The Impact of Baseline Intraocular Pressure on Initial Treatment Response in the LiGHT Trial: Selective Laser Trabeculoplasty versus Medication.

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Impact of Baseline IOP on Treatment Response in the LiGHT Trial

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ABSTRACT:

Purpose: The Laser in Glaucoma and Ocular Hypertension (LiGHT) Trial demonstrated the efficacy and safety of selective laser trabeculoplasty (SLT) compared to topical hypotensive medication as 1st-line therapy for ocular hypertension and open angle glaucoma. This sub-study explores the impact of pre-treatment (baseline) intraocular pressure (IOP) on treatment response for SLT and medication.

Design: Post hoc analysis of randomised control trial data.

Participants: 1146 eyes from 662 patients were included in this analysis: 559 eyes in the SLT group and 587 in the medication group.

Methods: IOP reduction at 8 weeks following treatment with either SLT or prostaglandin analogue (PGA) eye drop initiation was assessed at different levels of baseline IOP, and the groups were compared. Differences in absolute and percentage IOP lowering between SLT and PGA medication were tested with a linear mixed effects model. Differences in the probability of achieving ≥20% IOP lowering between SLT and PGA medication, at different levels of baseline IOP, was estimated using a logistic mixed effects model.

Main Outcome Measure: IOP lowering response to SLT versus PGA eye drops.

Results: Mean IOP was not significantly different between the groups, at baseline or 8 weeks following treatment initiation. Both treatments showed greater IOP lowering at higher baseline IOP and less IOP lowering at lower baseline IOP. SLT tended to achieve more IOP lowering

than PGA drops at higher baseline IOP. PGA drops performed better at lower baseline IOP, and the difference compared to SLT, in terms of percentage IOP reduction, was significant at baseline IOP ≤ 17 mmHg. There was a significant difference in the relationship between baseline IOP and probability of ≥20% IOP lowering between the two treatments (p = 0.01), with SLT being more successful than PGA at baseline IOP > 22.51 mmHg.

Conclusions: These data confirm previous reports of greater IOP lowering with higher baseline IOP for both SLT and topical hypotensive medication. In treatment naïve eyes, at higher baseline IOP, SLT was more successful at achieving ≥20% IOP lowering than PGA drops. At lower baseline IOP, a statistically greater percentage, but not absolute, IOP lowering was seen with PGA drops compared to SLT, although the clinical significance of this is uncertain.

INTRODUCTION:

Glaucoma is a progressive optic neuropathy characterised by visual field loss and is the leading cause of irreversible blindness worldwide[1]. Raised intraocular pressure (IOP) is the only known modifiable risk factor, and the mainstay of glaucoma therapy is to lower IOP in an effort to slow the progression of visual field loss[2].

The LiGHT Trial is the largest randomised controlled trial (RCT) to date to have assessed the primary treatment of ocular hypertension (OHT) and open angle glaucoma (OAG) with selective laser trabeculoplasty (SLT) versus eye drops[3]. SLT was shown to demonstrate superior disease control, with less need for glaucoma surgery (trabeculectomy) and cataract surgery, as well as being more cost effective, compared to eye drops.

Before the LiGHT Trial, the standard first-line treatment for OHT and OAG was the use of eye drops to lower IOP, which carried potential disadvantages such as local and systemic side effects and variable patient adherence. The LiGHT trial established SLT as a viable and superior first-line treatment for OHT and OAG and provided important evidence which helped to reshape clinical guidelines. Today, several key guidelines include SLT as an option for first-line treatment for OHT and OAG[4–6].

In a post-hoc analysis of LiGHT Trial data, Garg *et al.* demonstrated that higher baseline (pre-treatment) intraocular pressure (IOP) produced a greater degree of absolute and percentage IOP reduction at 8 weeks following initiation of both SLT and drops treatment[7]. Several other studies have demonstrated greater response to both SLT with higher baseline IOP[8–15]. Similar findings with the use of medication and increased IOP lowering with higher baseline IOP have been reported across the literature including within landmark trials[16–18].

However, while we know that higher baseline IOPs produce greater IOP lowering for both SLT and medication, it is unknown whether baseline IOP has a differential effect on the efficacy of SLT versus medication. Knowledge of these potential differences could assist clinicians in tailoring initial treatment for patients depending on baseline IOP. A personalised approach to treatment is also relevant in the context of evidence suggesting that patients prefer a one-time treatment with freedom from eye drops[19]. The purpose of this study was to compare the IOP lowering effect of primary SLT and primary medical treatment (prostaglandin analogue eye drops) at differing levels of baseline IOP.

METHODS:

This study was a post hoc analysis of the LiGHT Trial and included data collected at baseline and 8 weeks following a single intervention - either starting prostaglandin analogue (PGA) eye drops or administration of SLT. Data after this 8 week point was not included in the analysis and we present data only on initial IOP responses: the LiGHT Trial pragmatic study design mirrored clinical practice and followed a 'treat-to-target' approach after the first 8 weeks. Treatment was thus modified (added/repeated) if eyes did not meet the pre-defined Target IOP and after the 8 week point some eyes were receiving additional medications or repeat SLT (excluding only these eyes would have led to unacceptable risk of bias). All eyes included received either a single PGA daily, or a single session of SLT. Eyes receiving non-PGA medication were excluded, as were those that missed an 8 week IOP check.

The design of the LiGHT Trial has been described previously[20]. Briefly, consecutive eligible patients were identified at the clinics of 6 participating centers in the United Kingdom from

October 2012 to October 2014. Eligible patients had newly diagnosed, untreated OAG or OHT in 1 or both eyes and qualified for treatment according to National Institute of Clinical Excellence guidelines at the time[21]. Inclusion criteria were open angles on gonioscopy, visual field loss with mean deviation (VF MD) not worse than -12 decibels (dB) in the better eye or -15 dB in the worse eye, and, for OAG, corresponding damage to the optic nerve head. Patients were aged 18 years or older, able to read and understand English, had a visual acuity of 6/36 or better in the eyes to be treated, and no previous intraocular surgery, except uncomplicated phacoemulsification at least 1 year before randomisation. Patients were excluded if there were any contraindications to SLT, they were unable to use topical medical therapy, they had visually symptomatic cataract and wanted to undergo cataract surgery, or they were receiving active treatment for another ophthalmic condition.

Patients were assigned to either SLT or medical therapy (i.e. IOP-lowering eye drops) using an online randomisation tool (www.sealedenvelope.com). Disease severity and baseline intraocular pressure were used to set objective patient-specific IOP targets, treatment intensities, and monitoring intervals (adjusted on the basis of IOP control, disease stability, or adverse reactions). This approach was guided by a defined protocol, using decision support software based on published criteria[22–24].

The decision support software was informed by optic disc analysis using Heidelberg retina tomography (Heidelberg Engineering, Heidelberg, Germany), visual field assessment with the Humphrey Field Analyzer Mark II Swedish interactive threshold algorithm standard 24--2 (Carl Zeiss Meditec, Dublin, CA, USA) and IOP measurements (Goldmann applanation tonometry with daily calibration verification). Deviations from decision support-recommended interventions were permitted and were at the consultant's discretion; all deviations were recorded and have been reported[20,25].

