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Two-year visual field outcomes of the treatment for advanced glaucoma study (TAGS)

Giovanni Montesano, MD[1,2], Giovanni Ometto, PhD[1], Anthony King MD[3], David F. Garway-Heath, MD[2], David P. Crabb, PhD[1]

1. City, University of London, Optometry and Visual Sciences, London, UK
2. NIHR Biomedical Research Centre, Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, London, UK
3. Department of Ophthalmology, Nottingham University Hospital, Nottingham, UK

Corresponding author: David P. Crabb
Email: david.crabb.1@city.ac.uk
Phone number: +44 (0)20 7040 0191
Fax number: None
Address: City, University of London
Northampton Square, London
EC1V 0HB, United Kingdom

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Short title: Two-year visual field outcomes of TAGS

Precis

In the treatment for advanced glaucoma study (TAGS), trabeculectomy as first treatment did not significantly reduce the average global progression in advanced glaucoma at two years compared to medical treatment, but significantly reduced the proportion of progressing eyes.

Abstract

Purpose: to compare visual field (VF) progression between the two arms of the Treatment of Advanced Glaucoma Study (TAGS)

Design: post-hoc analysis of VF data from a two-arm multicenter randomized controlled clinical trial

Methods: 453 patients with newly diagnosed advanced open-angle glaucoma in at least one eye from 27 centers in the United Kingdom were randomized to either trabeculectomy (N = 227) or medications in their index eye (N = 226) and followed-up for two years with two 24-2 VF tests at baseline, 4, 12 and 24 months. We analyzed data for participants with a reliable VF (False positive rate < 15%) at baseline and at least two other time-points.

Main Outcome Measures: Average difference in rate of progression (RoP) was analyzed using a hierarchical Bayesian model. Time for each eye to progress from baseline beyond specific cut-offs (0.5, 1, 1.5 and 2 dB) was compared using survival analysis.

Results: 211 eyes in the trabeculectomy-first arm and 203 eyes in the medications-first arm were analyzed. The average RoPs (Estimate [95% Credible Intervals]) were -0.59 [-0.88, -0.31] dB/year in the medications-first arm and -0.40 [-0.67, -0.13] dB/year in the trabeculectomy-first arm. The difference was not significant (Bayesian p-value = 0.353). More eyes progressed in the medications-first arm: ≥0.5 dB (p = 0.001), ≥1dB (p = 0.014), ≥1.5dB (p = 0.071) and ≥2dB (p = 0.061).

Conclusions: there was no significant difference in the average RoP at two years. Initial trabeculectomy significantly reduced the proportion of progressing eyes.

Introduction

At present, the only treatment for glaucoma is the reduction of intraocular pressure (IOP)[1-3]. Trabeculectomy is the most commonly performed surgical intervention and has been proven to be more effective than medications (drops) in achieving lower IOP[4]. For this reason, clinical guidelines in the UK and Europe suggest that trabeculectomy be offered to patients with advanced glaucoma as the first line of treatment[5, 6]. No specific guidelines, with respect to the appropriate timing of surgical intervention, exist for North America[7, 8]. Evidence to support such recommendations is scant[5] and practitioners are often not keen to offer surgery owing to possible sight-threatening complications[5, 9]. As a result, patients are usually treated with drops and/or laser, and are offered surgery only when initial interventions prove ineffective.

The Treatment of Advanced Glaucoma Study (TAGS) is a recently completed multicentre randomised controlled trial (RCT) comparing medical versus surgical (trabeculectomy) treatments in patients presenting with previously untreated advanced open angle glaucoma (OAG)[10-12]. The primary outcome was vision related quality of life (QoL) measured using the Visual Function Questionnaire-25 (VFQ-25). Recently reported results indicated no difference in this primary outcome between

treatment arms for the period of the study (24 months)[11]. However, patient self-reported outcome measures have been shown to lack sensitivity in detecting visual deterioration from glaucoma[13].

