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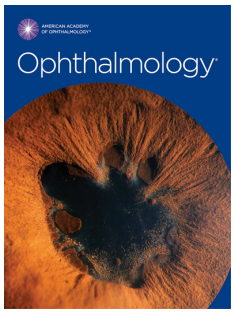

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Six-year rate of visual field progression in the Laser in Glaucoma and Ocular Hypertension (LiGHT) Trial

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Running head: Six-year visual field progression in LiGHT

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Abstract

Purpose: to compare the 6-year rate of visual field (VF) progression in the two arms of the Laser in Ocular Hypertension and Glaucoma Trial (LiGHT), comparing selective laser trabeculoplasty (SLT) and drops as first treatment in ocular hypertension (OHT) and open angle glaucoma (OAG).

Design: post-hoc analysis of data from randomized clinical trial

Subjects: patients with newly diagnosed OHT/OAG recruited in the LiGHT trial.

Methods: in each patient, we selected the better (baseline Mean Deviation, MD) eligible eye with at least 3 reliable VFs (false positive errors < 15%) over at least 6 months. We estimated the rate of MD progression using a published hierarchical linear mixed effect model (LMM), designed to increase precision by minimizing the effect of perimetric learning and test-retest noise. Secondary analyses were performed to assess: the differences in rate across baseline severity groups (OHT, mild OAG and moderate/severe OAG); the effect of glaucoma surgery and switch to SLT in the drops-first arm, by truncating the VF series; the effect of cataract and cataract surgery, by using the Mean Pattern Deviation (MPD) instead of the MD.

Main Outcome Measure: mean difference in the rate of VF MD progression between patients in the SLT-first and drops-first arm.

Results: Data from 710 eyes (482 with OAG, 354 in the SLT-first arm) were analysed. The two arms had similar baseline MD (p=0.7). The average intraocular pressure (IOP) during follow-up was 16.1 [14.2, 18.2] for the drops-first arm and 16.8 [14.6, 18.6] in the SLT-first arm (Median [Interquartile-range], p=0.057). The mean [95%-Credible interval] MD rate was -0.37 [-0.43, -0.31] dB/year in the drops-first arm and -0.26 [-0.31, -0.21] dB/year in the SLT-first arm (p = 0.007). When stratified by severity, this difference was significant only in mild OAG (p = 0.035, the largest sub-group). The secondary analyses largely confirmed the main results. The difference in MPD rate was also significantly slower in the SLT-first arm (p < 0.001).

Conclusions: first-line SLT was more effective than drops at preserving VF. SLT should be preferred as the first line of treatment in newly diagnosed OHT and OAG eyes.

The Laser in Glaucoma and Ocular Hypertension (LiGHT) trial is a multicentre randomised clinical trial comparing selective laser trabeculoplasty (SLT) and intraocular pressure (IOP) lowering drops as first treatment in newly diagnosed patients with ocular hypertension (OHT) and open angle glaucoma (OAG). The main outcome of the trial was reported at 3 years, demonstrating that SLT was more cost-effective than drops as a first treatment. Moreover, 74.2% of patients receiving SLT-first were drop-free at 3 years, while experiencing a reduced rate of glaucoma surgery[1]. The trial follow-up was then extended to 6 years, confirming these results[2].

One crucial aspect of the LiGHT trial was the rigorous definition of the target IOP and treatment escalation protocol, helped by a decision support software. This ensured that patients in both arms were treated to achieve their target IOP, reducing the interference from arbitrary treatment modifications by individual clinicians. Despite this, and despite similarly controlled IOP in the two arms, a longitudinal analysis of the visual fields (VFs) showed a higher proportion of fast progressing locations at 3 years in the drops-first arm compared to the SLT-first arm[3]. This may indicate better control of disease progression with SLT compared to drops, even when patients are treated to their target IOP.

VF metrics are affected by perimetric noise and learning, especially in newly diagnosed patients[4, 5]. We have recently published a modification of a hierarchical linear mixed model (LMM)[5], a standard approach to quantify VF progression. This improved LMM can estimate the rate of VF progression minimising the influence of perimetric noise and the positive bias introduced by learning, providing greater precision in estimating the rate of VF progression. This model has been validated on a large real-world dataset[5] and, more recently, on VF data from the United Kingdom Glaucoma Treatment Study (UKGTS)[4].

The objective of this research was to analyse the six-year rate of VF progression in the LiGHT trial and to test for potential differences between the SLT-first and the drops-first arm. Differently from previous analyses[3], we focused on the Mean Deviation (MD), a more commonly used index of perimetric loss. We tested these differences using the improved LMM, to provide more precise and generalisable estimates of distribution of the rates of VF progression[4, 5].