Treatment escalation followed international guidelines at the time from the American Academy of Ophthalmology Preferred Practice Patterns[26], the European Glaucoma Society[27], and South--East Asia Glaucoma Interest Group[28]. Measurements influencing treatment decisions were made by masked observers. Patients and clinicians were not masked to treatment allocation.

SLT was delivered according to a pre-defined protocol[20]. 360° of the trabecular meshwork were treated with 100 non overlapping shots (25 per quadrant, energy 0.3-1.4mJ). Primary medical treatment was initiated with single drug eye-drops. Drug classes for first-line, second-line or third-line treatment were defined as per NICE[21] and the European Glaucoma Society (EGS) guidance[27] at the time.

The study was conducted in accordance with Good Clinical Practice guidelines and adhered to the tenets of the Declaration of Helsinki. Institutional Review Board/Ethics Committee approval was obtained. All patients provided written informed consent before participation in the trial. The LiGHT Trial is registered at www.controlled-trials.com (registration number ISRCTN32038223).

Statistical methods:

The unit of analysis was the eye. All eligible study eyes that received SLT or medication at baseline were included in the analysis with appropriate measures taken to account for correlation among paired eyes within a subject. Baseline demographic and clinical characteristics were recorded and analysed for similarities between SLT and medication groups.

We evaluated the absolute and percentage IOP reduction at 8 weeks following primary SLT or medication therapy, across a range of baseline IOPs. Patients who underwent SLT were

compared to those who received drops. We also evaluated the probability of adequate IOP reduction following treatment, which was defined as ≥ 20% reduction from baseline.

Differences in the absolute and percentage IOP reduction at 8 weeks between SLT and medication were tested with a linear mixed effects model using the eye as the unit of analysis and the patient as a random factor to adjust for correlation between eyes from the same patient. We used two versions of the mixed effects model: the first only compared the two treatments (categorical factor); the second modelled the differences as a function of the baseline IOP, as a continuous covariate. An interaction between the treatment and the baseline IOP modelled the difference in the relationship (slope) between baseline IOP and IOP reduction in the two groups.

A mixed effects logistic model was used to estimate the probability of ≥ 20% IOP reduction. The logistic model was constructed similarly to the linear mixed effects model, with an interaction term to model the change in success rate at different levels of baseline IOP in the two groups. Predictors were treatment (categorical) and baseline IOP (continuous); their interaction modelled the difference in the relationship between the rate of ≥ 20% IOP reduction and baseline IOP for the two treatments. The p-values calculated for the different levels of baseline IOP were obtained from the same continuous relationship and are descriptive only. The model tested a single hypothesis, the difference in slope of the relationship between baseline IOP and the rate of achieving ≥ 20% IOP reduction.

The linear mixed effects models were fitted in R software version 4.3 (R Foundation for Statistical Computing, Vienna, Austria) using the *lme4* package. Fixed effects coefficients are conditional to the random effects for logistic mixed models. Therefore, the logistic mixed effects

model was fitted using the package *GLMMAdaptive*, to calculate marginal coefficient estimates for the population-level parameters.

Statistical significance was defined as a 2-sided P value < 0.05. The analyses presented here were not included in the trial's initial statistical analysis plan[29] and are thus exploratory.

RESULTS:

A total of 1146 eyes from 662 patients were included in this analysis. A total of 606 eyes (of 622 at baseline) were available for analysis in the primary medication group at the 8 week time point. 19 eyes were excluded from analysis in the medication group because they were being treated with medication other than PGAs, leaving 587 eyes for analysis in this study. A total of 559 eyes (of 611 eyes at baseline) were available for analysis at the 8 week time point in the primary SLT arm. Data was included from baseline and 8 weeks following a single intervention, either initiation of PGA medication or SLT.

Baseline characteristics were balanced between the two treatment arms (Tables 1 and 2); 169 eyes had OHT and 418 eyes had OAG in the PGA group compared to 195 eyes and 416 eyes in the SLT group. Mean baseline IOP was similar between the two groups, at 24.4 mmHg for patients treated with PGA eye drops and 24.5 mmHg for those treated with SLT. For the medication group, both eyes were eligible in 250 of 337 patients (74.1%), only the right eye was eligible in 41 patients (12.2%) and only the left eye was eligible in 46 patients (13.6%). For the SLT group, both eyes were eligible in 234 of 325 patients (72.0%), only the right eye was eligible in 45 patients (13.8%) and only the left eye was eligible in 46 patients (14.2%).

Table 3 summarises IOP response at 8 weeks following treatment initiation. There was no significant difference in mean IOP between the medication and SLT groups (p = 0.92). Absolute and % IOP lowering was also similar between the two groups at 8 weeks. Figure 1 illustrates the percentage IOP reduction against baseline IOP, for both treatment arms. Both PGA eye drops and SLT achieve less IOP reduction at lower baseline IOPs, and greater IOP reduction as baseline IOP increases. At baseline IOP ≥ 15 & < 20 mmHg, PGA eye drops achieved a mean percentage IOP reduction of 23.16% compared to 19.19% for SLT, at 8 week follow up. This increased to a mean percentage IOP reduction of 34.89% for PGA drops and 37.01% for SLT, at baseline IOP ≥ 30 mmHg.

We tested for differences between the groups by assessing the relationship between % IOP lowering and baseline IOP, for PGA drops and SLT (Figure 2). Both groups demonstrate linear slopes with increased % IOP reduction as baseline IOP increases. The slopes were significantly different between the 2 groups (p = 0.04), accounted for by a steeper slope for SLT (1.2749 +/- 0.1115 %/mmHg) compared to PGA drops (0.9661 +/- 0.1058 %/mmHg; both presented as slope estimate +/- standard error). This reflected increased % IOP reduction at higher baseline IOP, and less % IOP reduction at lower baseline IOP. This difference in slope was not significant when we similarly assessed SLT versus PGA drops but in the context of absolute IOP reduction (p = 0.428).

Figure 3 shows the difference between the treatment arms (SLT - drops) for absolute and % IOP reduction, at different levels of baseline IOP. Both upper and lower panels start in negative y-axis values at low baseline IOP, signifying that IOP lowering from PGA drops exceeds SLT at these levels of baseline IOP, and increase to positive values at higher baseline IOPs where the

IOP response from SLT was better. Only percentage reduction demonstrated a significant difference between the treatment arms, where the confidence intervals do not cross the line of no difference (dashed line).

Table 4 summarises the number of eyes achieving ≥ 20% IOP reduction across a range of baseline IOP levels. At baseline IOP of ≥ 30 mmHg, 98.1% of patients treated with SLT achieve ≥ 20% IOP reduction, compared to 85.6% of those treated with PGA drops. For baseline IOP between 20-25 mmHg and 25-30 mmHg, the results are similar between the 2 groups. For baseline IOP ≥ 15 & < 20, drops tended to perform better than SLT. We tested for differences between the groups using a mixed effects logistic model (Figure 4).