Visual field (VF) tests are an important clinical measure in glaucoma [5, 7, 14] and have been successfully used as a primary outcome in previous important glaucoma trials[2, 3, 15-20]. In the primary report of results from TAGS, the average difference in VF mean deviation (MD) between baseline and 24 months showed no difference between the two groups, despite an average 3 mmHg difference in IOP favouring trabeculectomy. However, TAGS was designed such that series of 24-2 VFs (Humphrey Field Analyzer [HFA], Zeiss Meditec, Dublin, CA) were collected at baseline, 4, 12 and 24 months; the main trial report did not take account of all these data. Previous RCTs[2, 15-20] recognised the importance of analysing localised change in VF data to detect treatment difference. Recently, a VF pointwise analysis using a hierarchical approach for estimating rate (speed) of VF loss in data from the Laser in Glaucoma and Ocular Hypertension Trial (LiGHT) showed differences in the treatment arms not seen in the primary QoL measure used in that trial[21]. We have recently validated and expanded the statistical methods used in the LiGHT VF analysis to account for these features and to maximally exploit the pointwise data from individual locations in the VF[22]. In this study we apply these methods to the serial VF data from TAGs with the objective of identifying whether there is a treatment difference between the study arms not seen in the primary outcome.

Methods

Participants

TAGS was a multicentre randomised controlled trial involving 27 centres across the United Kingdom. The study was approved by the East Midlands – Derby Research Ethics Committee (reference number 13/EM/0395) and adhered to the tenets of the declaration of Helsinki. Details of the study protocol have been reported elsewhere[10, 23]. Briefly, the study recruited patients with a new diagnosis of advanced open angle glaucoma (OAG), according to the Hodapp-Parrish-Anderson classification[24] of VF damage, including pigment dispersion, pseudoexfoliative and normal tension glaucoma, in one or both eyes. Exclusion criteria were angle closure or other forms of secondary glaucoma, inability to undergo surgery and high-risk of trabeculectomy failure (patients with a history of complicated cataract surgery or previous surgery involving violation of the conjunctiva, including vitreoretinal procedures). Participants were randomised to receive either trabeculectomy (augmented with Mytomicin C) or medical management as their first intervention. If both eyes were eligible, the less affected eye, according to the 24-2 HFA MD (MD) at baseline, was selected as the index eye and analysed, but both eyes received the same treatment. This choice was made to give patients with bilateral advanced glaucoma randomised to surgery the best chance of preserving vision in their better eye, as surgery was performed on the index eye first. For people randomised to trabeculectomy, medical treatment was initiated until surgery was performed (ideally within 3 months). Medications for participants randomised to medical treatment were escalated according to the NICE guidelines[5], based on clinical judgment. If medical treatment was deemed inadequate, augmented trabeculectomy was offered. Participants were followed up for 24 months for the primary endpoint. Clinical examinations included HFA VF testing (SITA Standard 24-2 testing grid), visual acuity, Goldmann applanation tonometry for intraocular pressure (IOP) measurement, and assessment for complications of treatment and the need for cataract surgery. The study recruited 453 participants (227 randomised to trabeculectomy). Baseline demographics of the sample have been previously described[11]. Relevant characteristics are reported in **Table 1**.

Visual field data

Two VF tests were performed at each trial visit at baseline, 4, 12 and 24 months. Therefore, each trial participant was scheduled to have a series of eight VFs, giving a total of 3624 planned VF test. Printouts were scanned by the individual centres and stored in a central repository at the clinical trials unit of the University of Aberdeen. For this study, scans were sent to City, University of London for digitization under a data transfer agreement. The pointwise sensitivity thresholds and the false positive (FP) rate were digitized using a bespoke optical character recognition algorithm and independently checked by two graders (GM and GO). We were able to digitize 3266 (90%) VFs from 452 patients (226 per arm). Remaining VFs were either not performed or not provided by the centres. We only analysed data from participants for whom at least three reliable VFs from at least three different time-points, including one at baseline, were available. Reliability was defined as FPs < 15%, as this has been shown to be the only reliable indicator of VF performance[25]. The final selection (see flowchart in **supplementary material, Figure S6**) included 414 (91%) participants, 211 randomised to have trabeculectomy first. Of these, 22 did not actually receive surgery and continued their treatment with drops. For the final selection, the median [Interquartile range] number of VFs per patient was 8 [5 - 8] for both trial arms.

Statistical analysis

Main outcome

The primary outcome measure for this work was the difference in overall rate of progression (RoP [dB/year]) of VF damage between the two trial arms in the index eye. RoP was estimated using a hierarchical mixed effect model described in detail elsewhere[26]. In short, the response variable was the point-wise sensitivity (in dB) over time (i.e. at each location). Time from baseline (in years) and the treatment allocation arm (coded as a binary discrete factor) were used as fixed effects. The interaction between these fixed effects modelled the difference in progression rate between the two arms (main outcome of interest). Observations were then grouped by location, VF cluster and eye in a hierarchical nested fashion, as previously described[26]. Clusters were defined according to Garway-Heath et al.[27] The method also accounts for the measurement floor at 0 dB by censoring the observations where no response was recorded (< 0 dB on the VF printout) as considering these observations as actual 0 dB measurements can introduce a bias in the estimated RoPs[26].

