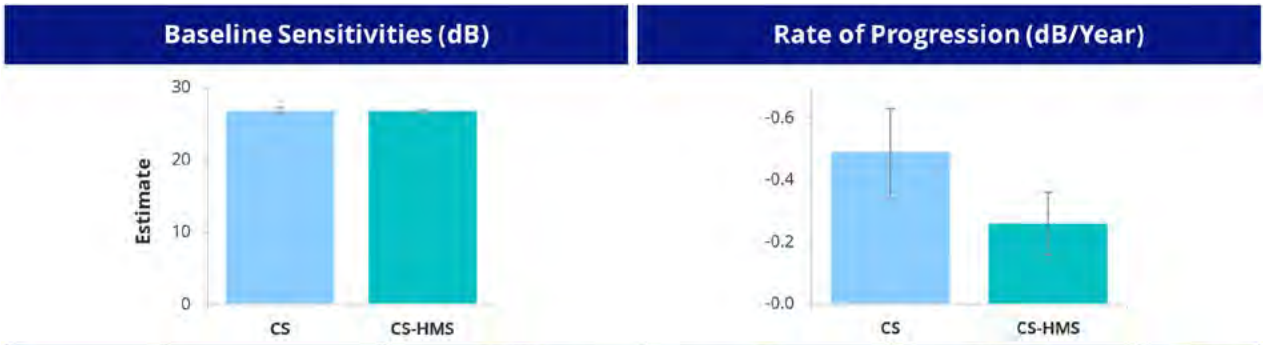
	CS-HMS (N = 352)	CS (N = 165)	P-value
Age (year)	70 [70, 80]	70 [70, 80]	0.665
Sex (Female/Male)	195/157	96/69	0.617
Race Asian	21	8	0.686
Black or AA	39	14	
Other	11	7	
White	281	136	
Corneal thickness (μm)	550 [530, 570]	550 [530, 580]	0.465
Baseline MD (dB)	-3.22 [-5.21, -1.71]	-2.82 [-5.16, -1.40]	0.639
Baseline IOP (mmHg)	18 [16, 20]	18 [16, 20]	0.691
Screening IOP (mmHg)	25 [23, 27]	25 [23, 27]	0.551
# Meds at baseline	1 [1, 2]	1 [1, 2]	0.699
# Post-operative VF	6 [5, 6]	6 [5, 6]	0.872
Follow-up time (years)	4.9 [4.8, 5.0]	4.9 [4.8, 5.0]	0.176

AA = African American; VF = Visual Field; MD = Mean Deviation; IOP = Intraocular pressure; CS = Cataract Surgery; HMS = HYDRUS Microstent

that the HORIZON trial had a 2:1 recruitment for HYDRUS eyes compared to cataract surgery-alone eyes.[28]

Table 2 shows the demographics of the 2 visual field groups to be evaluated in this analysis. Note that both arms had, on average, 4.9 years of VF follow-up data and an average of 6 VFs per eye, with all other characteristics being comparable between groups.[33,34]

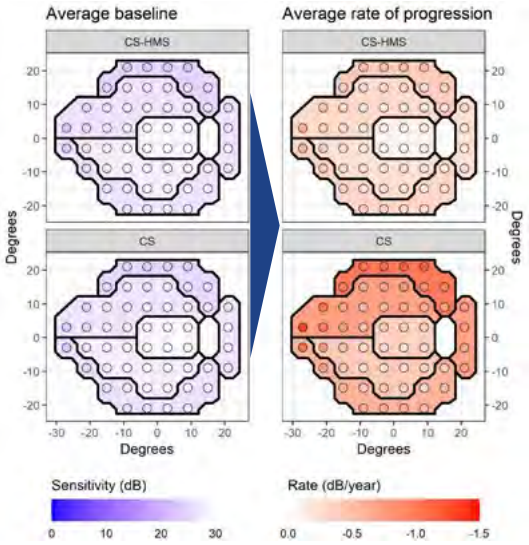
The primary outcome is displayed in Figure 10. As can be seen, the estimated baseline sensitivity values were comparable for both arms (left-sided bar graph); these were obtained by extrapolating the linear regression to the t_0 timepoint at the day of surgery. However, the rate of progression for the cataract surgery arm is -0.49 dB/year whereas the rate of progression for the HYDRUS arm is -0.26 dB/year. Note the Bayesian directional P-value (Pd, analogous to a P-value) for this difference of -0.23 dB/year.[33,34] Again, the relevance of P-values in a retrospective study is unclear.