This mixed effects logistic model was represented with regression curves plotting % of eyes achieving ≥ 20% IOP reduction versus baseline IOP (Figure 4). The two treatments achieved similar rates of ≥ 20% IOP reduction at the average baseline IOP of 24.4 mmHg ($p = 0.3$). There was a significant difference in the relationship between baseline IOP and probability of ≥ 20% IOP reduction between the two treatments ($p = 0.01$), with SLT being more successful than drops for baseline IOP values > 22.51 mmHg. The two treatments were substantially equivalent ($p \geq 0.8$) for a baseline IOP between 22.1 and 22.9 mmHg. Above and below this range of IOP the success of the two treatments diverged. Between 20.0 and 25.8 mmHg, the p value was ≥ 0.1 and between 20.0 and 27.6 mmHg the p value was ≥ 0.05. We chose a higher cut-off p value for equivalence and a scaled threshold of p values to account for potential for error in multiple testing.

We wanted to clarify whether the differences in probability of ≥ 20% IOP reduction between the 2 groups, at different levels of baseline IOP, were still present when we divided the cohort into OHT and OAG. Figure 5 shows regression curves for OHT on the left, and OAG on the right. In the upper panel (Figure 5A), the full range of baseline IOPs are included; the OHT curve is limited by low numbers of patients who had lower baseline IOP. For OHT eyes, there was no significant difference between the probability of ≥ 20% IOP reduction between the treatment groups ($p = 0.76$). For OAG, the difference between the treatment groups was similar to that of the overall cohort (i.e. Figure 4), whereby PGA drops tended to perform better at lower baseline IOP, and SLT tended to perform better at higher baseline IOP. Overall, there was a significant difference in the relationship between baseline IOP and probability of ≥ 20% IOP reduction between the two treatment groups for OAG ($p = 0.005$), reflecting the differential effect of baseline IOP on the response to PGA drops and SLT.

We wanted to determine whether the inclusion of lower pressures had a leverage effect on the above analysis, so we limited the analysis to OHT and OAG at baseline IOP > 21 mmHg (Figure 5B). A similar result was demonstrated for the OHT eyes, with closely correlated regression curves between the 2 treatment arms ($p = 0.93$). For OAG eyes, there was a significant difference between the treatment arms ($p = 0.02$), which was accounted for by an increased proportion of eyes in the SLT group achieving ≥ 20% IOP reduction. Similar analysis stratified by disease severity for OAG was not possible due to the small number of eyes. The majority of eyes with OAG were mild in severity (75.7% for PGA drops group, 74.3% in the SLT group).

We assessed our results in the context of central corneal thickness (CCT), to determine whether an effect existed. There was no significant relationship between CCT and IOP reduction ($p =$

0.2). There was a small increase in IOP reduction with decreasing CCT in both treatment arms, and conversely a small decrease in IOP reduction with increasing CCT, but this was not significant (see supplementary material).

Safety data for the LiGHT Trial has been reported elsewhere[3,7,30]. Transient IOP elevation following SLT (n=6) was not associated with higher baseline IOP (mean IOP 24 mmHg), compared to the overall cohort (24.42 mmHg).

DISCUSSION:

The mainstay of therapy for OHT and OAG is to lower IOP in order to slow the onset or progression of glaucomatous visual field loss. Eye drops have long been utilised as an effective means of achieving this[2,31]. However, recent evidence from the LiGHT Trial demonstrated the safety and efficacy of SLT as a first line treatment for OHT and OAG[3]. While there is established evidence for a greater IOP lowering effect with higher baseline IOP for both drops[16–18,31,32] and SLT[9,11,12], little is known about whether one treatment may be more influenced by baseline IOP than the other.

In this study, we explored the effect of baseline IOP on primary treatment response to drops and SLT, by post-hoc analysis of LiGHT Trial data. We showed that at 8 weeks following treatment, for both drops and SLT, there was greater IOP lowering as baseline IOP increased, (Figure 1). At baseline IOP ≥ 25 mmHg, SLT tended to perform better compared to PGA drops (Figure 1 and Table 4). This was most apparent at baseline IOP ≥ 30 mmHg. At lower baseline IOP, both treatment arms demonstrated less IOP lowering effect at 8 weeks. At baseline IOP < 20 mmHg,

there was a trend towards greater absolute IOP lowering and a higher proportion of eyes achieving ≥ 20% IOP reduction with drops compared to SLT.

Overall, without accounting for baseline IOP, there were no significant differences in pre- and post-treatment IOP between SLT and drops (Tables 2 and 3). The differences in absolute IOP reduction between the treatment arms, at different baseline IOPs, were not statistically significant (Figure 3). Differences in % IOP reduction between the treatment arms, at different baseline IOPs, did reach significance at lower baseline IOPs of 10-17 mmHg (Figure 3), where drops performed better. However, there were low numbers of eyes at this level of baseline IOP. There was a significant difference in the relationship between baseline IOP and probability of ≥ 20% IOP reduction between the two treatments ($p = 0.01$, Figure 4). SLT had a greater probability of ≥ 20% IOP reduction at baseline IOP > 22.51 mmHg. At baseline IOP ≥ 30 mmHg, 105 of 107 eyes (98%) in the SLT group achieved ≥ 20% IOP reduction compared to 77 of 90 eyes (86%) in the drops group.

We also modelled the interaction between baseline IOP and probability of ≥ 20% IOP reduction between the two treatments, but divided the cohort into OHT and OAG (Figure 5). Across the entire range of baseline IOPs (Figure 5A), the OAG curve showed a similar curvilinear pattern to the overall cohort and there remained a significant difference between drops and SLT in terms of the probability of ≥ 20% IOP lowering ($p = 0.005$). However, for OHT eyes only, the regression curve showed a non-significant difference between the treatment arms ($p = 0.76$), with a trend towards a higher probability of ≥ 20% IOP lowering with SLT compared to drops. When we limited the analysis to baseline IOP > 21 mmHg (Figure 5B), to consider a comparable range of

starting pressures, the findings were similar. The difference in response between the two treatments, for OAG eyes, was accounted for in part by less reliable IOP lowering with PGA drops at higher baseline IOPs (Figure 5). For OHT eyes, drops maintained reliable IOP lowering at higher baseline IOP. It is interesting to consider whether this represents a different physiological response to treatment arising due to differences in trabecular meshwork (TM) pathophysiology between OAG and OHT eyes. For example, does progressive TM dysfunction associated with established OAG render the eye less susceptible to the effects of eye drops, and why are the same findings not observed with SLT? These considerations remain speculative, and to our knowledge, there are no other reports suggesting a differential effect of PGA drops on OAG versus OHT. However, the original series of RCTs which investigated the efficacy of latanoprost did not report on IOP lowering subdivided by OAG and OHT groups[33–35].

It is also important to note that inferences from these data must consider the potential impact of non-adherence and instillation technique with the use of eye drops, factors which are circumvented with a standardised SLT approach. We also explored regression curves for different severities of OAG, but low patient numbers in moderate and severe OAG groups precluded meaningful results.