These models are complex to estimate with maximum likelihood methods. Therefore, we used R (R Foundation for Statistical Computing) and JAGS (Just Another Gibbs Sampler[28]) to estimate the parameters through Bayesian computation, as previously described[26]. Details of the computation are provided as **supplementary material**. Bayesian computation does not produce p-values. However, a similar metric, with little difference in interpretation, is derived from the Bayesian *P-direction*[29]. We will denote this index as p_d, while p will be reserved for the conventional frequentist p-value. For both metrics, the threshold for statistical significance was 0.05.

Analysis was performed using both the original randomisation (*intention-to-treat*) and the actual treatment received (*analysis by treatment received*), since 22 patients randomised to trabeculectomy were kept on medical treatment and did not undergo surgery. Finally, the analysis was also repeated with standard maximum likelihood (ML) methods (*lme4* package for R[30]) using a simplified model that did not account for censoring and VF clusters (results reported in **supplementary material**).

No power or sample size calculation was performed as these were all post-hoc analyses of trial data.

Secondary outcomes

The primary analysis was repeated using the VF clusters as fixed effects (details in **supplementary material**) so that the mean regional baseline VF damage and RoPs could be explicitly modelled and compared. Other analyses, listed below, were performed by fitting individual hierarchical models to each eye, as previously described[26] (i.e. each eye was modelled in isolation independently of their randomisation) to assess how treatment affected individual patients and localised progression

- *Time to visual field progression:* for each eye, a progression event was defined as an estimated global change from baseline by more than four pre-defined cut-off values (0.5, 1, 1.5 and 2 dB) over the observation period. The time to the event (in years) was estimated as cut-off/RoP and censored at the last actually observed time point. A Cox proportional hazard model was used to compare the two arms at each cut-off. Note that, for this analysis, all the data in the series were used to estimate when the event occurred. This improved accuracy, as events could be detected in between visits, and reduced the impact of noise fluctuations.
- *Time to convert to perimetric blindness for each location:* estimates of time to cross 0 dB sensitivity threshold were obtained for each location in each eye from the fitted slopes and

intercepts. This analysis was limited to locations with an estimated intercept > 0 dB at baseline. A Cox proportional hazard model was used to compare the two arms. Correlations among locations from the same eyes were accounted for using a robust variance estimation and a cluster term (*survival* package in R[31]). The comparison was limited to the actual observation time. The same analysis was repeated by only considering the 12 locations within the central 10 degrees, to evaluate the impact on central vision.

- *Local progression rate:* Finally, the RoP of the fastest progressing cluster and the 5 fastest locations with intercept > 0 dB were extracted for each eye. The distribution of the RoP of fastest cluster and of the average RoP of the 5 fastest locations were compared using a non-parametric test (Mann-Whitney).

A supplementary analysis was also performed to evaluate differences in the distribution of all point-wise slopes. The detailed methodology and results are reported as **supplementary material**.

Results

Main outcome

Eyes in the two arms of the study, for both the intention-to-treat and analysis by treatment received, had similar average baseline VF sensitivity as estimated by the intercepts of the model (**Table 2**), as it would be expected from a RCT. Mean RoP (intention-to-treat) was -0.58 and -0.39 dB per year for the medication first and trabeculectomy first arm respectively; the 20% difference was not statistically significant (p_d = 0.353). Similarly, there was no difference with an analysis by treatment received (RoP -0.55 and -0.43 dB per year for medication first and the trabeculectomy first respectively, p_d = 0.553). Comparing individual VF clusters (secondary outcome) confirmed these results. The largest difference in mean RoP was recorded for the paracentral superior cluster (Cluster 2) but the effect was still not statistically significant (p_d = 0.159). **Table 2** reports the results for the intention-to-treat analysis in detail. Results for the analysis by treatment received are reported as **supplementary material, Table S1**. Similar results were obtained with standard ML frequentist methods (see **supplementary material, Table S2**). **Figure 1** graphically shows the average spatial distribution of VF damage at baseline and RoP for the two arms.