		CS-HMS	CS	Difference	P_{d+}
Main selection	Baseline (dB)	26.73 [26.43, 27.03]	26.74 [26.30, 27.18]	0.01 [-0.52, 0.54]	0.9618
	RoP (dB/year)	-0.26 [-0.36, -0.16]	-0.49 [-0.63, -0.34]	-0.23 [-0.40, -0.05]	**0.0138**

CS: Cataract surgery; **HMS**: Hydrus microstent; **RoP**: Rate of progression **Pd** is a Bayesian directional p-value

Figure 10: Primary outcome of the full-group Rate of Progression between arms of the study. The authors reported Pd-values for this retrospective analysis.[33,34]



		CS-HMS	CS	Difference	p_d
Cluster 1 (peripheral superior)	**Baseline (dB)**	23.86 [23.42, 24.29]	24.06 [23.44, 24.68]	0.20 [-0.58, 0.94]	0.602
	RoP (dB/year)	-0.27 [-0.40, -0.15]	-0.58 [-0.77, -0.40]	-0.31 [-0.54, -0.08]	**0.006**
Cluster 2 (paracentral superior)	**Baseline (dB)**	26.26 [25.86, 26.66]	26.33 [25.75, 26.92]	0.07 [-0.63, 0.77]	0.839
	RoP (dB/year)	-0.26 [-0.39, -0.16]	-0.57 [-0.75, -0.40]	-0.30 [-0.51, -0.09]	**0.004**
Cluster 3 (macular)	**Baseline (dB)**	29.78 [29.50, 30.05]	29.84 [29.44, 30.25]	0.06 [-0.43, 0.55]	0.794
	RoP (dB/year)	-0.25 [-0.34, -0.17]	-0.38 [-0.51, -0.25]	-0.13 [-0.29, 0.03]	0.099
Cluster 4 (paracentral inferior)	**Baseline (dB)**	28.15 [27.80, 28.50]	28.01 [27.48, 28.54]	-0.14 [-0.77, 0.48]	0.675
	RoP (dB/year)	-0.31 [-0.41, -0.20]	-0.44 [-0.59, -0.28]	-0.13 [-0.32, 0.06]	0.171
Cluster 5 (peripheral inferior)	**Baseline (dB)**	25.98 [25.62, 26.33]	25.86 [25.34, 26.41]	-0.10 [-0.73, 0.53]	0.753
	RoP (dB/year)	-0.28 [-0.38, -0.16]	-0.48 [-0.64, -0.32]	-0.20 [-0.40, -0.01]	**0.041**
Cluster 6 (temporal)	**Baseline (dB)**	26.47 [26.10, 26.83]	26.50 [25.94, 27.04]	0.02 [-0.64, 0.67]	0.927
	RoP (dB/year)	-0.19 [-0.31, -0.07]	-0.49 [-0.67, -0.30]	-0.30 [-0.52, -0.08]	**0.007**

Figure 11: Secondary outcomes of the cluster Rates of Progression between groups. The Bayesian directional P-value (Pd, analogous to a P-value) indicated that only the macular and pericentral inferior clusters were not significantly different. The graphic on the left represents the same findings on the tabular entries, with similar baseline cluster and location sensitivities; however, the cluster-specific rates of progression are represented graphically, showing greater progression in all clusters of the cataract surgery-alone group, but at varying amounts. The authors reported Pd-values for this retrospective analysis.[33,34]

When evaluating the rates of progression for the Garway-Heath clusters, Figure 11 shows that only two of the six cluster-specific rates of progression (macular and inferior paracentral) were lower in the HYDRUS group by 0.13 dB/year. The remaining four of six cluster-specific rates of progression were lower in the HYDRUS group by 0.20 to 0.31 dB/year. The Bayesian directional P-values are also listed, however, as stated previously, their relevance in a retrospective study is unclear.[33,34]