It is not clear why higher baseline IOP produces greater IOP lowering effect, both in absolute and relative terms, following SLT and drops. One theory is that a higher pressure gradient may facilitate greater trabecular outflow after SLT[13]. This assumption could be extended to medical therapy which targets aqueous outflow. It has also been suggested that the mechanism of action of SLT, by improving aqueous outflow via the TM[36], may explain the observed greater response with elevated baseline IOP[12]. With higher baseline IOP in OHT and POAG, there is presumably greater resistance to outflow at the level of the TM, and perhaps greater potential

for IOP lowering with a treatment that targets that pathway. This could also explain the more reliable IOP reduction at higher baseline IOP observed with SLT compared to PGA drops reported in this study - with PGA targeting primarily the unconventional pathway and SLT targeting the TM directly, where outflow obstruction is highest. A 'floor effect' to IOP lowering dependent on the post-TM pathway (including episcleral venous pressure) has also been suggested as a reason for less efficacy with SLT at lower baseline IOP[12]. This concept may also help to explain why PGA drops, largely avoiding this pathway, appear to perform better than SLT at lower baseline IOP, the clinical relevance of which is considered below.

At lower baseline IOP < 20 mmHg, PGA drops tended to produce greater percentage (but not absolute) IOP lowering compared to SLT (see table 1 and Figure 3). When we assessed this with a linear mixed effects model (Figure 3), baseline IOPs of $\leq$ 17 mmHg reached significance.

While the numbers of eyes were small at this level of baseline IOP (40 eyes for the drops group, 34 eyes for the SLT group), it is an observation which prompts the question as to whether drops should be preferentially used over SLT for lower baseline IOP? The Collaborative Normal Tension Glaucoma Study demonstrated a slower rate of visual field loss in cases where IOP had been lowered by 30% or more[37]. Using similar inclusion criteria, 20% of eyes in the LiGHT SLT group achieved $\geq$ 30% IOP reduction at 8 weeks, compared to 30% of eyes that received PGA eye drops - demonstrating a modest response for both drops and SLT. Supporting this modest response to a single treatment in NTG patients, a Japanese RCT reported 13-15% IOP reduction with a single agent, either latanoprost or timolol[38]. There is some evidence for the efficacy of SLT in normal tension glaucoma[39–41]; Lee et al demonstrated a 22% reduction in IOP following a single SLT treatment, compared to washout baseline IOP[40]. The study allowed for re-introduction of eye drops and while SLT produced a 41% reduction in medication burden,

absolute success without medication (> 20% reduction from washout baseline IOP) was achieved in only 11.1%. The above findings would suggest that most patients with NTG will require treatment escalation beyond an initial treatment of either medication or laser, in order to achieve adequate IOP lowering, i.e. more than one eye drop or SLT plus drops. A clinically safe and efficient approach would be to offer SLT as a first-line therapy for all suitable patients, and to add topical therapy if adequate IOP lowering is not achieved with SLT alone.

This report has several strengths. To our knowledge, this is the first study to assess IOP lowering in the context of baseline IOP for PGA drops and SLT in a direct comparison. It uses data derived from a prospective multicenter RCT with broad entry criteria that maximize its generalizability. Limiting our analysis to the initial (8 week) IOP response allowed for a data set independent of later clinical decisions which needed to account for disease severity and target IOP, as part of the LiGHT Trial treat-to-target design. In addition, previous work has demonstrated the initial (8 week) IOP response for SLT to be predictive of drop-free disease control at 36 months[7], which supports the use of this time point as an indicator of clinical response. We limited our data to PGA drops in the medication arm, and excluded 19 eyes which were on medications other than PGA, in order to achieve an unmixed dataset for medical therapy. We also performed analysis to include all types of medication, but the results were not significantly different.

An obvious limitation is that this analysis was post hoc, and the sample size of LiGHT was determined on the basis of a power calculation to analyze the primary outcome of health-related quality of life. We did not perform a post hoc power calculation for the IOP-lowering parameters considered in this report, because limitations have been reported with such calculations[42]. However, as previously reported[7], narrow (<1 mmHg) CIs for our pointwise estimates of differences in early IOP lowering between OHT versus OAG eyes and primary SLT versus

topical medication suggest that the study had an adequate sample size to detect a clinically important difference if it exists. This did not apply to analysis of subgroups with lower baseline IOP, where our findings were limited by smaller patient numbers. It should also be noted that the LiGHT Trial treatment algorithm did not take into account CCT as part of the decision to initiate treatment for glaucoma (although this was included for OHT). However, in our results, CCT has a minimal effect on treatment response to SLT or PGA eye drops which is not statistically significant and is unlikely to be of clinical relevance (see supplementary material).

In conclusion, we report that both primary SLT and primary drops treatment for OHT and OAG demonstrate an IOP lowering effect that is dependent on baseline IOP. For both treatments, there is greater IOP lowering at higher baseline IOP and less IOP lowering at lower baseline IOP. There were modest but significant differences in the relationship between baseline IOP and percentage IOP reduction, as well as the probability of ≥ 20% IOP reduction, between the two treatment arms. At higher baseline IOP, SLT performed better and these findings were supported by large group sizes. At lower baseline IOP, drops performed better, but the clinical relevance of this finding was limited by lower numbers of eyes. Whilst we seem to have demonstrated a larger initial IOP reduction with PGA drops at 8 weeks for patients with low baseline IOPs, this does not necessarily translate into a broad recommendation to initiate therapy with drops rather than SLT. Many other factors must clearly be taken into account, such as adherence, side effects, tolerability of treatment, and other additional findings of greater visual field preservation with SLT despite comparably treated IOPs[43].

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FIGURE LEGENDS:

Figure 1. Percentage IOP reduction.

Graph demonstrating mean percentage IOP reduction at different levels of baseline IOP, for drops (red) versus SLT (blue) treatment arms. Values for mean percentage IOP reduction are shown below the graph. Numbers in each group are labelled within the bars. Error bars = standard error of the mean (SEM). IOP = intraocular pressure.

Figure 2. Slope of Percentage IOP reduction versus baseline IOP.

Graph of % IOP reduction versus baseline IOP for treatment with drops (red) and SLT (blue). The slope of the lines is significantly different between the 2 groups ($p = 0.04$), with SLT producing greater % IOP reduction at higher baseline IOP compared to drops. At lower baseline IOP, drops produced greater % IOP reduction. Error bars represent +/- SD.

Figure 3. IOP lowering difference (SLT - drops) between treatment arms against baseline IOP.

The graphs show the estimated difference in IOP reduction between the two arms for different levels of baseline IOP (SLT - PGA drops). The error bars represent the 95%-Confidence Intervals (CIs). A significant difference is indicated by 95%-CIs not crossing the line of no difference (dashed). Notice how the relationship is essentially constant for absolute reduction, showing no difference between the two arms at any baseline IOP. The difference in percentage reduction, however, changes with the level of baseline, reflecting the significant difference in the interaction term of the linear mixed effects model.

Figure 4. Regression curves demonstrating probability of ≥ 20% IOP reduction at different levels of baseline IOP.