Secondary outcomes

In the intention-to-treat analysis, a significantly higher proportion of eyes showed a change of at least 0.5 dB (p = 0.001) and 1 dB (p = 0.014) from baseline in the medication first arm (**Figure 2**). Significance was not reached for the 1.5 dB and 2 dB cut-offs. Similar results were obtained when performing the analysis by treatment received (**supplementary material, Figure S4**), indicating a different proportion of slow and moderate progressors, but similar amounts of fast progressors. We could not find any statistically significant difference in the time to perimetric blindness in the intention-to-treat analysis either when examining the whole VF (p = 0.079) or just the central 10 degrees (p = 0.096). Similar results were found in the analysis by treatment received (whole VF: p = 0.191; central 10 degrees: p = 0.218). Further details are reported as **supplementary material (Figure S5)**.

There was no statistically significant difference in the distribution of the average RoP of the 5 fastest progressing locations or the fastest progressing cluster (see **Figure 3**).

Discussion

Our main outcome did not show any statistically significant difference in the rate of VF progression in patients randomised to trabeculectomy first compared to medication first after 24 months of follow-up. We also explored possible differences in localised progression, by analysing the average progression rate for different VF clusters, by comparing the RoP of the fastest cluster and the average RoP of the 5 fastest locations in each eye and, finally, by comparing the time to estimated perimetric blindness of individual locations. These comparisons all failed to reach significance. However, we found a significantly higher percentage of eyes progressing beyond specific cut-offs from baseline sensitivity, indicating lower frequency of progressive VF loss in eyes receiving trabeculectomy first.

Our work is novel because it provides a detailed evaluation of VF progression in patients with advanced glaucoma having primary medical or surgical intervention in an RCT. Differences in RoP between the treatment arms of the trial were quantified through a hierarchical model able to fully exploit the information from individual locations in the VF. Moreover, our model accounted for the censoring of VF data at 0 dB, avoiding the floor effect which may cause positive bias in the estimated RoP, especially with advanced VF loss[26]. Our secondary analyses evaluated progression in different VF clusters, localised progression and point-wise conversion to perimetric blindness (estimated sensitivity below 0 dB).

Taken together, our main results suggest equivalence in terms of progression of VF damage between the two treatment approaches within the first two years after initiating treatment, but there is also evidence to suggest that the small difference observed might increase in the future. This is consistent with the main results of the trial[11] which shows no difference in vision related QoL between the two arms at the two-year time point. These results are clinically important, and may reflect the differences observed in the control of the IOP between the two arms[11].

More indications of a possible difference come from our secondary VF analyses. The time to VF progression (**Figure 2**) showed a significantly higher proportion of slow/moderate progressors in the medication first arm. The difference did not reach significance in fast progressors, likely because of the smaller sample size. This analysis is key to understanding the effect of treatment on individual patients, rather than the average effect across the cohort. This result is in partial agreement with similar previous randomised clinical trials comparing primary medical and surgical treatment, such as the Collaborative Glaucoma Intervention Study (CIGTS)[32], which reported marginally (4%) more progressing eyes in patients with early glaucoma in the medication first arm compared to the trabeculectomy first arm. However, later analyses of the same cohort showed a significant difference in MD between the two arms of the trial for patients with advanced baseline damage at 7 and 9 years, despite not showing any significant difference up to 5 years[20]. Similarly, the small differences in the average RoP observed in our cohort might amplify over a longer follow-up period. Similar results were obtained by analysing progression of individual clusters the cluster and locations. One relevant observation from the evaluation for our cohort of patients was that the number of locations converting to perimetric blindness (estimated sensitivity < 0 dB), was slightly higher for the medications first arm. The difference was, however, not statistically significant. Finally, we could not find any statistically significant difference in local progression, tested by examining the rate of the fastest progressing cluster and the average RoP of the 5 fastest progressing locations for each eye. This analysis allowed us to examine differences in progression rates in the regions of the VF progressing most rapidly, that might not be well captured by the main analysis on the difference in mean RoP. A similar approach has proven useful when analysing VF data from LiGHT[22], in which

most of the difference between the two arms of the trial was located in the extreme negative tails of the distributions of point-wise progression slopes. An additional analysis, more akin to the one performed by Wright et al.[22], is reported as **supplementary material**.