Figure 12 shows the results of the analysis for the fastest location and cluster for both groups; the fastest location and cluster were found in the cataract surgery-alone arm, with the fastest location in the cataract surgery arm showing a rate of loss of 2.48 dB/year as opposed to a rate of loss of 1.55 dB/year in the HYDRUS group. The cluster analysis also showed the greatest cluster-specific rate of loss at 1.37 dB/year in the cataract surgery-only arm as compared to a cluster-specific rate of loss of 0.79 dB/year in the HYDRUS group.[33,34] The graphic shows that the superior visual fields had the greatest rates of loss in both groups, which is consistent with the clinical findings of visual field loss in patients with primary open-angle glaucoma.[36-38]

	CS Mean [95% Confidence Intervals]	CS-HMS Mean [95% Confidence Intervals]
Fastest location	-2.48 dB/year [-2.95, -2.00]	-1.55 dB/year [-1.88, -1.23]
Fastest cluster	-1.37 dB/year [-1.77, -0.98]	-0.79 dB/year [-1.06, -0.52]

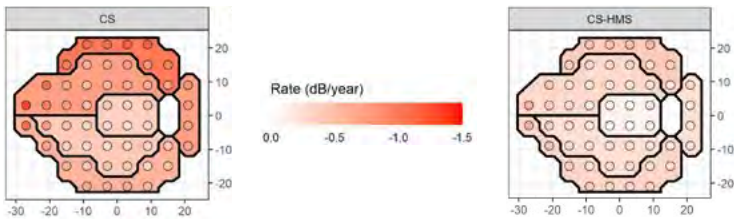


Figure 12: Fastest Rates of Progression in Location and Cluster were found in the cataract surgery-alone group.[33,34] Note that the superior visual fields and locations in both groups had greater rates of loss, consistent with clinical VF findings in glaucoma.[36-38]

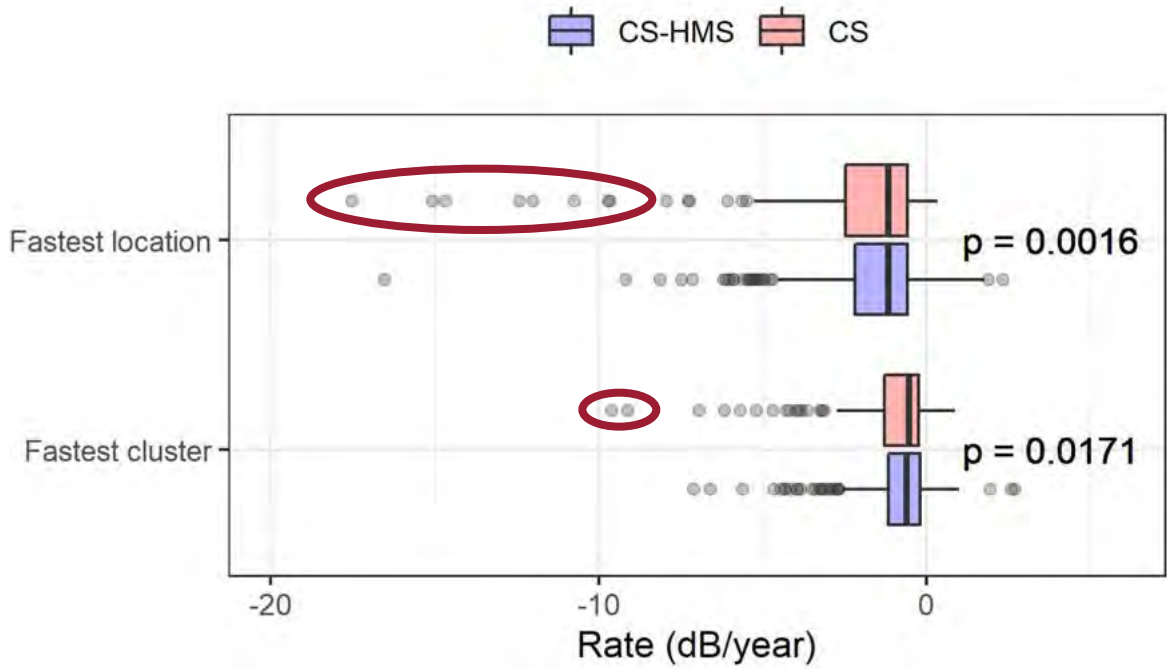


Figure 13: The boxplots represent the distribution of the rate of progression of the fastest progressing clusters and locations in the HYDRUS (CS-HMS) arm and the cataract surgery-alone arm (CS). The boxes enclose the interquartile range, and the vertical midline indicates the median. Note the larger tails in the cataract surgery-alone arm (red ovals). The authors reported P-values for this retrospective analysis.[33,34]