Methods

Study cohort and randomization

The LiGHT Trial design has been described previously in detail. The study was conducted in accordance with good clinical practice guidelines and adhered to the tenets of the Declaration of Helsinki. Ethical approval was granted by local boards. All patients provided written informed consent before participation. The LiGHT Trial is registered at www.controlled-trials.com (identifier, ISRCTN32038223). The protocol is available at https://www.journalslibrary.nihr.ac.uk/programmes/hta/0910440/#/.

The trial recruited patients newly diagnosed with OAG or OHT in one or both eyes, qualifying for treatment according to the guidelines from the United Kingdom National Institute for Health and Care Excellence (NICE). Eligible eyes were required to have visual acuity 6/36 or better in the eligible eye(s), no previous intraocular surgery, except uncomplicated phacoemulsification at least one year before randomization, no contraindications to SLT, no symptomatic cataract, no other ophthalmic conditions requiring treatment. Patients with OAG were eligible if they had a MD > -12 dB in the better eye or > -15 dB in the worse eye, with corresponding damage on the optic nerve head. Patients were randomized to receive either IOP-lowering eye drops or SLT as their first treatment, the latter followed by IOP-lowering eye drops if required. Randomisation was stratified by diagnosis (OAG or OHT) and treatment centre. The main outcome measure was health related quality of life measured with the EQ-D5 questionnaire[1].

Disease stratification and treatment escalation followed the NICE guidelines. The guidelines were implemented in a clinical decision-support software. The recommendation from the software was based on optic disc analysis using Heidelberg Retina Tomography (Heidelberg Engineering), automated VF assessment with the Humphrey Field Analyzer II Swedish interactive threshold algorithm standard 24-2 (Carl Zeiss Meditec), and intraocular pressure (IOP) measurements (Goldmann applanation tonometry with daily calibration verification).

Disease severity (OHT and mild, moderate, or severe OAG), target IOP and monitoring intervals were based on the Canadian Target IOP Workshop guidelines[6]. VF testing followed the visit schedules, with no test clustering. Treatment was escalated if IOP was above target by more than 4 mmHg at a single visit, or by 2-3 mmHg on 2 consecutive visits (without proof of VF or optic disc stability), or there was evidence of disease progression regardless of IOP.

Treatments

SLT was performed following a predefined protocol, treating 360° of the trabecular meshwork. For the first 3 years of the trial, only one additional SLT retreatment was allowed, in the absence of adverse events from the first SLT. The next escalation was medical treatment. After the first 3 years, patients were allowed a third SLT treatment.

Single-drug eye drops (latanoprost as first line) were prescribed after randomization for patients in the drops-first arm and for patients whose IOP remained above target after initial SLT. Drop treatment was changed or increased if the IOP was above target or in case of adverse reactions to the current drops. Systemic carbonic anhydrase inhibitors were only used as a temporary measure prior to surgery.

Patients in the drops-first arm were not allowed SLT for the first 3 years; failure of topical treatment resulted in glaucoma surgery (trabeculectomy). After the first 3-years, patients in the drops-first arm were allowed SLT.

Statistical analysis

This was a post-hoc analysis of prospectively collected data from the LiGHT trial. All analyses were performed in R (R Foundation for Statistical Computing, Vienna, Austria). The primary outcome measure was the change in the rate in VF-MD progression in the **better eligible eye**, according to the baseline MD. The better eligible eye was chosen to maximize the accuracy in measuring progression, minimizing the effect of perimetric noise and measurement floor. We included eyes with at least 3 reliable tests over at least 6 months of follow-up. Reliability was defined as a false positive error rate < 15%[7]. The average rate of progression and the effect of treatment was measured using a published Bayesian hierarchical model (or LMM).

The LMM has been described in detail elsewhere[5] and validated with real-world datasets[5] and data from clinical trials[4]. Briefly, the LMM provides population estimates (often called fixed effects) while capturing the inter-individual variability in rates of progression with random effects for intercepts and slopes. In standard LMMs, the distribution of random slopes is assumed to be Gaussian. Rates of MD progression are however known for having a skewed distribution, with a longer negative tail[5, 8, 9]. The average rate is also positively biased by the effect of perimetric learning[5], especially in naïve patients.

Our LMM models the rates of progression as a combination of two distributions: a sign-reversed exponential and a Gaussian distribution. The sign-reversed exponential produces only negative values and captures the assumption that VF cannot truly improve[10], i.e. the 'true' rate of progression. The standard deviation of the Gaussian distribution models the effect of perimetric test-retest noise (estimated directly from the data). When positive, the mean of the Gaussian distribution provides an estimate of the average learning effect. Because the two components are estimated separately at a population level, this LMM allows us to test for changes in the distribution of the 'true' rates of progression, reducing the effect from learning and perimetric noise. Note that the slope for each eye is modelled as the sum of two random draws, one from the exponential and one from the Gaussian distribution. Therefore, the two components cannot be separated for an individual eye. There is also no prior constraint that the draw from the Gaussian distribution or its mean be positive.