Our analysis has limitations. The limited follow up time (2 years) is short in the context of a median life expectancy at diagnosis of around 14 years[33] and this makes the identification of statistically significant differences challenging, especially with advanced damage[34, 35] because it is well known that VF variability increases with the amount of damage.[25] The relatively small difference in progression rates between treatment arms is expected because all patients are treated to low IOPs in advanced glaucoma. The IOP reduction achieved in both arms of TAGS was about 3 mmHg greater than that achieved in CIGTS[32]. The increased test variability was partially addressed by having two repetitions of the VF test at each time point and the use of a trend analysis over an event-based analysis. Our modelling technique also eliminates the bias introduced by the floor effect at 0 dB[26]. However, it cannot overcome the fact that many locations would provide limited information, being at or very close to the 0 dB limit. One possibility for future trials could be to test these patients with macular testing patterns, such as the 10-2. The time-to-progression estimates might also be influenced by the effect of developing cataract. Non-glaucoma related changes in vision from a treatment should also be considered as part of the effect, as they can negatively impact QoL. Lens opacity was not graded in the trial, however, the number of patients needing cataract surgery was not different between the two arms (12% for the medication first arm and 13% for the trabeculectomy first arm)[11]. Still, a small significant difference was found in logMAR visual acuity at 24 months (0.07, 95% CIs 0.02-0.11, p = 0.006)[11], possibly indicating more lens opacity in the trabeculectomy first arm. This could have caused non-glaucomatous VF worsening in the trabeculectomy first group, reducing the measured differences between the two arms. Metrics that correct for generalised loss, such as Pattern Deviation maps, are not appropriate to quantify advanced glaucomatous damage[36, 37] and were therefore not considered for this analysis. However, in a study of glaucoma patients undergoing cataract surgery, visual acuity improved by 0.17 logMAR, yet there was a negligible impact on the VF with a difference in MD of only 0.06 dB[38]. Therefore, we consider it unlikely that developing cataract has greatly influenced the difference between the treatment groups. One important final note is that lack of a significant difference does not necessarily indicate equivalence. This is especially true for our results, where many non-significant p-values were smaller than 0.1, and this should be taken into account when interpreting the results. Finally, most patients included in TAGS were Caucasian, and this might limit generalizability to other populations. Future investigations will focus on the specific role of IOP control and other relevant baseline characteristics of disease progression in TAGS.