559 Logistic curves demonstrating the rate of ≥ 20% IOP reduction from baseline for varying levels of Baseline
560 IOP, across all disease severities. The blue curve represents response for patients treated with SLT. The red
561 curve indicates response for patients treated with eye drops. P=0.01, mixed effects logistic regression.
562

563 Figure 5. Response curves for OHT and OAG.

564 Regression curves to demonstrate the rate of ≥ 20% IOP reduction for varying levels of Baseline IOP, for
565 OHT (left) and open angle glaucoma of all severities (right). The upper panel shows results across all
566 baseline IOPs, whereas the lower panel shows results limited to baseline IOP > 21 mmHg. The blue curve
567 represents response for patients treated with SLT. The red curve indicates response for patients treated
568 with eye drops. Across all baseline IOPs: OHT, p = 0.76; for OAG, p = 0.005. For baseline IOP > 21 mmHg:
569 OHT, p = 0.93; OAG, p = 0.02; mixed effects logistic regression.

Figure 1

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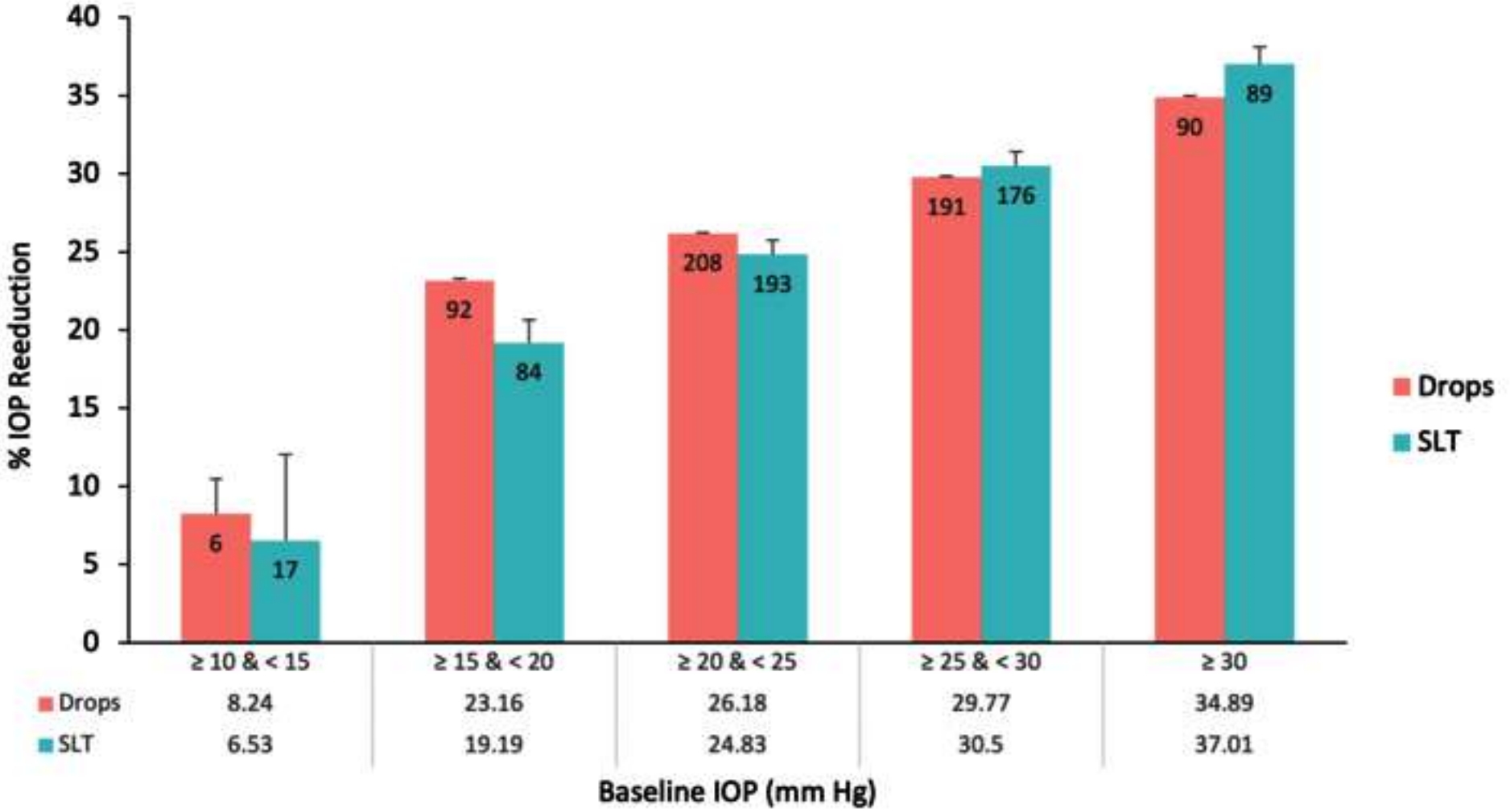