We used JAGS and the package *R2jags* for R (R Foundation for Statistical Computing, Vienna) to run Markov Chain Monte Carlo sampling of the posterior distributions. We used four parallel chains with a thinning interval of 10 samples and a burn-in of 5000 samples. We monitored all population-level parameters and we considered the chains to have converged when the Gelman-Rubin diagnostic metric was < 1.05 (minimum of 9,500 samples per chain after thinning and burn-in). The posterior samples from the four chains were merged and used to calculate 95% credible intervals (95% CIs) and a Bayesian metric similar to a frequentist two-sided P-value (P) as described by Makowski et al.[11] and used in previous analyses by our group[4, 12, 13].

Secondary analyses

The following secondary analyses were also performed:

- Rate of MD progression using series truncated at the first SLT treatment in the drops-first arm and at the first trabeculectomy for any patient
- Rate of MD progression stratified by baseline severity (see study description). Moderate and severe OAG were grouped together for this analysis, due to the low number of eyes with advanced glaucoma.
- Rate of MD progression selecting the worse eligible eye (**supplementary material**)
- Rate of MD progression selecting one eligible eye at random per patient, when both eligible (**supplementary material**)
- Rate of Mean Pattern Deviation (MPD) progression. This analysis was conducted because there was a significantly higher proportion of cataract surgery procedures in the drops-first arm[2, 3]. The MPD is the average of the pattern deviation values, which would minimize the effect of optical media opacity.

Results

Patients' characteristics

We included 710 eyes of 710 patients (99% of the whole randomised cohort, N = 718) for the main analysis (354 in the SLT-first arm). Relevant descriptive statistics are reported in **Table 1**. As expected, there was no significant difference for any of the baseline characteristics. For follow-up, consistent with previous reports, fewer eyes in the SLT-first arm required IOP-lowering medications, with 72% of them being drop-free at 6 years. There was a statistically significantly higher proportion of eyes undergoing trabeculectomy surgery and cataract surgery in the drops-first arm. Cataract surgery was performed for visual improvement and not for IOP control. There were smaller differences in the average IOP, which was slightly higher in the SLT-first arm, and the IOP variability (standard deviation), which was lower in the SLT-first arm. Only 1 eye had a best measured VA < 6/24 at baseline.

Rate of MD progression

The results are summarised in **Table 2**. The deterioration rate in MD was -0.37 [-0.43, -0.31] dB/year in the medications-first arm and -0.26 [-0.31, -0.21] dB/year in the SLT-first arm (29.1 [9.1, 45.8]% slower, p = 0.007) compared to the drops-first arm. The distributions of the observed rates of MD progression are shown in **Figure 1**. The results were similar when the series were truncated to the first SLT treatment in the drops-first arm and at the time of trabeculectomy surgery in either arm: the MD rate was -0.36 [-0.43, -0.30] dB/year in the medications-first arm and -0.26 [-0.31, -0.21] dB/year in the SLT-first (28 [6.3, 45.7]% slower, p = 0.015) compared to the drops-first arm (figure in **supplementary material**).

When stratified by severity (**Table 2** and **Figure 2**), eyes with more advanced stages showed progressively faster average rates of progression. The rate was approximately 30% slower in the SLT-first arm for all groups, but this was statistically significant only in the Mild OAG group ($p = 0.035$ in the entire series, $p = 0.008$ in the truncated series).

In the entire series, the rate of MPD progression was -0.22 [-0.26, -0.18] dB/year in the drops-first arm and -0.12 [-0.15, -0.10] in the SLT-first arm ($p < 0.001$). In the truncated series, the rate of MPD progression was -0.22 [-0.26, -0.18] dB/year in the drops-first arm and -0.12 [-0.15, -0.09] in the SLT-first arm ($p < 0.001$).

A similar trend was seen when selecting the worse eligible eye, but the rates were more similar between the two arms and there was no statistically significant difference (see **supplementary material**). Note that 198 patients (97 receiving SLT-first) had only one eye eligible, which was included in both analyses. Selecting one eye at random for patients with both eyes eligible resulted in a 300:410 split between better and worse eye and largely replicated the significant results obtained with the better eye selection (see **supplementary material**).

Discussion

This analysis reports the effect of the first IOP lowering treatment (SLT or drops) on the rate of VF progression in patients with OHT or OAG from the LiGHT trial at 6 years. We found a significantly slower rate of VF progression in eyes treated with SLT-first. This difference was also proportionally similar across the different severity subgroups (approximately 30% slower in the SLT-first arm) but was only statistically significant for mild OAGs.