The distribution of the rates of progression for the fastest location and clusters was plotted and shown in Figure 13. Note that for both the distribution of locations and clusters, there is the presence of a larger tail in the cataract surgery-alone arm.[33,34]

To evaluate the global progression of the VF beyond a predefined threshold when starting from the estimated sensitivity on the day of surgery (preoperative data were excluded), an exploratory Cox survival analysis was performed. The survival events were defined at the 2.5 dB threshold (defined as an adverse event in the HORIZON trial), as well as at three 1 dB steps beyond this threshold (3.5 dB, 4.5 dB and 5.5 dB). To avoid extrapolating beyond the available data, all eyes that were estimated to reach a defined survival event beyond their actual observation period were censored at the time of their last follow-up. Based on the P-values for the exploratory analysis of this retrospective study, there appeared to be a significant difference at only the 5.5 dB threshold (P=0.017), indicating that the cataract surgery-alone arm had a larger proportion of fast progressors, but similar proportions of slow and moderate progressors as compared to the HYDRUS arm.[33,34] This small group of fast progressors at the 5.5 dB loss survival event in the cataract surgery-alone arm may likely attribute for the global, cluster and pointwise location differences between groups.

When the overall rates of progression were evaluated with regards to the IOP, a time-weighted mean IOP accounting for the bias towards more-frequent, earlier (and likely lower) IOP measurements was calculated by linearly interpolating between the recorded IOP values of each eye and densely resampling the interpolated curve at 1-day intervals. The mean of these values was defined as the IOP for each group. These time-weighted mean IOP values were incorporated into the multivariate mixed effect model used for the main outcome, which was modified to include the mean IOP as a predictor. The interaction with time from surgery was used to model the effect of IOP control on progression rate. The model outcomes showed that the time-weighted average IOP had an effect on the RoP of -0.06 dB/year/mmHg, which when multiplied by the small difference of the mean time-weighted IOP, showed only a -0.04 dB/year proportion of the total -0.23 dB/year RoP difference (17%).[34]

LIMITATIONS OF THE MODEL

This post-hoc analysis has several practical limitations. First, this analysis has currently been limited to use in an academic setting due to the complex nature of the data and the analysis. Second, the Garway-Heath clusters are approximations of the anatomic location of the retinal nerve fibers and there is likely overlap between clusters. Third, the HORIZON Trial population was composed of early or moderate glaucoma subjects undergoing cataract surgery; these results might not be applicable to subjects with other glaucoma etiologies. Fourth, the clinical relevance of these visual field findings has not been well established. Fifth, the five-year span of the HORIZON data was sufficient to identify differences in the visual field rate of progression between the two groups using a hierarchical methodology, however, glaucoma is a long-term disease that is difficult to predict without prolonged clinical follow-up. Sixth, the small difference in overall IOP control based on clinic DIOP measurements between groups in HORIZON does not appear to account for the differences in the rates of progression between groups. Finally, it is currently not possible to reliably predict fast or slow progressors within a population. Certainly, criteria to measure this was not applied to the inclusion/exclusion criteria of the HORIZON trial; having said this, it is uncertain whether the distribution of fast progressors was different within the baseline HORIZON population. This is a factor that should be considered to possibly account for the differences seen in the final post-hoc analysis.