Figure 2

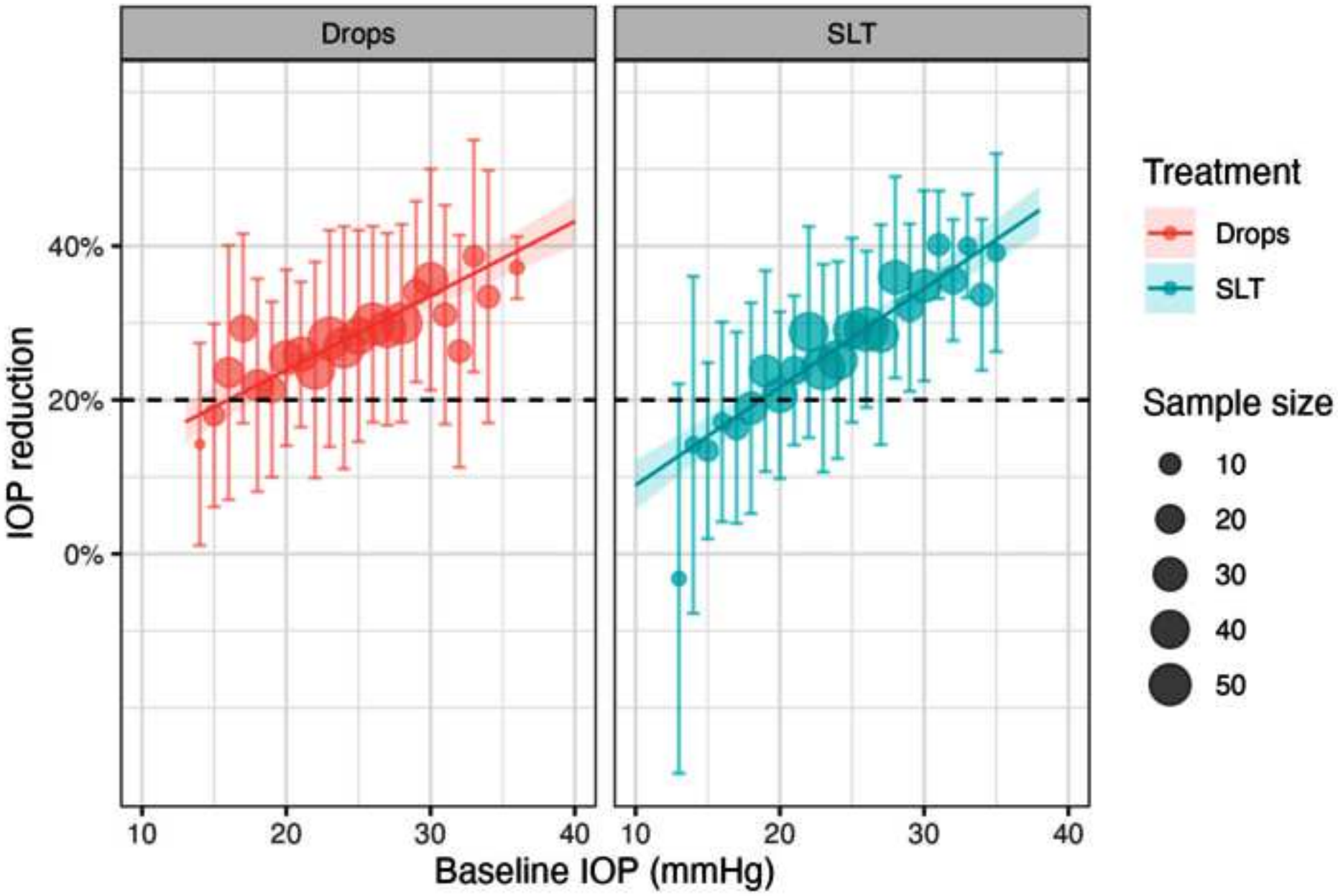

Figure 3

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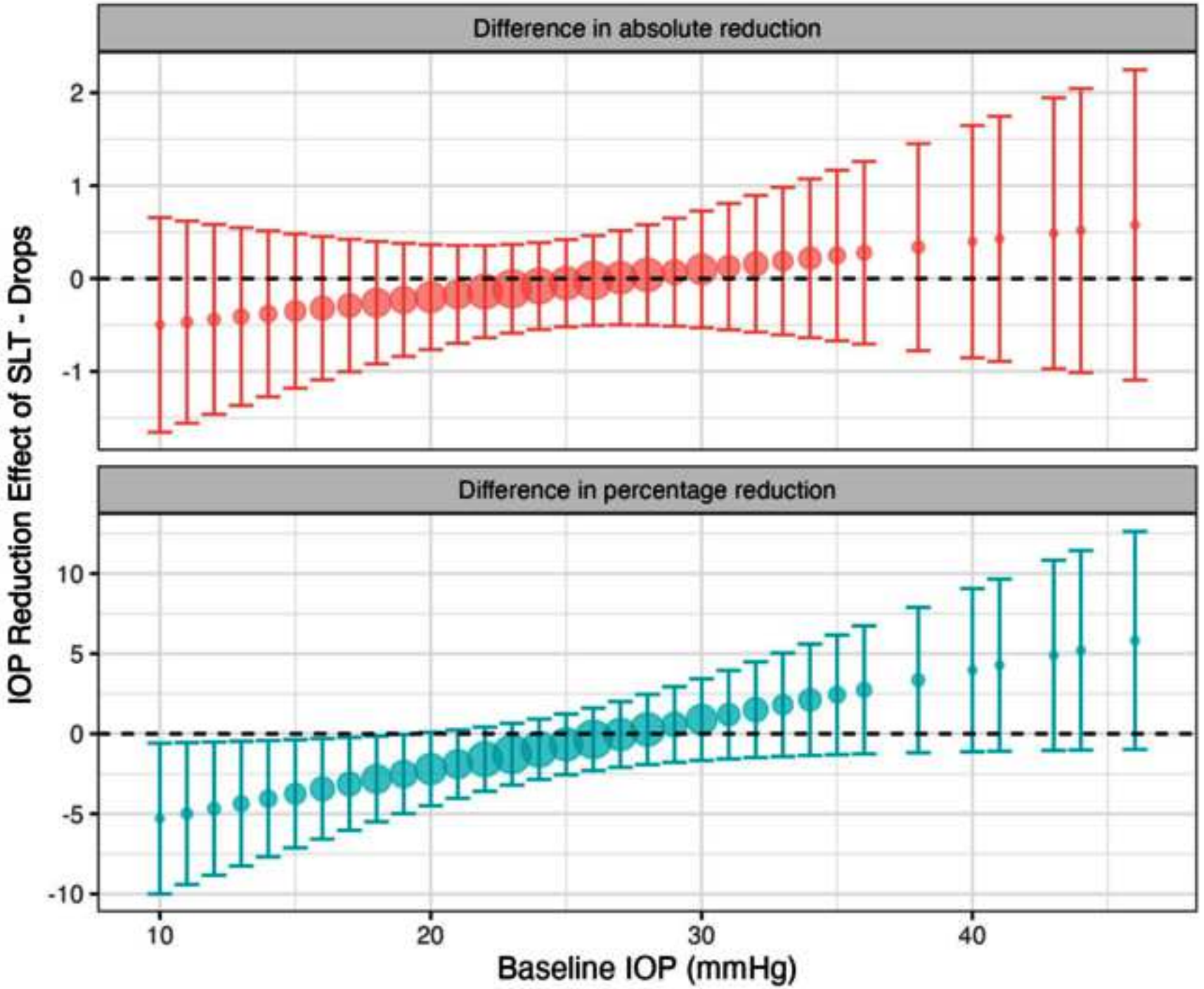