These results confirm previous significant differences observed at 3-years[3] in pointwise rates of progression. These findings are particularly relevant because of the specific design of the LiGHT trial: both arms were treated to achieve a protocol-defined target IOP following a pre-specified treatment escalation procedure, eliminating the effect of variations and potential biases introduced through management decision. This is reflected by the similar IOP achieved in both arms (**Table 1**). Of interest is that the average IOP was marginally higher in the SLT-first arm. This was likely a consequence of the fact that the target IOP could be revised if glaucoma progression was observed. Glaucoma progression events and treatment escalation were indeed more common in the drops-first arm[2, 3], in agreement with our results.

The slower rate of progression in the SLT-first arm could have different explanations. One could be a better control of IOP via a non-drop dependent mechanism. This would reduce IOP fluctuations which could happen outside the monitoring sessions in glaucoma clinics, either because of gaps in dosing or fluctuating compliance. The effect of IOP variability on progression is still controversial. Recent evidence from UKGTS have shown no effect of IOP standard deviation on progression, after controlling for the effect of average IOP[14]. Similar

results were obtained in the early manifest glaucoma treatment trial (EMGT)[15]. However, the true IOP might be poorly characterized by infrequent in-clinic measurements. Larger upward fluctuations could determine a higher IOP on average and might happen outside clinic appointments, due to poor compliance[16] and pharmacokinetics of different medications. Drop-independent IOP lowering methods, such as SLT, may reduce such variability[17, 18] and allow better estimation of the true average IOP with in-clinic assessments. A similar trend has been detected in other trials comparing drops and drop-independent mechanisms of IOP control, such as minimally invasive glaucoma surgery: in the HORIZON trial, the rate of VF progression was significantly slower in eyes that received the cataract surgery in combination with the Hydrus microstent compared to the control group, receiving only cataract surgery, despite very similar medicated IOP in both arms[12]. Another possible explanation for these findings is the time required to achieve IOP control, which might be shorter with SLT compared to a step-wise approach required with drops. In the LiGHT trial, more treatment escalations were required in the drops-first arm[2], inevitably delaying the time to achieve the target IOP compared to the SLT-first arm. We explored this hypothesis by analysing the time to achieve the first IOP reading at or below target in the two arms (see **supplementary material**). For our cohort, the time to achieve the target IOP was shorter the SLT-first arm (0.69 [0.66, 0.69] months, median [95%-Confidence Interval]) than the drops-first arm (2.24 [2.1, 2.3] months, $p < 0.001$). Whether this time lag is enough to explain the observed difference would require a comprehensive modelling of the time-varying effect of IOP on VF deterioration and will be the objective of future work. Another important factor that might explain the difference is the effect of prostaglandin-analogues (first line in LiGHT) on the biomechanical properties of the cornea[19, 20], which might influence the IOP measured with Goldmann applanation tonometry[21] in the Medications-1st group.

We chose to report the analysis of the entire series of VF data as the main results because this would be closer to an intention-to-treat analysis for the LiGHT trial[22]. However, the interpretation of these results needs to account for other confounders to understand the direct impact of treatment. More patients received glaucoma surgery in the drops-first arm, and a proportion of patients in the drops-first arm received SLT treatment after the first 3 years (see **Table 1**). We accounted for these confounders by repeating our analysis after truncating the VF series at the time of glaucoma surgery for both arms and at the time of SLT in the drops-first arm, with no meaningful changes to our results. Cataract surgery was also performed more frequently in the drops-first arm (**Table 1**) and predicting its effect MD progression is not straightforward. Cataract surgery was performed to treat the development of visually significant cataract; this could have caused non-glaucomatous deterioration of the MD. At the same time, visual improvement after cataract surgery could have improved the MD and introduced a positive bias in the rates of progression. To address both these confounders, we have performed a secondary analysis using the MPD, the average of pattern deviation values, which would eliminate generalized changes in the VF. This analysis also confirmed the main results, showing a significantly slower progression in

the SLT-first arm. Other metrics, such as the visual field index (VFI), use information from PD to provide an estimate of VF loss that is less affected by media opacity[23]. However, the VFI is by design capped at 100%, introducing a ceiling effect[24]. This would influence the estimation of learning and might mask progression in early damage[24]. The MPD analysis also allowed us to replicate, within the context of our novel Bayesian model, the pointwise PD analysis reported in our 3-year VF report for LiGHT[3]. It should be noted, however, that all methods relying on PD can potentially underestimate glaucoma progression[25].