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Figure legends

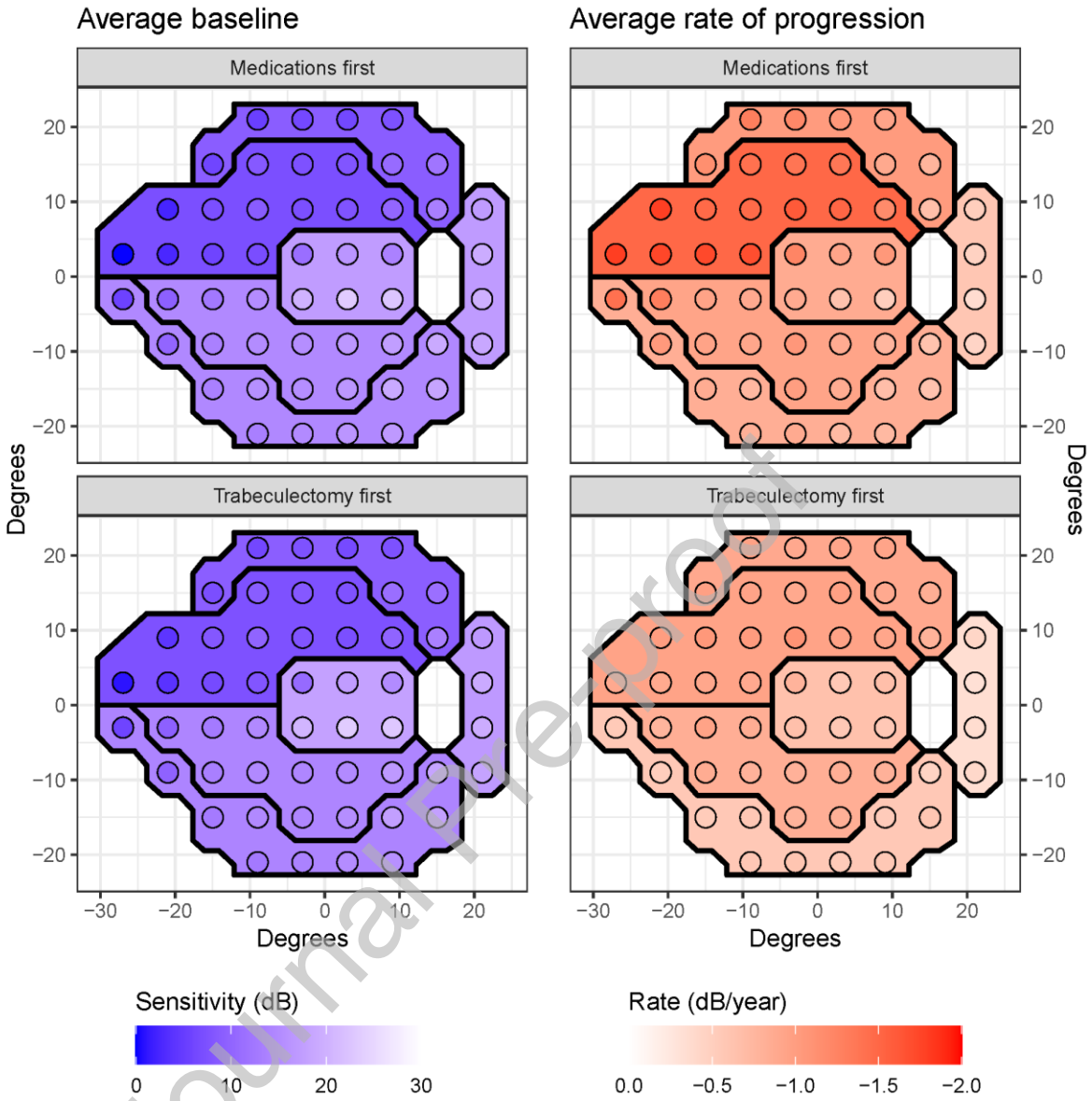

Figure 1. Average baseline damage and rate of progression for each location and Garway-Heath cluster. Unlike the estimates reported in Table 2, these plots are produced by averaging estimates from fits on individual eyes.