SUMMARY

Over time, the clinical relevance of visual fields has improved and remains a relevant functional indicator of a patient's glaucoma status. With this increased relevance and awareness, standardized automated perimetry has become an essential tool for patients with glaucoma. Software protocols built into the standardized automated perimeters have been an excellent way to observe ongoing changes in a patient's visual field functional status, but newer models have, over several years, attempted to better predict progression of visual field loss. Some of the earlier models paved the way towards the creation of better models. One of these latest approaches includes a hierarchical model that has the ability to describe the rates of progression between groups as well as at Garway-Heath clusters and at point locations using raw sensitivity data gathered from automated perimetry. Models that can censor 0 dB readings may provide practical advantages to obtaining results that can identify deeper insight into identified patterns of visual field loss. This model has been used in several clinical trials including the LiGHT trial and the TAGS Study; it was also applied in a retrospective, post-hoc manner to the 5-year visual field data of the HORIZON Trial. This post-hoc analysis revealed a difference in the rates of progression between the two groups as a whole, within clusters and at point locations. However, it was apparent that there were a greater number of fast progressors in the cataract surgery-alone group that could account for these differences. A number of limitations do apply to this analysis, and they must be understood to interpret these findings within the context of the clinical data. The insights gathered from this analysis can further guide studies designed to delve deeper into the clinical application of these improved prediction models.

IMPORTANT PRODUCT INFORMATION

CAUTION: Federal law restricts this device to sale by or on the order of a physician.

INDICATIONS FOR USE: The Hydrus Microstent is indicated for use in conjunction with cataract surgery for the reduction of intraocular pressure (IOP) in adult patients with mild to moderate primary open-angle glaucoma (POAG).

CONTRAINDICATIONS: The Hydrus Microstent is contraindicated under the following circumstances or conditions: (1) In eyes with angle closure glaucoma; and (2) In eyes with traumatic, malignant, uveitic, or neovascular glaucoma or discernible congenital anomalies of the anterior chamber (AC) angle.

WARNINGS: Clear media for adequate visualization is required. Conditions such as corneal haze, corneal opacity or other conditions may inhibit gonioscopic view of the intended implant location. Gonioscopy should be performed prior to surgery to exclude congenital anomalies of the angle, peripheral anterior synechiae (PAS), angle closure, rubeosis and any other angle abnormalities that could lead to improper placement of the stent and pose a hazard. The surgeon should monitor the patient postoperatively for proper maintenance of intraocular pressure. The surgeon should periodically monitor the status of the microstent with gonioscopy to assess for the development of PAS, obstruction of the inlet, migration, or device-iris or device-cornea touch. The Hydrus Microstent is intended for implantation in conjunction with cataract surgery, which may impact corneal health. Therefore, caution is indicated in eyes with evidence of corneal compromise or with risk factors for corneal compromise following cataract surgery. Prior to implantation, patients with history of allergic reactions to nitonal, nickel or titanium should be counseled on the materials contained in the device, as well as potential for allergy/hypersensitivity to these materials.

PRECAUTIONS: If excessive resistance is encountered during the insertion of the microstent at any time during the procedure, discontinue use of the device. The safety and effectiveness of use of more than a single Hydrus Microstent has not been established. The safety and effectiveness of the Hydrus Microstent has not been established as an alternative to the primary treatment of glaucoma with medications, in patients 21 years or younger, eyes with significant prior trauma, eyes with abnormal anterior segment, eyes with chronic inflammation, eyes with glaucoma associated with vascular disorders, eyes with preexisting pseudophakia, eyes with pseudoexfoliative or pigmentary glaucoma, and when implantation is without concomitant cataract surgery with IOL implantation. Please see a complete list of Precautions in the Instructions for Use.

ADVERSE EVENTS: The most frequently reported finding in the randomized pivotal trial was peripheral anterior synechiae (PAS), with the cumulative rate at 5 years (14.6% vs 3.7% for cataract surgery alone). Other Hydrus postoperative adverse events reported at 5 years included partial or complete device obstruction (8.4%) and device malposition (1.4%). Additionally, there were no new reports of persistent anterior uveitis (2/369, 0.5% at 2 years) from 2 to 5 years postoperative. There were no reports of explanted Hydrus implants over the 5-year follow-up. For additional adverse event information, please refer to the Instructions for Use.

MRI INFORMATION: The Hydrus Microstent is MR-Conditional meaning that the device is safe for use in a specified MR environment under specified conditions.

Please see the Instructions for Use for complete product information.

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