Interestingly, we found that the difference between SLT- and drops-first arms was much smaller and not statistically significant when selecting the worse eligible eye (see **supplementary material**). Eyes with more advanced baseline damage are known for having higher test-retest variability[26] and greater influence from the perimetric floor over the course of their follow-up[27]. These considerations were behind the choice of the better eligible eye for our primary analysis. While these observations would easily explain the aggregated results, they do not fully justify the findings of the analysis stratified by baseline severity. For example, when selecting the worse eye, the rate of MD progression in mild OAG eyes was essentially identical in the drops-first arm (-0.37 [-0.47, -0.29] dB/year, **see supplementary**) but faster in the SLT-first arm (-0.31 [-0.40, -0.23] dB/year) compared to our main analysis. Of course, this discrepancy could be explained by the different number of eyes in this category when selecting the worse eye (N= 346) as opposed to the better eye (N =404). Nevertheless, an event analysis in the same patients comparing disease progression between the two arms in the worse eligible eye showed a significantly larger rate of deterioration in the drops-first arm[2]. This definition of progression was based on a more comprehensive evaluation, which included structural parameters and direct assessment by a clinician. A more detailed analysis of the time-varying effect of IOP might help clarify these discrepancies and will be the objective of future work. It should be noted that, despite attempting to minimise the effect of perimetric noise, the ability of the model to isolate the distribution of 'true' rate is still limited by the amount of noise in the data. This might have influenced the accuracy of the estimates in the worse-eye selection and in the severity sub-group analysis. However, we further confirmed our results by repeating our analyses selecting one eye at random when both eligible. These results were similar to the better-eye selection and are reported as **supplementary material**.

In this analysis, we used an improved hierarchical LMM, specifically designed to capture important features of glaucomatous VF progression. Simple averages of MD rates of progression, which would be calculated by standard LMMs, suffer from limitations that reduce the generalizability and interpretability of the results. Mainly, they assume a Gaussian distribution for the rates, which fails to capture the negative skew of rate of progression data[5, 9]. Differently from other similar examples in the literature[8, 9], our model does not simply attempt to describe the distribution of the data. Instead, it offers clearly interpretable estimates, allowing one to distinguish the effect of treatment on the 'true' rate of progression, assumed to be only negative, from the effect of perimetric learning and

noise[4]. We have shown this to be a powerful tool to improve the understanding of the effect of IOP in the United Kingdom Treatment Study (UKGTS)[4]. Isolating the distribution of 'true' rates of progression is also crucial when analysing data from trials, such as LiGHT, recruiting newly diagnosed patients, who are likely to exhibit a significant amount of perimetric learning. We expect the estimates from the distribution of 'true' rates to be more generalizable and less ambiguous when interpreted in terms of percentage change. For example, important clinical targets, such as target IOP[6], are defined based on an expected percentage reduction of the rate of progression, assuming, just like our model, that 'true' glaucoma can only worsen over time. Estimating a proportional effect of treatment, such as SLT and drops, becomes ambiguous when the observed rates are close to zero or even positive because of the bias induced by learning[4, 28]. Our estimates help to remove this ambiguity. At the same time, the estimates for the observed rate of progression, which would be obtained with a standard LMM, can be obtained by simply adding the estimates for the mean 'true' rate and learning[5]. This facilitates the comparison with previous literature. The effect of learning was similar between the two arms, as expected in an RCT, with more substantial differences only appearing in moderate/advanced group, likely because of the small sample size and intrinsically higher VF variability. As a sensitivity analysis, we have repeated all our analyses constraining the learning effect to be the same for both arms (**supplementary material**), with no meaningful change in our results. Future developments will focus in integrating more detailed structural data[4], such as from Optical Coherence Tomography imaging, which was not performed in the LiGHT trial. This would be helpful to isolate the effect of confounders, such as VF change due to cataract development rather than glaucoma progression.

The results from this analysis support the generalizability of our findings. For example, the 'true' rate estimates obtained from the different severity groups show that, despite notable differences in the rates of progression, the proportional effect of SLT remained relatively similar and close to 30% across all subgroups (**Table 2**). It is interesting to contrast this finding with the large differences in the estimated learning effect, which was larger for more advanced disease. This is expected, because worse MD measurements at presentation are more likely to be biased by regression to the mean induced by a selection cut-off[5]. The estimated learning would also absorb the effect of this bias, providing more accurate estimates. Because of the consistent proportional effect across severity groups, the smaller sample size is likely to be responsible for the lack of a statistically significant difference in the moderate/advanced group. This proportionality is also important when translating the effect into absolute reduction in the average rate of progression: a 0.11 dB/year reduction might appear small, but this effect would be larger for faster progressing patients. Moreover, a 30% reduction in the rate of MD progression is generally considered clinically meaningful in a treated population, for example in the context of neuroprotection trials[5, 29-31]. Finally, average rates hide important information about the rapidly progressing patients who are those most at risk of symptomatic vision loss. The exponential component of our model

captures this explicitly. For example, the proportion of patients with a 'true' rate faster than -0.5 dB/year can be simply calculated as $e^{(0.5/Rate)}$. The -0.37 dB/year average rate in the Medications-1st arm translates to 26% of the eyes being fast progressors, much greater than the 15% estimated from the -0.26 dB/year average rate in the SLT-1st arm.