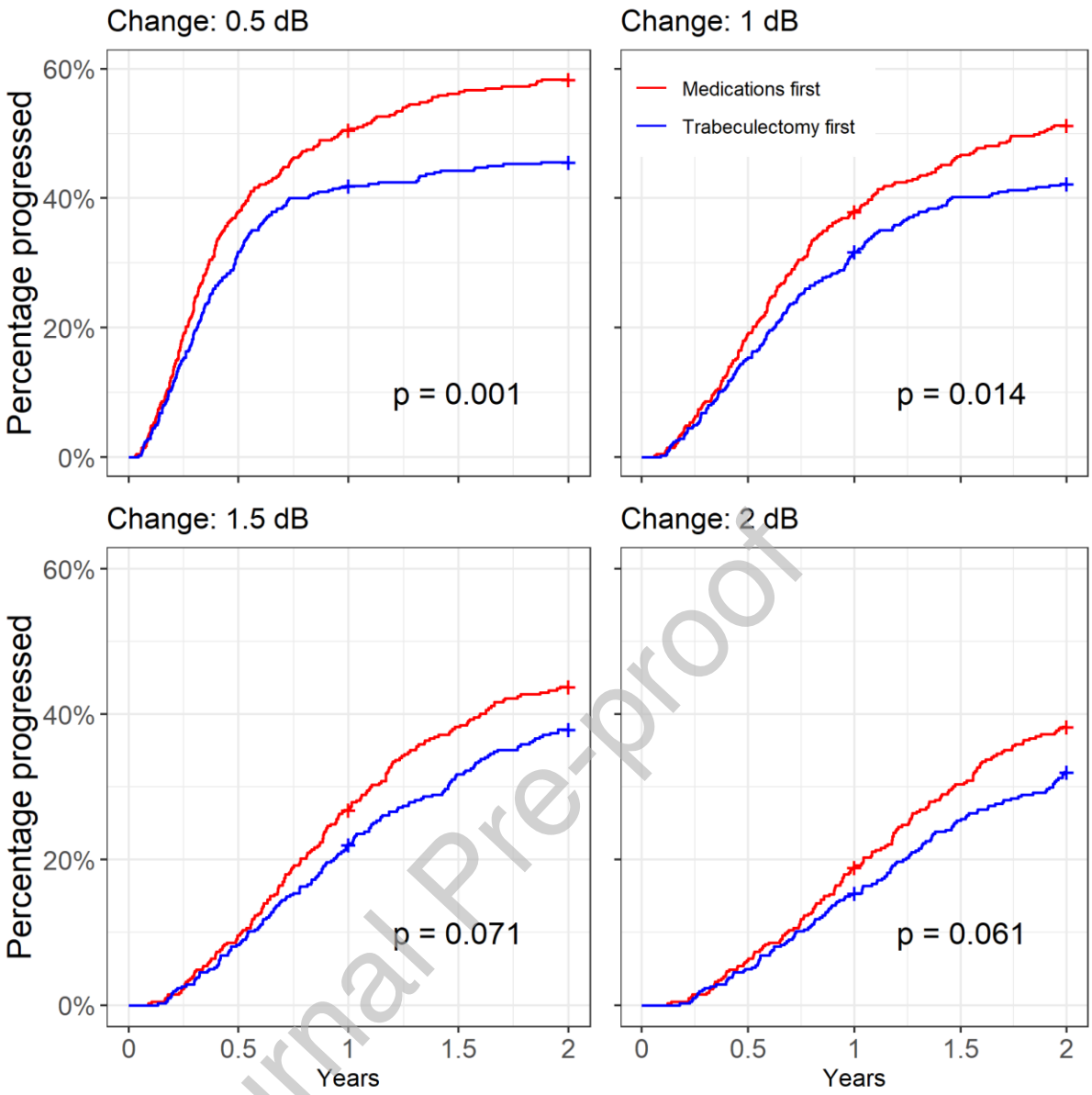

Figure 2. Estimated time to observe a change from baseline for different cut-offs. P-values were calculated with a proportional hazard model. Cross marks indicated censored data.

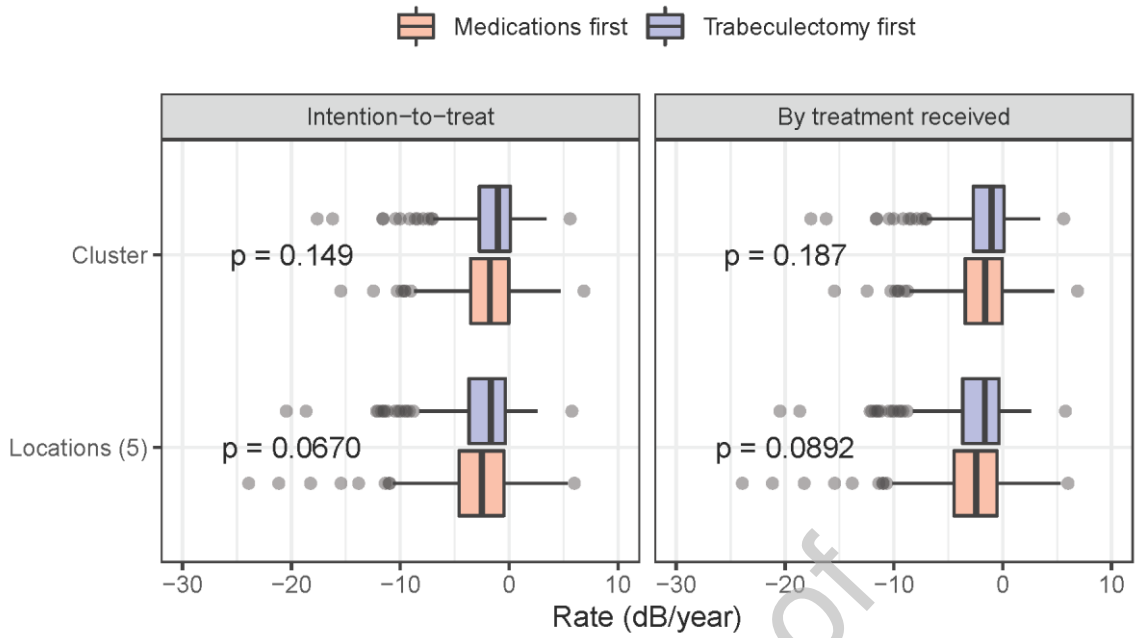

Figure 3. Comparison of the rate of progression for the fastest cluster and the average of the five fastest locations for each eye. Estimates obtained from individual fits on each eye. P-values obtained with a Mann-Whitney test.

	Medications first (n=226)	**Trabeculectomy first (n=227)**
Mean (SD) age, years	68 (12.4)	67 (12.2)
Male sex	147 (65%)	156 (69%)
Ethnicity:		
White	191 (85)	182 (80%)
Afro-Caribbean	27 (12%)	32 (14%)
Asian—India/Pakistan/Bangladesh	4 (2%)	8 (4%)
Asian—Oriental	0 (0%)	2 (1%)
Mixed heritage	1 (<1%)	0 (0%)
Other	2 (1%)	3 (1%)
Missing	1 (<1%)	0 (0%)
Glaucoma diagnosis:		
Primary OAG (including NTG)	220 (97%)	219 (96%)
Pigment dispersion syndrome	4 (2%)	5 (2%)
Pseudoexfoliation syndrome	2 (1%)	3 (1%)
Lens status:		
Phakic	209 (92%)	212 (93%)
Pseudophakic	17 (8%)	15 (7%)
Mean (SD) central corneal thickness, µm	541 (36); n=223	539.4 (36); n=226
Glaucoma medications at baseline:		
Prostaglandin analogue	182 (81%)	186 (82%)
β blocker	52 (23%)	52 (23%)