Figure 4

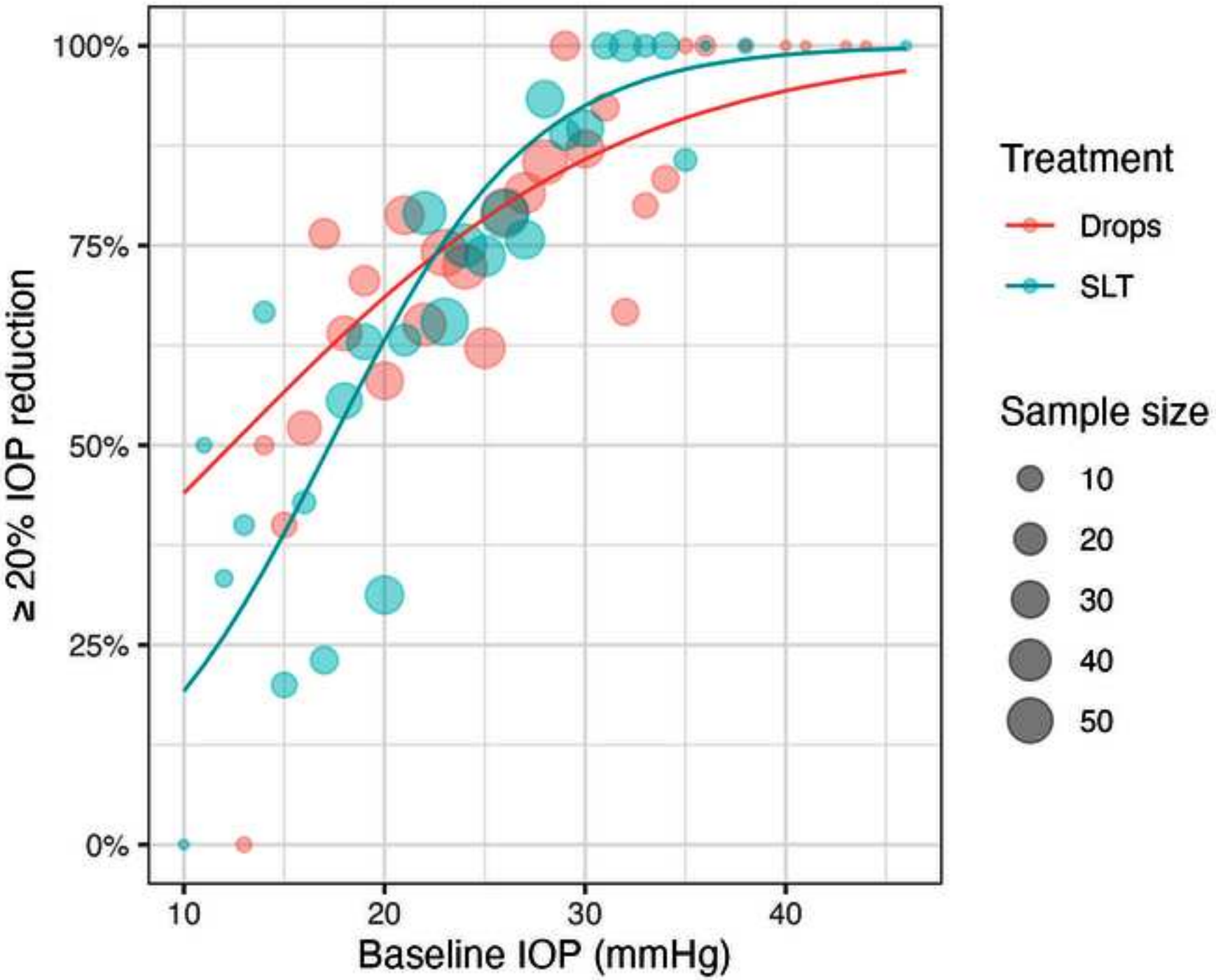


Figure 5

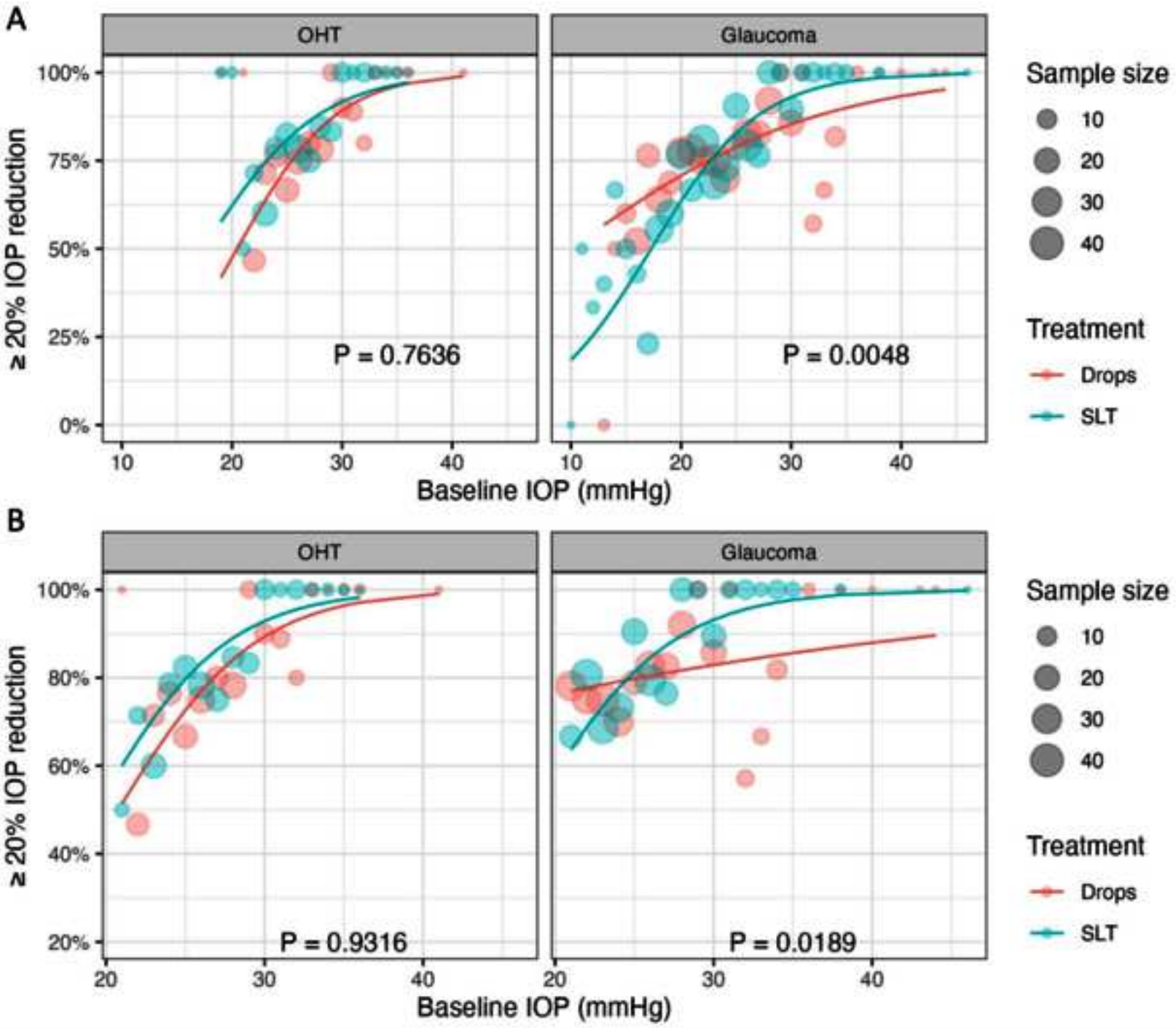


Table 1. Baseline demographic and clinical characteristics for medication and Selective Laser Trabeculoplasty arms.

	Drops (337 patients, 587 eyes)	**SLT (325 patients, 559 eyes)**
Age (yrs), mean (SD)	63.2 (11.6)	63.4 (12.1)
Sex		
Male	183 (54.3)	199 (56.1)
Female	154 (45.7)	156 (43.9)
Ethnic Origin		
Black	58 (17.2)	77 (21.7)
White	248 (73.6)	242 (68.2)
South Asian	26 (7.7)	22 (6.2)
Other	5 (1.5)	14 (3.9)
Diagnosis (eyes), (%)		
OHT	169 (28.8)	195 (31.9)
OAG	418 (71.2)	416 (68.1)
Family history of glaucoma of 1st degree relative		
Yes	98 (29.1)	107 (30.2)
No	239 (70.1)	247 (69.8)

Data are presented as number of patients (%), unless otherwise specified. SD = standard deviation; OHT = ocular hypertension; OAG = open angle glaucoma. Self-defined ethnicity; Black ethnicity refers to Caribbean, African, and any other black background, South Asian ethnicity refers to Indian, Pakistani, Bangladeshi, and any other South Asian background, Other ethnicity refers to Chinese and any other ethnic groups.

Table 2. Baseline ocular characteristics for medication and Selective Laser Trabeculoplasty arms.