It is also noteworthy that the average 'true' rate measured in the drops-first arm (-0.37 [-0.43, -0.31] dB/year) was almost identical to the one measured from a large real-world cohort of more than 3,000 patients from five glaucoma clinics in the United Kingdom (−0.38 [−0.40, −0.36] dB/year)[5]. This suggests not only that the treatment algorithm implemented in LiGHT was reflective of clinical practice, but also that our results are generalisable to a wide population. That said, these results were obtained within the tightly controlled environment of a clinical trial and it is difficult to predict how they might differ in the context of clinical practice. On the one hand, less consistent patient adherence to medical treatment might result in an even larger clinical benefit from controlling the IOP with SLT. On the other hand, more variability in clinical management and in the recording of disease progression might dilute the effect that could be measured using data from clinics.

There are limitations related to the fact that this was a post-hoc analysis of prospectively collected data. The main outcome measure for LiGHT was health related quality of life[1], meaning that the trial was not primarily powered to detect differences in VF progression. The long follow-up and the large number of patients recruited provide a high degree of confidence in the results. However, this limitation should be considered when evaluating the results and would certainly affect the precision of the sub-group analyses, especially for the smaller moderate/advanced OAG sub-group.

In conclusion, our results demonstrate that SLT as first IOP lowering treatment can more effectively prevent VF progression compared to drops, substantially reducing the speed of MD progression. These results have important implications regarding the choice of initial therapy. The exact mechanisms for this effect are still unclear and might be related to a more consistent control of IOP, shorter time to achieve target pressure and less reliance on patients' compliance with treatment.

Figure legends

Figure 1. The top panels show the distributions of the linear regression slopes of MD over time in the two arms. The black line represents the fit from the model. Note that this representation uses the average standard deviation of noise estimated from the model. In reality, the model considers the differences in the number of tests and length of follow-up for each eye. The bottom panels show the estimated components of the distributions. Notice how the exponential component ('true' rate, in red) captures the longer negative tail in the drops-first arm. SLT = Selective Laser Trabeculoplasty.

Figure 2. Estimated rates of MD progression for the overall sample and by severity groups. This is a graphical representation of the results reported in Table 2. The dots represent the central estimates. The whiskers represent the 95%-Credible Intervals. MD = Mean Deviation.

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Characteristic	**Medications first**, N = 356[1]	**SLT first**, N = 354[1]	**p-value**[2]
Patients' demographics			
Baseline age (years)	63 (54, 71)	65 (54, 72)	0.4
Sex			0.5
Female	164 (46%)	155 (44%)	
Male	192 (54%)	199 (56%)	
Ethnicity			0.5
White	255 (72%)	242 (68%)	
Black/Black British	66 (19%)	76 (21%)	
Asian/Asian British	28 (7.9%)	23 (6.5%)	
Chinese	1 (0.3%)	2 (0.6%)	
Other	6 (1.7%)	11 (3.1%)	
Baseline eye characteristics			
Visual acuity (logMAR)	0.00 (-0.06, 0.10)	0.02 (-0.06, 0.10)	0.5
Baseline IOP (mmHg)	24 (21, 28)	24 (21, 27)	>0.9
Target IOP (mmHg)	18 (16, 21)	19 (16, 21)	0.6
CCT (um)	554 (532, 576)	552 (526, 577)	0.5
Severity			>0.9
OHT	113 (32%)	115 (32%)	
Mild OAG	203 (57%)	201 (57%)	
Moderate/severe OAG	40 (11%)	38 (11%)	
PXF	8 (2.2%)	4 (1.1%)	0.2
Baseline MD (dB)	-1.4 (-3.6, -0.20)	-1.6 (-3.6, -0.32)	0.7
Baseline PSD (dB)	2.1 (1.7, 3.6)	2.1 (1.7, 3.4)	0.8
Follow-up (years)	5.8 (4.9, 6.0)	5.8 (4.9, 6.0)	0.2
Tests (N)	12 (10, 15)	12 (10, 15)	0.5
Clinical management			
Average IOP (mmHg)	16.1 (14.2, 18.2)	16.8 (14.6, 18.6)	0.057
IOP variability (mmHg)	2.2 (1.7, 3.1)	2.1 (1.5, 2.8)	0.035
Highest IOP (mmHg)	20.0 (18.0, 24.0)	21.0 (18.0, 23.0)	0.7
Average N medications	1.0 (1.0, 1.3)	0.0 (0.0, 0.9)	<0.001
Final N medications	1.0 (1.0, 2.0)	0.0 (0.0, 1.0)	<0.001
Drop free	21 (5.9%)	257 (73%)	<0.001
SLT	101 (28%)	354 (100%)	<0.001
Glaucoma surgery	18 (5.1%)	6 (1.7%)	0.013
Cataract surgery	50 (14%)	30 (8.5%)	0.019