Carbonic anhydrase inhibitor	33 (15%)	45 (20%)
α agonist	4 (2%)	7 (3)
Diamox (taken orally)	2 (1%)	6 (3%)
Ocular comorbidity	50 (22%)	50 (22%)
Age related macular degeneration	4 (8%)	6 (12%)
Cataract	42 (84%)	42 (84%)
Vascular occlusion	1 (2%)	2 (4%)
Diabetic retinopathy	1 (2%)	1 (2%)
Other	6 (12%)	9 (18%)
Mean (SD) VFMD, dB	−15.26 (6.34)	−14.91 (6.36)
Mean (SD) logMAR visual acuity	0.17 (0.26); n=223	0.15 (0.25)
Mean (SD) intraocular pressure, mm Hg:		
At diagnosis	25.9 (8.4); n=223	26.9 (9.1); n=226
At baseline	19.0 (5.7); n=221	19.4 (6.2); n=222

Table 1. Baseline characteristic of the cohort recruited for the trial. Data reported as Number (Percentage) unless otherwise indicated. SD = Standard Deviation; VFMD = Visual Field Mean Deviation; OAG = Open Angle Glaucoma; NTG = Normal Tension Glaucoma; logMAR = logarithm of the Minimum Angle of Resolution

		Medications first	Trabeculectomy first	Difference	p_d
Intention-to-treat					
Global	**Baseline (dB)**	14.24 [13.19, 15.25]	14.10 [13.10, 15.11]	-0.13 [-1.55, 1.31]	0.857
	RoP (dB/year)	-0.59 [-0.88, -0.31]	-0.40 [-0.67, -0.13]	0.19 [-0.20, 0.58]	0.353
Cluster 1	**Baseline (dB)**	9.52 [8.03, 11.01]	9.83 [8.40, 11.32]	0.31 [-1.86, 2.39]	0.769
	RoP (dB/year)	-0.58 [-0.99, -0.18]	-0.47 [-0.87, -0.07]	0.11 [-0.45, 0.66]	0.717
Cluster 2	**Baseline (dB)**	7.69 [6.08, 9.39]	8.36 [6.76, 9.94]	0.67 [-1.66, 2.97]	0.559
	RoP (dB/year)	-0.81 [-1.20, -0.40]	-0.41 [-0.79, -0.03]	0.39 [-0.16, 0.93]	0.159
Cluster 3	**Baseline (dB)**	18.79 [17.71, 19.85]	18.89 [17.82, 19.97]	0.10 [-1.40, 1.62]	0.896
	RoP (dB/year)	-0.78 [-1.08, -0.48]	-0.67 [-0.97, -0.38]	0.10 [-0.31, 0.52]	0.623
Cluster 4	**Baseline (dB)**	15.60 [14.00, 17.17]	14.87 [13.23, 16.50]	-0.73 [-3.04, 1.50]	0.543
	RoP (dB/year)	-0.70 [-1.03, -0.37]	-0.37 [-0.70, -0.04]	0.33 [-0.14, 0.79]	0.162
Cluster 5	**Baseline (dB)**	15.40 [13.93, 16.93]	14.50 [12.98, 15.95]	-0.90 [-3.04, 1.13]	0.404
	RoP (dB/year)	-0.45 [-0.77, -0.13]	-0.24 [-0.57, 0.09]	0.21 [-0.25, 0.68]	0.368
Cluster 6	**Baseline (dB)**	19.14 [17.96, 20.34]	18.82 [17.64, 20.02]	-0.32 [-1.98, 1.38]	0.698
	RoP (dB/year)	-0.15 [-0.53, 0.22]	-0.30 [-0.67, 0.07]	-0.14 [-0.68, 0.38]	0.590

Table 2. Population estimates [95% Credible Intervals] for the visual field baseline damage and rate of progression, globally and by Garway-Heath cluster. Note that the baseline is reported as the intercept of the models. Cluster 1 = peripheral superior; Cluster 2 = paracentral superior; Cluster 3 = central; Cluster 4 = paracentral inferior; Cluster 5 = peripheral inferior; Cluster 6 = temporal (see also Figure 2). RoP = Rate of Progression.