	Drops (587 eyes)	**SLT (559 eyes)**
Diagnosis at trial initiation (eyes), (%)		
Ocular hypertension	169 (28.8)	195 (31.9)
Mild OAG	309 (52.6)	309 (50.6)
Mod OAG	74 (12.6)	67 (11.0)
Severe OAG	25 (6.0)	40 (6.6)
Visual acuity (LogMAR)	0.05 (0.14)	0.08 (0.18)
Visual field mean deviation (dB)	-3.05 (3.6)	-3.03 (3.4)
HRT rim area (mm^2)	1.14 (0.36)	1.16 (0.36)
Intraocular pressure (mmHg)	24.38 (5.02)	24.46 (5.19)
CCT (µm)	551.44 (36.31)	550.64 (38.13)
Pseudo-exfoliation (eyes), (%)	11 (1.87)	5 (0.82)
Pseudophakia (eyes), (%)	30 (5.11)	39 (6.38)

Data are presented as mean (SD), unless otherwise specified. SD = standard deviation; OAG = open angle glaucoma; logMAR = logarithm of the minimum angle of resolution; HRT = Heidelberg Retina Tomography; CCT = central corneal thickness; dB = decibels.

Table 3. Intraocular pressure response at 8 weeks following treatment with either medication or selective laser trabeculoplasty.

	Drops (587 eyes)	**SLT (559 eyes)**	**P value**
IOP at 8 weeks	17.33 (4.2)	17.31 (3.67)	0.92
Mean IOP reduction	7.04 (4.25)	6.93 (4.24)	0.52
% IOP reduction	28.02 (14.12)	27.15 (14.31)	0.28

Data are presented as mean (SD). SD = standard deviation; IOP = intraocular pressure. Statistical comparison was made using mixed effects model to account for random effects.

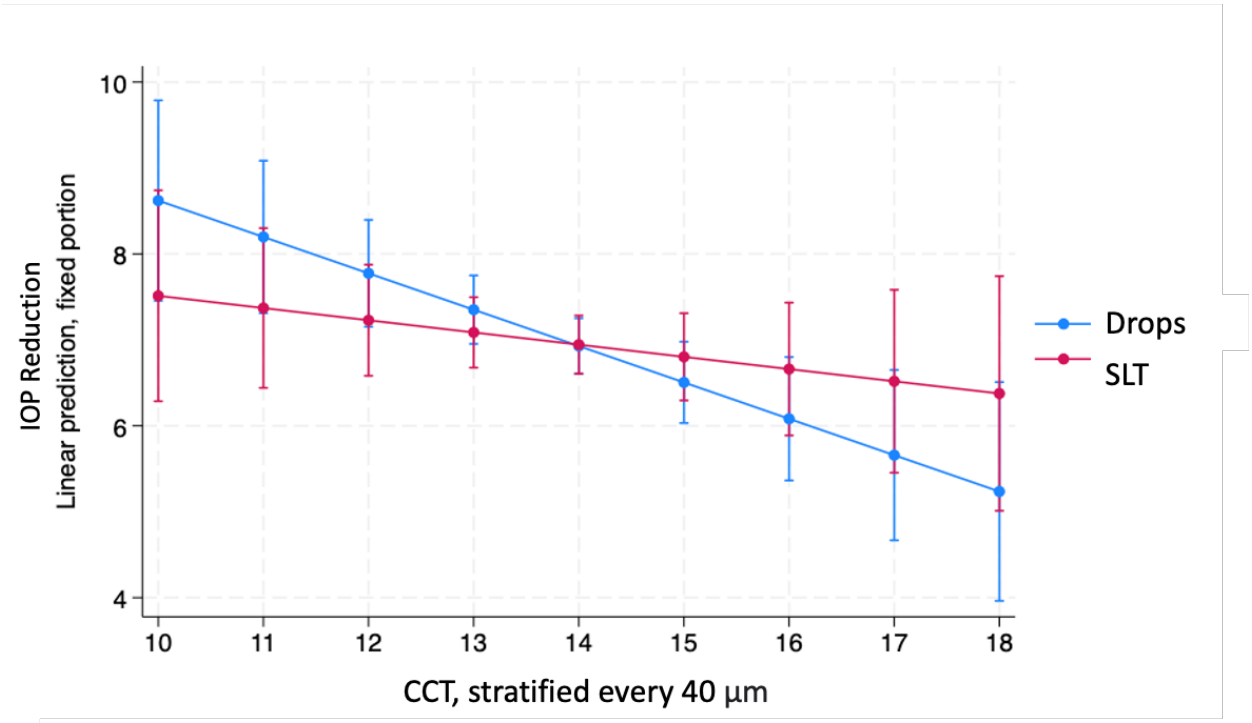
Table 4: Proportion of eyes achieving ≥ 20% IOP reduction, comparing drops and SLT, for different ranges of baseline IOP.

Baseline IOP (mmHg)	Proportion of eyes achieving ≥ 20% IOP reduction, % (n)	
	Drops	**SLT**
Overall	76% (446/587)	78.1% (477/611)
≥ 10 & < 15	33.3% (2/6)	50% (9/18)
≥ 15 & < 20	64.1% (59/92)	51.2% (43/84)
≥ 20 & < 25	73.1% (152/208)	75.5% (163/216)
≥ 25 & < 30	81.7% (156/191)	84.4% (157/186)
≥ 30	85.6% (77/90)	98.1% (105/107)

IOP = intraocular pressure.

Supplementary Material

Supplementary Figure 1. Linear prediction modelling IOP reduction, baseline IOP and CCT.



In a mixed model with IOP Reduction as the dependent variable and including baseline IOP and CCT as independent variables, using SLT as an interaction term, there was no significant relationship between CCT and IOP reduction ($P > 0.05$). As CCT decreased, IOP reduction increased, and as CCT increased, IOP reduction decreased. This effect was slightly more pronounced for the medication group, but the difference was not significant. Error bars represent 95% confidence intervals.

Supplementary Material

Supplementary table 1. IOP reduction stratified by thick and thin CCT.

Including all baseline IOPs	Drops			SLT		
	IOP Reduction	% reduction	≥20% reduction	IOP Reduction	% reduction	≥20% reduction
All CCT	7 (4.3)	27.9 (14.1)	456/606 (75.2%)	6.9 (4.2)	27.1 (14.3)	427/561 (76%)
CCT < 555	7.1 (4.4)	28.8 (14.4)	238/317 (75.1%)	6.7 (4)	27.4 (13.7)	228/299 (76.3%)
CCT > 555	6.8 (4.2)	26.6 (13.9)	207/277 (74.7%)	7.2 (4.4)	26.8 (15)	195/256 (76.2%)
Difference between thick and thin CCT	0.3 mmHg	1.4%	0.4%	0.5 mmHg	0.6%	0.1%

Absolute IOP reduction, % IOP reduction and proportion of eyes achieving ≥20% IOP reduction. Data are presented as mean (SD) or % where appropriate. Thin CCT (< 555 μm) produced slightly higher IOP reduction compared to thick CCT (> 555 μm), reflecting the linear model in supplementary figure 1. This effect size was negligible and the difference is presented in the lowest row.

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