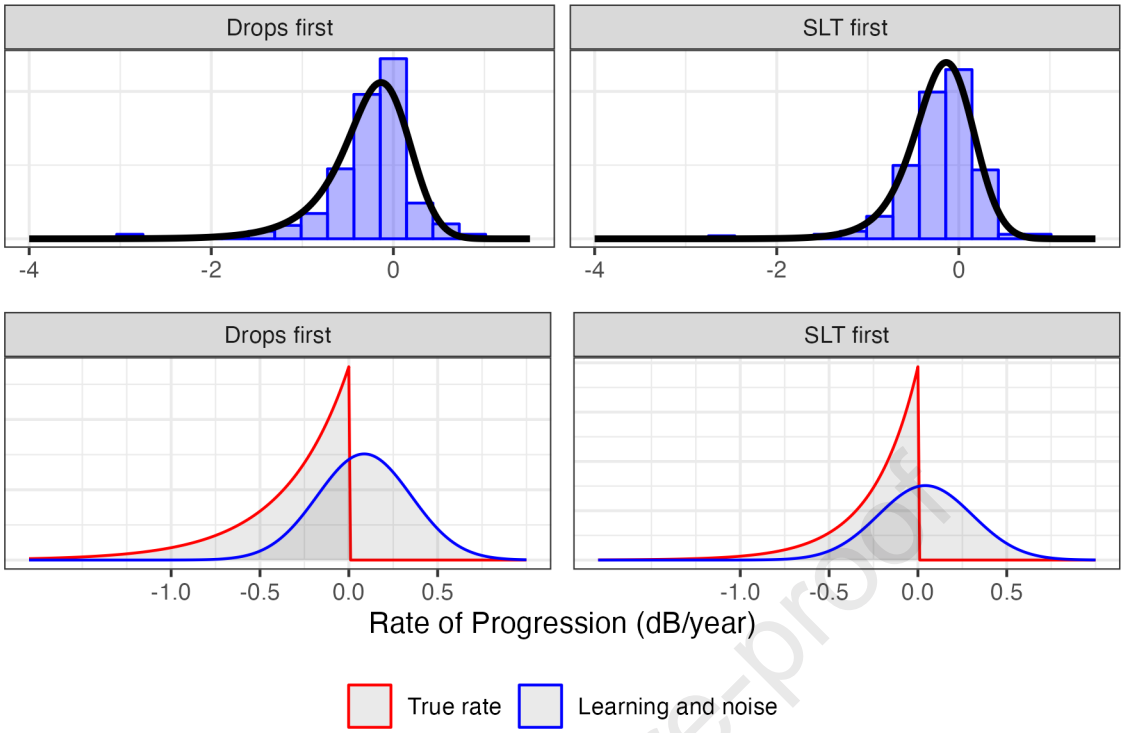
[1]Median (IQR); n (%)

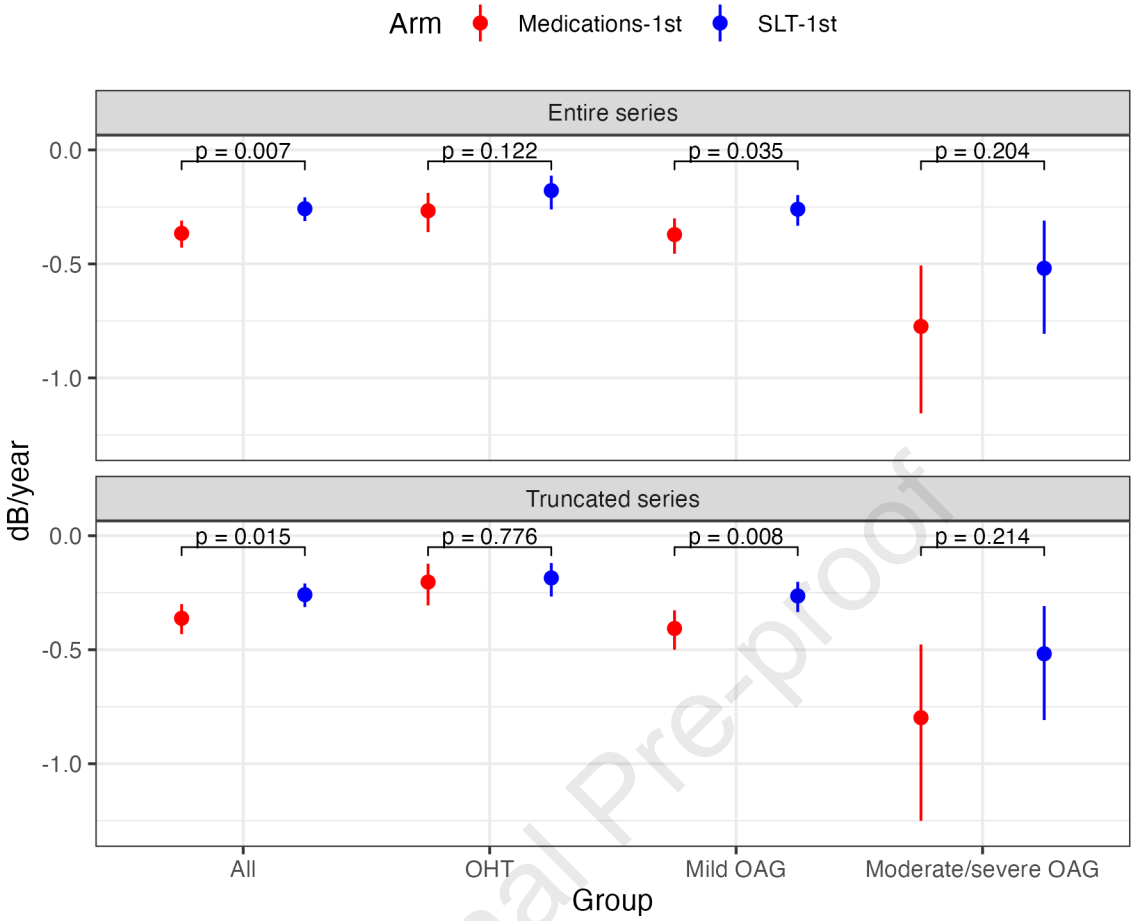
[2]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

Table 1. Descriptive statistics for the two arms. SLT = Selective Laser Trabeculoplasty; MAR = Minimum Angle of Resolution, best recorded, including pinhole; IOP = Intraocular Pressure; CCT = Central Corneal Thickness; MD = Mean Deviation; PSD = Pattern Standard Deviation; OHT = Ocular Hypertension; OAG = Open Angle Glaucoma; PXF = Pseudoexfoliation; IQR = Interquartile Range.

	Rate (dB/year)			Learning (dB/year)	
Group (N)	Medications-1st	SLT-1st	P	Medications-1st	SLT-1st
Entire series					
All (710)	-0.37 [-0.43, -0.31]	-0.26 [-0.31, -0.21]	0.007	0.09 [0.03, 0.14]	0.04 [-0.01, 0.10]
OHT (228)	-0.27 [-0.36, -0.19]	-0.18 [-0.26, -0.11]	0.122	0.03 [-0.06, 0.12]	0.03 [-0.05, 0.12]
Mild OAG (404)	-0.37 [-0.46, -0.30]	-0.26 [-0.33, -0.20]	0.035	0.07 [0.00, 0.14]	0.04 [-0.03, 0.11]
Moderate/severe OAG (78)	-0.77 [-1.16, -0.51]	-0.52 [-0.81, -0.31]	0.204	0.45 [0.23, 0.70]	0.08 [-0.12, 0.29]
Truncated series					
All (710)	-0.36 [-0.43, -0.30]	-0.26 [-0.31, -0.21]	0.015	0.09 [0.03, 0.15]	0.05 [-0.01, 0.10]
OHT (228)	-0.20 [-0.31, -0.12]	-0.19 [-0.27, -0.12]	0.776	-0.03 [-0.14, 0.08]	0.04 [-0.04, 0.13]
Mild OAG (404)	-0.41 [-0.50, -0.33]	-0.26 [-0.33, -0.20]	0.008	0.09 [0.01, 0.17]	0.04 [-0.02, 0.11]
Moderate/severe OAG (78)	-0.80 [-1.25, -0.48]	-0.52 [-0.81, -0.31]	0.214	0.53 [0.29, 0.80]	0.09 [-0.10, 0.30]

Table 2. Estimates [95%-Confidence Intervals] for the 'true' rates of MD progression and the learning effect, for the overall sample and by severity groups. The estimates are reported for the entire series and for the series truncated at glaucoma surgery for both arms and at the first SLT treatment in the drops-first arm. P-values for the learning effect are omitted for clarity. The difference was only significant ($p < 0.05$) for the Moderate/advanced group. SLT = Selective Laser Trabeculoplasty; MD = Mean Deviation; OHT = Ocular Hypertension; OAG = Open Angle Glaucoma.





Selective laser trabeculoplasty as first treatment reduced the rate of visual field progression compared to drops in the Laser in Glaucoma and Ocular Hypertension Trial.